Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin D supplementation for chronic liver diseases in adults (Review)

Bjelakovic M, Nikolova D, Bjelakovic G, Gluud C

Bjelakovic M, Nikolova D, Bjelakovic G, Gluud C.
Vitamin D supplementation for chronic liver diseases in adults.
Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD011564.
DOI: 10.1002/14651858.CD011564.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 6
OBJECTIVES 6
METHODS 6
RESULTS 11
Figure 1. 12
Figure 2. 15
Figure 3. 16
Figure 4. 18
Figure 5. 20
Figure 6. 21
Figure 7. 22
DISCUSSION 23
AUTHORS' CONCLUSIONS 26
ACKNOWLEDGEMENTS 26
REFERENCES 27
CHARACTERISTICS OF STUDIES 38
DATA AND ANALYSES 72
Analysis 1.1. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 1: 1.1 All-cause mortality 77
Analysis 1.2. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 2: 1.1 All-cause mortality according to vested interest 78
Analysis 1.3. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 3: All-cause mortality according to vitamin D status at entry 79
Analysis 1.4. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 4: All-cause mortality according to form of vitamin D 80
Analysis 1.5. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 5: All-cause mortality (best-worst-case and worst-best-case scenarios) 82
Analysis 1.6. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 6: Liver-related mortality 83
Analysis 1.7. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 7: Serious adverse events 84
Analysis 1.8. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 8: Liver-related morbidity 84
Analysis 1.9. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 9: Health-related quality of life 85
Analysis 1.10. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 10: Non-serious adverse events 86
Analysis 1.11. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 11: Failure of rapid virological response 88
Analysis 1.12. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 12: Failure of early virological response 88
Analysis 1.13. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 13: Failure of sustained virological response 89
Analysis 1.14. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 14: Acute cellular rejection in liver transplant recipients 89
Analysis 1.15. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 15: Vitamin D status (ng/mL) 89
Analysis 1.16. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 16: Bone mineral density (g/cm) 90
Analysis 1.17. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 17: Aspartate aminotransferase (IU/L) 90
Analysis 1.18. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 18: Alanine aminotransferase (IU/L 91
Analysis 1.19. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 19: Alkaline phosphatases (IU/L) 91
Analysis 1.20. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 20: Gamma-glutamyl transpeptidase (IU/L) 91
Analysis 1.21. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 21: Bilirubin (mg/dL) 92
Analysis 1.22. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 22: Triglyceride (mg/dL) 92
Analysis 1.23. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 23: Cholesterol (mg/dL) 92
Analysis 1.24. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 24: LDL cholesterol (mg/dL) 92
Analysis 1.25. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 25: Albumin (g/L) 93

Analysis 1.26. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 26: HDL cholesterol (mg/dL) 93
Analysis 1.27. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 27: Calcium (mg/dL) 93
Analysis 1.28. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 28: Glucose (mg/dL) 94
Analysis 1.29. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 29: Phosphorus (mg/dL) 94
Analysis 1.30. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 30: Adiponectin (µg/mL) 94
Analysis 1.31. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 31: Insulin (mIU/mL) 95
Analysis 1.32. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 32: Parathyroid hormone (pg/mL) 95
Analysis 1.33. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 33: C-reactive protein (mg/L) 95
ADDITIONAL TABLES 96
APPENDICES 103
WHAT'S NEW 104
HISTORY 104
CONTRIBUTIONS OF AUTHORS 105
DECLARATIONS OF INTEREST 105
SOURCES OF SUPPORT 105
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 105
NOTES 105
INDEX TERMS 106

[Intervention Review]

Vitamin D supplementation for chronic liver diseases in adults

Milica Bjelakovic[1], Dimitrinka Nikolova[2], Goran Bjelakovic[3], Christian Gluud[2]

[1]Clinic of Gastroenterology and Hepatology, Clinical Centre Nis, Nis, Serbia. [2]Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen, Denmark. [3]Department of Internal Medicine, Medical Faculty, University of Nis, Nis, Serbia

Contact: Goran Bjelakovic, goranb@junis.ni.ac.rs.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: Edited (no change to conclusions), published in Issue 10, 2021.

Citation: Bjelakovic M, Nikolova D, Bjelakovic G, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. *Cochrane Database of Systematic Reviews* 2021, Issue 8. Art. No.: CD011564. DOI: 10.1002/14651858.CD011564.pub3.

ABSTRACT

Background

Vitamin D deficiency is often reported in people with chronic liver diseases. Improving vitamin D status could therefore be beneficial for people with chronic liver diseases.

Objectives

To assess the beneficial and harmful effects of vitamin D supplementation in adults with chronic liver diseases.

Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded, and Conference Proceedings Citation Index-Science. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. We scanned bibliographies of relevant publications and enquired experts and pharmaceutical companies as to additional trials. All searches were up to November 2020.

Selection criteria

Randomised clinical trials that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention in adults with chronic liver diseases. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)), or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol), 25-hydroxyvitamin D (calcidiol), or 1,25-dihydroxyvitamin D (calcitriol)).

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We used GRADE to assess the certainty of evidence.

Main results

We included 27 randomised clinical trials with 1979 adult participants. This review update added 12 trials with 945 participants. We assessed all trials at high risk of bias. All trials had a parallel-group design. Eleven trials were conducted in high-income countries and 16 trials in middle-income countries. Ten trials included participants with chronic hepatitis C, five trials participants with liver cirrhosis, 11 trials participants with non-alcoholic fatty liver disease, and one trial liver transplant recipients. All of the included trials reported the baseline vitamin D status of participants. Participants in nine trials had baseline serum 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL), whilst participants in the remaining 18 trials were vitamin D insufficient (less than 20 ng/mL). Twenty-four trials administered vitamin D orally, two trials intramuscularly, and one trial intramuscularly and orally. In all 27 trials, the mean duration of vitamin D supplementation was 6 months, and the mean follow-up of participants from randomisation was 7 months. Twenty trials (1592

participants; 44% women; mean age 48 years) tested vitamin D_3 (cholecalciferol); three trials (156 participants; 28% women; mean age 54 years) tested vitamin D_2; four trials (291 participants; 60% women; mean age 52 years) tested 1,25-dihydroxyvitamin D; and one trial (18 participants; 0% women; mean age 52 years) tested 25-hydroxyvitamin D. One trial did not report the form of vitamin D. Twelve trials used a placebo, whilst the other 15 trials used no intervention in the control group. Fourteen trials appeared to be free of vested interest. Eleven trials did not provide any information on clinical trial support or sponsorship. Two trials were funded by industry.

We are very uncertain regarding the effect of vitamin D versus placebo or no intervention on all-cause mortality (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.51 to 1.45; 27 trials; 1979 participants). The mean follow-up was 7 months (range 1 to 18 months). We are very uncertain regarding the effect of vitamin D versus placebo or no intervention on liver-related mortality (RR 1.62, 95% CI 0.08 to 34.66; 1 trial; 18 participants) (follow-up: 12 months); serious adverse events such as hypercalcaemia (RR 5.00, 95% CI 0.25 to 100.8; 1 trial; 76 participants); myocardial infarction (RR 0.75, 95% CI 0.08 to 6.81; 2 trials; 86 participants); thyroiditis (RR 0.33, 95% CI 0.01 to 7.91; 1 trial; 68 participants); circular haemorrhoidal prolapse (RR 3.00, 95% CI 0.14 to 65.9; 1 trial; 20 participants); bronchopneumonia (RR 0.33, 95% CI 0.02 to 7.32; 1 trial 20 participants); and non-serious adverse events. The certainty of evidence for all outcomes is very low.

We found no data on liver-related morbidity such as gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, ascites, or liver cancer. There were also no data on health-related quality of life.

The evidence is also very uncertain regarding the effect of vitamin D versus placebo or no intervention on rapid, early, and sustained virological response in people with chronic hepatitis C.

Authors' conclusions

Given the high risk of bias and insufficient power of the included trials and the very low certainty of the available evidence, vitamin D supplementation versus placebo or no intervention may increase or reduce all-cause mortality, liver-related mortality, serious adverse events, or non-serious adverse events in adults with chronic liver diseases. There is a lack of data on liver-related morbidity and health-related quality of life. Further evidence on clinically important outcomes analysed in this review is needed.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for chronic liver diseases

Review question

Is vitamin D supplementation beneficial or harmful for adults with chronic liver diseases?

Background

The available evidence on vitamin D and chronic liver diseases in adults is inconclusive. The aim of this systematic review (a summary of results of available healthcare trials) was to analyse the benefits and harms of the different forms of vitamin D in people with chronic liver diseases.

Study characteristics

Twenty-seven trials with 1979 adult participants provided data for this review. This review update added 12 trials with 945 participants. The 1979 trial participants were randomly assigned to vitamin D compared with placebo (dummy pill) or no treatment. Eleven trials were conducted in high-income countries, and 16 trials in middle-income countries. The age range of the participants was 28 years to 61 years, and on average 44% were women. Ten trials included people with chronic hepatitis C, five trials people with liver cirrhosis, 11 trials people with non-alcoholic fatty liver disease, and one trial liver transplant recipients. There were no trials including people with chronic hepatitis B or inherited liver diseases. All of the included trials reported the baseline vitamin D status of participants. Vitamin D administration lasted on average six months, and most trials used the cholecalciferol (vitamin D_3) form.

Funding

Fourteen trials appeared to be free of vested interest that could bias the trial results. Eleven trials may not have been free of vested interest, as they did not provide any information on clinical trial support or sponsorship. Two trials were funded by industry. We found no difference between trials without industry support compared to trials at risk of industry support in our analysis.

Key results

There is not enough evidence to determine whether vitamin D has beneficial or harmful effects, or has little to no effect on chronic liver diseases in adults. There were too few participants in the individual trials as well as in our evidence synthesis. The trials were at high risk of bias so we lack fair assessments of the benefits and harms of vitamin D in this population. Neither benefits nor harms of vitamin D supplementation in people with chronic liver diseases can be excluded. There were no trials including people with chronic hepatitis B and inherited liver diseases.

Quality of the evidence

We judged all trials to be at high risk of bias (that is an underestimation or overestimation of the true intervention effect). The certainty of evidence is very low.

Currentness of evidence

The evidence is current to November 2020.

Summary of findings 1. Vitamin D compared with placebo or no intervention for chronic liver diseases in adults

Vitamin D compared with placebo or no intervention for chronic liver diseases in adults

Patient or population: people with chronic liver diseases
Setting: in- and outpatients
Intervention: vitamin D
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with vitamin D				
All-cause mortality Follow-up: mean 7 months (1 to 18 months)	Study population		RR 0.86 (0.51 to 1.45)	1979 (27 RCTs)	⊕⊖⊖⊖ very low [1]	
	21 per 1000	18 per 1000 (11 to 30)				
Liver-related mortality Follow-up: 12 months	Study population		RR 1.62 (0.08 to 34.66)	18 (1 RCT)	⊕⊖⊖⊖ very low [2]	No information was available to calculate absolute effects.
	-	-				
Serious adverse events Follow-up: mean 10.5 months (6 to 12 months)	Study population		-	-	⊕⊖⊖⊖ very low [3]	
	Several serious adverse events were reported: hypercalcaemia (RR 5.00, 95% CI 0.25 to 100.8; 1 trial; 76 participants); myocardial infarction (RR 0.75, 95% CI 0.08 to 6.81; 2 trials; 86 participants); thyroiditis (RR 0.33, 95% CI 0.01 to 7.91; 1 trial; 68 participants); circular haemorrhoidal prolapse (RR 3.00, 95% CI 0.14 to 65.9; 1 trial; 20 participants); bronchopneumonia (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants).					
Liver-related morbidity	Study population		-	(0 RCTs)	-	
	-	-				
Health-related quality of life	Study population		-	(0 RCTs)	-	
	-	-				

Non-serious adverse events Follow-up: mean 7 months (3 to 12 months)	Study population 1 trial reported 1 single non-serious adverse event, and another trial reported 16 single non-serious adverse events, for a total of 17 types of non-serious adverse events.		-	-	⊕⊖⊖⊖ very low [3]
Failure of sustained virological response Follow-up: mean 16 months (6 to 18 months)	Study population 484 per 1000	315 per 1000 (203 to 489)	RR 0.65 (0.42 to 1.01)	630 (7 RCTs)	⊕⊖⊖⊖ very low[4]

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

CI: confidence interval; **RCT:** randomised clinical trial; **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.

[1]Downgraded because of risk of bias (1 level) (all trials were at high risk of bias); and imprecision (2 levels) (few events, and the optimal information size of 63,116 participants (based on a proportion of 2% in the control group, a relative risk reduction of 20%, an alpha of 1.25%, and a beta of 10%) was not met; wide CI which included both benefits and harms).
[2]Downgraded because of risk of bias (1 level) (the trial was at high risk of bias); and imprecision (2 levels) (very few events, and wide CI which included both benefits and harms).
[3]Downgraded because of risk of bias (1 level) (all trials were at high risk of bias); and imprecision (2 levels) (very few events, and wide CI which included both benefits and harms).
[4]Downgraded because of risk of bias (1 level) (all trials were at high risk of bias); imprecision (2 levels) (the optimal information size of 7570 participants (based on a proportion of 48% in the control group, a relative risk reduction of 20%, an alpha of 1.25%, and a beta of 10%) was not met); inconsistency (1 level) (considerable heterogeneity); and indirectness (3 levels)(sustained virological response is a surrogate outcome).

BACKGROUND

Vitamin D is either synthesised in the skin (vitamin D_3 (cholecalciferol)) or is obtained from dietary sources (vitamin D_3 or vitamin D_2 (ergocalciferol)). Vitamin D_3 and D_2 do not have biological activity. Both forms are metabolised in the liver to 25-hydroxyvitamin D (calcidiol) and in the kidneys to the biologically active form known as 1,25-dihydroxyvitamin D (calcitriol), which functions as a steroid-like hormone (Wesley Pike 2005). The effects of 1,25-dihydroxyvitamin D are mediated by its binding to vitamin D receptors in the cells (Wesley Pike 2005). Renal production of 1,25-dihydroxyvitamin D is regulated by parathyroid hormone levels, by serum calcium and phosphorus levels, and by the phosphaturic hormone fibroblast growth factor-23 (Kovesdy 2013).

Description of the condition

Vitamin D status is determined by the measurement of the serum 25-hydroxyvitamin D level (Lips 2004; Dawson-Hughes 2005; Bischoff-Ferrari 2009). A number of methods are used to measure vitamin D status (radioimmunoassay; high-performance/pressure liquid chromatography (HPLC); liquid chromatography-tandem mass spectrometry (LC-MS/MS); and more recently chemiluminescent immunoassay (CLIA)) (Atef 2018). The accuracy of these methods varies significantly. HPLC and LC-MS/MS can measure vitamin D_2 and D_3 independently and are considered as the gold standard (Hollis 2008).

Optimal sun exposure and dietary intake are related to optimal vitamin D status. The US Institute of Medicine recommended target serum 25-hydroxyvitamin D levels of 20 ng/mL (50 nmol/L) (IOM 2011). Based on the systematic review prepared by the US Institute of Medicine, there are insufficient data to determine the safe upper limit of serum 25-hydroxyvitamin D levels (IOM 2011). However, serum 25-hydroxyvitamin D concentrations above 50 ng/mL (125 nmol/L) are considered potentially harmful (IOM 2011). The International Osteoporosis Foundation and the Endocrine Society Task Force recommend a target serum 25-hydroxyvitamin D level of 30 ng/mL (75 nmol/L) (Dawson-Hughes 2010; Holick 2011).

The worldwide prevalence of suboptimal vitamin D status is estimated to be high (Lips 2010; Van Schoor 2011; Hilger 2014). The major causes of vitamin D deficiency are insufficient exposure to sunlight, decreased dietary intake, skin pigmentation, obesity, and advanced age (Lips 2006; Holick 2007; Tsiaras 2011; SACN 2016). One systematic review of prospective and intervention studies that assessed the effect of vitamin D status on non-skeletal outcomes suggested that low vitamin D status in a wide spectrum of diseases may be a marker of ill health (Autier 2014).

Vitamin D undergoes important biotransformation in the liver. The liver also plays a critical role in the inactivation of vitamin D. Because vitamin D is metabolised by the liver, abnormal vitamin D metabolism might be expected to be associated with chronic liver diseases. Vitamin D deficiency has been frequently reported in people with chronic liver diseases (Arteh 2010; Malham 2011; Kitson 2012; Lim 2012; Stokes 2013; Skaaby 2014). There is evidence that low vitamin D status is associated with increased mortality in chronic liver diseases (Putz-Bankuti 2012; Wang 2013; Stokes 2014; Finkelmeier 2015; Paternostro 2017).

Description of the intervention

Vitamin D can be administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or as an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol), 25-hydroxyvitamin D (calcidiol), or 1,25-dihydroxyvitamin D (calcitriol)). Vitamin D supplementation prevents osteoporosis and osteomalacia (Lips 2006). It is speculated that vitamin D supplementation may confer benefits beyond the skeletal system, including chronic liver diseases (Davis 2007; Kitson 2012; Han 2013; Elangovan 2017).

How the intervention might work

Vitamin D supplementation may have beneficial effects on bone disorders in people with chronic liver diseases (Guañabens 2010; Luxon 2011). Vitamin D supplementation has also been suggested as a potential therapeutic in people with chronic hepatitis B infection (Farnik 2013; Mahamid 2013); chronic hepatitis C infection (Petta 2010; Gutierrez 2011; Bitetto 2012; Cacopardo 2012; Cholongitas 2012; Luong 2012); autoimmune hepatitis (Luong 2013a); non-alcoholic fatty liver disease (Geier 2011; Eliades 2013; Kwok 2013; Eliades 2015); primary biliary cirrhosis (Li 2013; Luong 2013b); alcoholic cirrhosis (Trépo 2013; Konstantakis 2016); and hepatocellular carcinoma (Chiang 2011; Lange 2013). It is currently unclear how vitamin D exerts its postulated beneficial effects apart from possibly correcting vitamin D serum levels to something seemingly more normal (Zittermann 2014).

Why it is important to do this review

Observational studies reported a high prevalence of vitamin D insufficiency across a spectrum of chronic liver diseases (Arteh 2010; Lim 2012; Han 2013; Finkelmeier 2014). However, the available evidence on the benefits and harms of vitamin D supplementation in people with chronic liver diseases is insufficient and inconsistent. Meta-analyses of observational studies and interventional trials in people with chronic hepatitis B or C virus infection and non-alcoholic fatty liver disease found contradictory results (Villar 2013; Kitson 2014: Mosannen 2017; Tabrizi 2017; Kim 2018; Hariri 2019; Hu 2019; Mansour-Ghanaei 2019; Sharifi 2019). Results of our previous systematic reviews indicate that vitamin D_3 supplementation may potentially prolong life span in adults from the general population (Bjelakovic 2014a), but this observation has been effectively contradicted by recent large randomised clinical trials (Scragg 2017; Manson 2019), and vitamin D does not seem to have an effect on cancer occurrence and cardiovascular diseases (Bjelakovic 2014b; Scragg 2018; Manson 2019; Bischoff-Ferrari 2020).

OBJECTIVES

To assess the beneficial and harmful effects of vitamin D supplementation in adults with chronic liver diseases.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials, irrespective of blinding, publication status, or language.

Types of participants

Adults (aged 18 years or over) diagnosed with a chronic liver disease (alcoholic, non-alcoholic fatty liver disease, post-hepatitis B and C, cholestatic, inherited, and autoimmune diseases).

Types of interventions

Experimental

Vitamin D at any dose and for any duration, administered as monotherapy or in combination with calcium. The route of administration could be enteral (orally) or parenteral. Vitamin D could be administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or as an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol), 25-hydroxyvitamin D (calcidiol), or 1,25-dihydroxyvitamin D (calcitriol)).

Control

Placebo (identical in appearance and smell) or no intervention.

Concomitant interventions were allowed if used equally in all intervention groups.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Liver-related mortality.
- Serious adverse events. Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. Serious adverse events were defined as any outward medical occurrence that was life-threatening; resulted in death, or persistent or significant disability; or any medical event that may have jeopardised the person; or required intervention to prevent it (ICH-GCP 1997). We considered all other adverse events as non-serious (see Secondary outcomes below).

Secondary outcomes

- Liver-related morbidity (gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, ascites, liver cancer).
- Health-related quality of life (any valid continuous outcome scale used by the trialists).
- Non-serious adverse events.
- Failure of virological response at week four (without rapid virological response), at week 12 (without early virological response), and at six months after treatment (sustained virological response) (e.g. without clearance of hepatitis B virus DNA (HBV-DNA) or hepatitis C virus ribonucleic acid (HCV-RNA) from serum).
- Acute cellular rejection in liver transplant recipients.
- Vitamin D status.
- Bone mineral density.
- Biochemical indices (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases, gamma-glutamyl transpeptidase, albumin, bilirubin, triglyceride, cholesterol, calcium, glucose, phosphorus, adiponectin, insulin, parathyroid hormone, C-reactive protein).

Covariates, effect modifiers, and confounders

We recorded any possible covariates, effect modifiers, and confounders such as dosage and form of vitamin D, dosing schedule, duration of supplementation, duration of follow-up, mean age, risk of bias, calcium co-administration, other medications, compliance, and attrition.

Timing of outcome measurement

We applied no restrictions regarding duration of the intervention or length of follow-up. We assessed outcome data at the end of the trial follow-up period.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (maintained and searched internally by the Cochrane Hepato-Biliary Group Information Specialist via the Cochrane Register of Studies Web; 24 November 2020), the Cochrane Central Register of Controlled Trials (CENTRAL; 24 November 2020) in the Cochrane Library, MEDLINE Ovid (1946 to 24 November 2020), Embase Ovid (1974 to 24 November 2020), LILACS (Latin American and Caribbean Health Science Information database) (BIREME; 1982 to 24 November 2020), Science Citation Index Expanded (Web of Science, 1900 to 24 November 2020), and Conference Proceedings Citation Index-Science (Web of Science; 1990 to 24 November 2020). The search strategies with the time spans of the searches are provided in Appendix 1.

We also searched ClinicalTrials.gov (www.clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/). There were no language limitations.

Searching other resources

We contacted experts and the main manufacturers of vitamin D to enquire as to unpublished randomised trials. We identified additional trials by searching the reference lists of the included trials and systematic reviews, meta-analyses, and health technology assessment reports.

Data collection and analysis

One review author (MB) performed the electronic searches. Two review authors (GB and DN) independently participated in the manual searches and identified trials eligible for inclusion from the search results.

Selection of studies

Two review authors (MB and GB) independently scanned the abstract, title, or both of every record retrieved to identify studies for further assessment. We investigated all potentially relevant articles as full text. One review author (GB) listed the excluded studies along with the reasons for their exclusion. When a discrepancy occurred in the trial selection, we consulted one review author (CG) to reach consensus. If resolving disagreement was not possible, we added the article to those 'awaiting assessment', and contacted the trial authors for clarification. We also contacted trial authors when information required to make an assessment was not found in the published trial reports. Inter-rater agreement for trial selection was measured using the Kappa statistic (Cohen 1960).

Agreement between the review authors was very good (Kappa = 0.85). We included an adapted PRISMA flow diagram of study selection (Moher 2009).

Data extraction and management

For studies that fulfilled the inclusion criteria, three review authors (GB, DN, and MB) independently extracted the relevant population, intervention characteristics, and risk of bias components using standard data extraction templates. We identified any duplicate publications. Disagreements were resolved by discussion or by consultation with another review author (CG) when required.

Dealing with duplicate publications and companion papers

In the case of duplicate publications and companion papers of a primary study, we maximised our yield of information by simultaneous evaluation of all available data.

Assessment of risk of bias in included studies

Two review authors (GB and DN) independently assessed the risk of bias of each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018b). We used the following definitions in our risk of bias assessment.

Allocation sequence generation

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

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. Investigators were unaware of allocation sequence (e.g. if allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal allocation is not mentioned so that intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence.

Blinding of participants and personnel

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

Blinded outcome assessment

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

Incomplete outcome data

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

Selective outcome reporting

- Low risk of bias: the trial reported all predefined outcomes. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial had begun, we did not consider those outcomes to be reliable.
- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes.
- High risk of bias: the study authors did not report one or more of the predefined outcomes.

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. academic bias) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. authors had conducted trials on the same topic).

Overall risk of bias

We judged a trial to be at overall low risk of bias if we assessed the trial at low risk of bias for all of the above domains. We judged a trial to be at high risk of bias if we assessed the trial as having an unclear risk of bias or a high risk of bias in one or more of the risk of bias domains.

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes, we calculated and presented risk ratios (RR) with 95% confidence intervals (CI). We planned to calculate and present Peto's odds ratio for rare events such as all-cause mortality and liver-related mortality. As there were no differences between the results with Peto's odds ratio and the RR for these two outcomes, we presented the results with RR (Deeks 2021).

Continuous outcomes

For continuous outcomes, we calculated and presented mean differences (MD) with 95% CI.

In the case of time-to-event data, we planned to plot and meta-analyse estimates of hazard ratios (HR) and 95% CIs as presented in the study reports using the generic inverse-variance method in Review Manager 5 (Review Manager 2020).

Unit of analysis issues

The unit of analysis was the participant as randomised to the intervention group of a clinical trial. In trials with one experimental and one control parallel-group design, we compared the experimental intervention group versus the control group. In trials with parallel-group design with more than two intervention groups, we compared the combined vitamin D groups versus the placebo or no intervention group.

For cross-over trials, we planned to include the relevant data from the first trial period to avoid residual effects from the treatment (Higgins 2011; Higgins 2021). In order to avoid repeated observations on trial participants, we recorded all time points for these observations, but we used the trial data at the longest follow-up for analysis (Higgins 2011; Higgins 2021).

We planned to include cluster-randomised trials and assess risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Higgins 2021).

Dealing with missing data

We attempted to obtain relevant missing data from study authors whenever we lacked important numerical data, such as number of screened or randomised participants, or if there was a lack of data regarding the performance of intention-to-treat (ITT) analyses, or data on as-treated or per-protocol participant analyses, which prevented us from performing our analyses appropriately. We investigated attrition rates (e.g. dropouts, losses to follow-up, and withdrawals) and critically appraised issues of missing data (e.g. last-observation-carried-forward and imputation methods).

Regarding the primary outcomes, we included trial participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios (Hollis 1999).

- 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.

Assessment of heterogeneity

We identified heterogeneity by visual inspection of the forest plots, and by using a standard Chi^2 test and a significance level of $\alpha = 0.1$ (Higgins 2002; Higgins 2003).

We interpreted the I^2 statistic as follows (Higgins 2021):

- 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.

For heterogeneity adjustment of the required information size in the Trials Sequential Analysis, we used diversity (D_2), as the I^2 statistic used for this purpose consistently underestimates the required information size (Wetterslev 2009).

When we found considerable heterogeneity, we attempted to determine the potential reasons for it by examining the individual trial and subgroup characteristics.

Assessment of reporting biases

To assess the potential existence of publication bias, we planned to use a funnel plot in an exploratory data analysis of the outcome all-cause mortality, if 10 or more trials were included (Higgins 2021). There are several explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design of small trials, and publication bias.

We performed adjusted rank correlation, Begg 1994, and a regression asymmetry test, Egger 1997, for detection of bias. We considered a P value of less than 0.10 as significant in these analyses.

Data synthesis

Meta-analysis

We performed statistical analyses according to the guidelines described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

For the statistical analyses, we used Review Manager 5 (Review Manager 2020), Trial Sequential Analysis version 0.9.5.10 beta (TSA 2017), Stata 8.2 (StataCorp 2005), and SigmaStat 3.0 (Sigma Stat 2003). We analysed the data using both fixed-effect (DeMets 1987), and random-effects (DerSimonian 1986), models for meta-analyses. We presented the results of the random-effects model analyses. If there were statistically significant discrepancies in the results (e.g. one model giving a significant intervention effect, and the other model giving no significant intervention effect), we

presented both models, but considered the more conservative point estimate of the two as the most informative (Jakobsen 2014a). The more conservative point estimate is the estimate closest to one (for dichotomous outcomes) or zero effect (for continuous outcomes). If the two-point estimates were equal, we used the estimate with the widest CI as our main result of the two analyses (Jakobsen 2014a). For dichotomous outcomes, we calculated RR, and for continuous outcomes we calculated MD or standardised mean difference (SMD) for health-related quality of life. For all association measures, we used 95% CIs. We performed the analyses using the ITT principle, that is including all randomised participants irrespective of completeness of data. Participants with missing data were included in the analyses using a carry forward of the last observed response. Accordingly, participants who had been lost to follow-up were counted as being alive.

We compared the intervention effects in subgroups of trials using the method described by Borenstein and colleagues (Borenstein 2009), and implemented it in Review Manager 5 analyses.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis comparing trials at low risk of bias to trials at unclear or high risk of bias in order to assess the risk of bias to intervention effects (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018b). Given that all trials were at high risk of bias, we were not able to conduct this subgroup analysis.

We conducted the following subgroup analyses.

- According to the aetiology of the chronic liver disease, as vitamin D may have a different effect on the outcome all-cause mortality in people with chronic liver disease of different aetiology (e.g. non-alcoholic fatty liver disease, chronic hepatitis C, liver cirrhosis, liver transplant recipients):
  - people with non-alcoholic fatty liver disease compared to people with chronic hepatitis C;
  - people with non-alcoholic fatty liver disease compared to people with liver cirrhosis;
  - people with non-alcoholic fatty liver disease compared to liver transplant recipients.
- According to vested interests. Trials at low risk of vested interests compared to trials at unclear or high risk of vested interests (Lundh 2017).
- According to vitamin D status at entry (vitamin D sufficient compared to vitamin D insufficient participants). As some participants in some trials had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL serum), whilst some participants in other trials were vitamin D insufficient (less than 20 ng/mL serum), we conducted this post hoc subgroup analysis.
- According to the different forms of vitamin D used for supplementation, as vitamin D form may have a different effect on the outcome all-cause mortality:
  - vitamin D_3 compared with placebo or no intervention;
  - vitamin D_2 compared with placebo or no intervention;
  - 25-dihydroxyvitamin D compared with placebo or no intervention;
  - 1,25-dihydroxyvitamin D compared with placebo or no intervention.

Sensitivity analysis

In addition to the sensitivity analyses described in Dealing with missing data, we used Trial Sequential Analysis as a sensitivity analysis to assess imprecision.

Trial Sequential Analysis

We controlled apparently significant beneficial and harmful intervention effects (potential type I errors) and neutral intervention effects (potential type II errors) with Trial Sequential Analysis to evaluate if these effects could be caused by random errors (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2011; Thorlund 2017; TSA 2017; Wetterslev 2017). The underlying assumption of Trial Sequential Analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial was published in a year, we added trials alphabetically according to the last name of the first author.

We used Trial Sequential Analysis because cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To control for random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008). The required information size calculation should account for the diversity, present in the meta-analysis (Wetterslev 2008; Wetterslev 2009). We assessed the diversity-adjusted required information size (DARIS) for the three primary and the first four secondary outcomes presented in the Summary of findings 1, by adjusting for multiplicity, using a P value of 0.125, a risk of type II error of 10%, and the observed diversity of the included trials in the random-effects model meta-analysis (Jakobsen 2014a). For dichotomous outcomes, we used the proportion in the control group in the meta-analysis and a relative risk reduction of 20%. For the continuous outcome health-related quality of life, we would have used the standard deviation (SD) divided by 2 as the minimal relevant difference plus the SD of the difference for calculating the DARIS.

We constructed trial sequential monitoring boundaries for benefit, harm, or futility, based on the DARIS (Thorlund 2017). These boundaries determined the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit or harm before the diversity-adjusted required information size is reached, firm evidence may be established, and further trials may be superfluous. In contrast, if the boundary is not surpassed, it is most likely necessary to continue doing trials to detect or reject a certain intervention effect. This can be determined by assessing if the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility. A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa/ (Thorlund 2017), and in Wetterslev 2017.

In Trial Sequential Analysis, imprecision is downgraded two levels if the accrued number of participants is below 50% of the DARIS, and one level if it is between 50% and 100% of DARIS. We did

not downgrade if the cumulative Z-curve crossed the monitoring boundaries for benefit, harm, or futility, or if DARIS was reached.

See also Dealing with missing data.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using GRADEpro GDT (GRADEpro GDT). We used the GRADE approach to assess the quality of a body of evidence, that is the extent of certainty on which one can be confident that an estimate of effect or association reflects the item being assessed. The certainty of a body of evidence considers within-study risk of bias, directness of the evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses), imprecision of results (wide CIs, optimal information size criterion), and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Schünemann 2013; Guyatt 2017). We presented the following outcomes: all-cause mortality, liver-related mortality, serious adverse events, liver-related morbidity, health-related quality of life, non-serious adverse events, and failure of sustained virological response. After each outcome, we provided the mean and range of follow-up, or end of follow-up when there was only one trial that provided data.

These grades of certainty are defined as follows.

- 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.

RESULTS

Description of studies

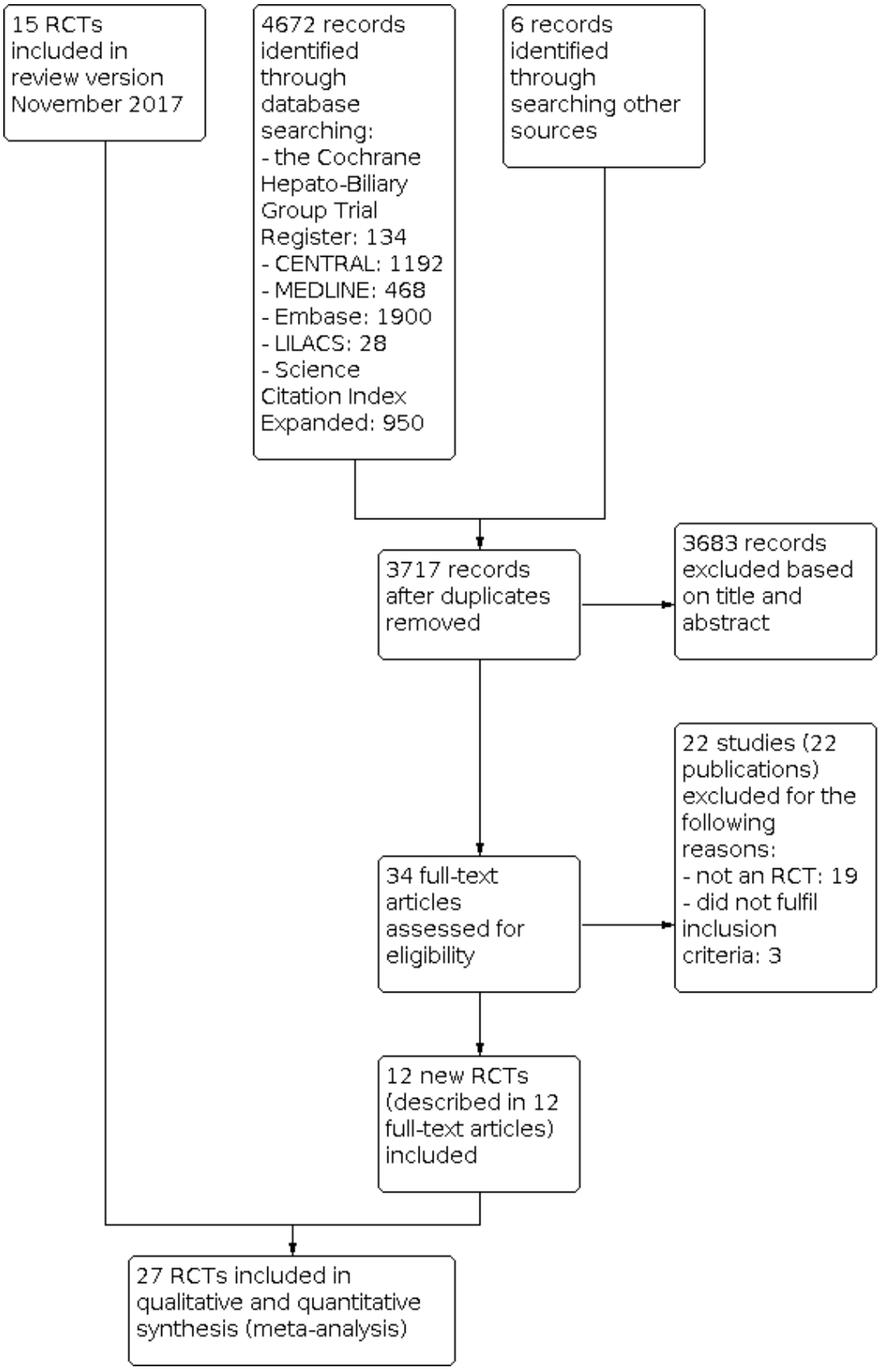
In the previous version of this review, we included 15 randomised trials (described in 19 references) with 1034 participants providing data for analyses (Bjelakovic 2017). As described below, our updated searches resulted in the inclusion of an additional 12 randomised trials.

Results of the search

We identified 4672 references of possible interest through the updated electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (134 records); the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (1192 records); MEDLINE Ovid (468 records); Embase Ovid (1900 records); LILACS (28 records); and Science Citation Index Expanded and Conference Proceedings Citation Index-Science (950 records). We identified an additional two ongoing trials through searching databases of ongoing trials, and four records from reference lists. We excluded 961 duplicates and 3683 clearly irrelevant references through reading of abstracts. Accordingly, we retrieved 34 references for further assessment. Of these, we excluded 19 references because they were not randomised trials, and three references because they did not fulfil our inclusion criteria.

Consequently, we included 12 new randomised trials (described in 12 references) in this updated review version; a total of 27 trials (31 references) with 1979 participants provided data for our analyses (Figure 1).

Figure 1. Study flow diagram.



Included studies

For details of the included studies, see Characteristics of included studies; Table 1; Table 2; Table 3.

All 27 included trials used a parallel-group design, with two (Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Sharifi 2014; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Barchetta 2016; Boonyagard 2016; Foroughi 2016; Pilz 2016: Vosoghinia 2016: Jha 2017; Komolmit 2017a; Komolmit 2017b; Sakpal 2017; Behera 2018; Geier 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019; Jeong 2019) or three intervention groups (Mobarhan 1984; Xing 2013; Lorvand Amiri 2016; Dabbaghmanesh 2018). The trials were published from 1984 to 2019 (Table 1).

The trials were conducted in Africa (Esmat 2015), Asia (Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Xing 2013; Sharifi 2014; Yokoyama 2014; Atsukawa 2016, Foroughi 2016; Lorvand Amiri 2016; Vosoghinia 2016; Boonyagard 2016; Jha 2017; Komolmit 2017a; Komolmit 2017b; Sakpal 2017; Behera 2018; Dabbaghmanesh 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019; Jeong 2019); Europe (Barchetta 2016; Pilz 2016; Geier 2018), and North America (Mobarhan 1984). Eleven trials were conducted in high-income countries (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Atsukawa 2016; Barchetta 2016; Pilz 2016; Geier 2018; Jeong 2019), and 16 trials were conducted in middle-income countries (Table 2) (Xing 2013; Sharifi 2014; Esmat 2015; Boonyagard 2016; Foroughi 2016; Lorvand Amiri 2016; Vosoghinia 2016; Jha 2017; Komolmit 2017a; Komolmit 2017b; Sakpal 2017; Behera 2018; Dabbaghmanesh 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019).

Participants

A total of 1979 participants were randomly assigned in the 27 trials. The number of participants in each trial ranged from 18 to 148 (median 84). The mean age of participants was 48 years (range 28 years to 61 years). The mean proportion of women was 44% (Table 1).

Ten trials included participants with chronic hepatitis C (Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Vosoghinia 2016; Komolmit 2017a; Komolmit 2017b; Behera 2018; Jeong 2019); five trials participants with liver cirrhosis (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Pilz 2016; Jha 2017); 11 trials participants with non-alcoholic fatty liver disease (Sharifi 2014; Barchetta 2016; Boonyagard 2016; Foroughi 2016; Lorvand Amiri 2016; Sakpal 2017; Dabbaghmanesh 2018; Geier 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019); and one trial liver transplant recipients (Table 2) (Xing 2013).

All of the included trials reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in nine trials had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL) (Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Atsukawa 2016; Foroughi 2016; Vosoghinia 2016; Behera 2018; Geier 2018; Komolmit 2017a). Participants in the remaining 18 trials had baseline 25-hydroxyvitamin D levels considered to be vitamin D insufficient (less than 20 ng/mL) (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Xing 2013; Sharifi 2014; Esmat 2015; Barchetta 2016; Boonyagard 2016; Lorvand Amiri 2016; Pilz 2016; Jha 2017; Komolmit 2017b; Sakpal 2017; Dabbaghmanesh 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019; Jeong 2019).

Experimental interventions

One trial did not report form and dose of vitamin D (Boonyagard 2016). One trial with three intervention groups administered 1,25-dihydroxyvitamin D combined with calcium gluconate in one intervention group, calcium gluconate alone in another intervention group, and placebo in a third group (Xing 2013). We thus compared the 1,25-dihydroxyvitamin D plus calcium gluconate group versus the calcium gluconate group and placebo group combined. Another trial with three intervention groups used vitamin D_3 singly in one intervention group, vitamin D_3 combined with calcium carbonate in another intervention group, and placebo in a third group (Table 3) (Lorvand Amiri 2016). We thus compared the first two groups together versus the placebo group. One trial with three intervention groups administered 25-dihydroxyvitamin D in one intervention group, vitamin D_2 in another intervention group, and no intervention in a third group (Mobarhan 1984). We compared vitamin D groups together versus the no intervention group. Another trial with three intervention groups administered 1,25-dihydroxyvitamin D in one intervention group, vitamin D_3 in another intervention group, and placebo in a third group (Dabbaghmanesh 2018). We compared the vitamin D groups together versus the placebo group.

Vitamin D_3 (cholecalciferol)

Vitamin D was administered as vitamin D_3 (cholecalciferol) in 20 trials (1592 participants; 44% women; mean age 48 years) (Abu-Mouch 2011; Nimer 2012; Sharifi 2014; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Barchetta 2016; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Jha 2017; Sakpal 2017; Behera 2018; Dabbaghmanesh 2018; Geier 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019; Jeong 2019). Vitamin D_3 was tested orally in 24 trials. Two trials administered vitamin D_3 intramuscularly (Sakpal 2017; Hosseini 2018), and one trial administered vitamin D_3 intramuscularly and orally (Jha 2017). Vitamin D_3 was administered daily in 11 trials (Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Atsukawa 2016; Barchetta 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Behera 2018; Geier 2018; Jeong 2019); weekly in five trials (Esmat 2015; Foroughi 2016; Dabbaghmanesh 2018; Taghvaei 2018; Hussain 2019); twice a week in one trial (Sharifi 2014); in a single dose in two trials (Sakpal 2017; Hosseini 2018); and in a single dose and daily in one trial (Jha 2017). Mean daily dose of vitamin D_3 was 2791 international units (IU). The duration of supplementation in trials using vitamin D_3 was 8 to 48 weeks (mean 24 weeks). The length of the follow-up period was from 8 to 72 weeks (mean 28 weeks) (Table 3).

Vitamin D_2 (ergocalciferol)

Vitamin D was administered as vitamin D_2 (ergocalciferol) in three trials (156 participants; 28% women; mean age 54 years) (Mobarhan 1984; Komolmit 2017a; Komolmit 2017b). Vitamin D_2 was tested in a dose of 50,000 IU orally, two or three times weekly for one year in one trial (Mobarhan 1984), and 60,000 to 100,000 IU orally weekly in two trials (Komolmit 2017a; Komolmit 2017b). Mean daily dose of vitamin D_2 was 11,429 IU. The duration of supplementation and follow-up in trials using vitamin D_2 was 6 to 52 weeks (mean 21 weeks). The length of the follow-up period was from 6 to 52 weeks (mean 21 weeks) (Table 3).

1,25-dihydroxyvitamin D (calcitriol)

Vitamin D was administered as 1,25-dihydroxyvitamin D in four trials (291 participants; 60% women; mean age 52 years) (Shiomi 1999a; Shiomi 1999b; Xing 2013; Dabbaghmanesh 2018). 1,25-dihydroxyvitamin D was tested singly, orally, and daily in two trials (Shiomi 1999a; Shiomi 1999b). One trial administered 1,25-dihydroxyvitamin D combined with calcium (Xing 2013). One trial with a parallel-group design and three arms tested 1,25-dihydroxyvitamin D and vitamin D_3 in separate arms (Dabbaghmanesh 2018). The dose of 1,25-dihydroxyvitamin D was 1.0 µg in two trials (Shiomi 1999a; Shiomi 1999b), and 0.25 µg in two trials (Xing 2013; Dabbaghmanesh 2018). Mean daily dose of 1,25-dihydroxyvitamin D was 0.625 µg. The duration of supplementation and follow-up in trials using 1,25-dihydroxyvitamin D was four to 52 weeks (mean 30 weeks) (Table 3).

25-hydroxyvitamin D (calcidiol)

Vitamin D was administered as 25-hydroxyvitamin D in one trial (18 participants; 0% women; mean age 52 years) (Mobarhan 1984). 25-hydroxyvitamin D was tested at a dose of 800 IU/day to 2000 IU/day, orally, for one year (Table 3).

Control interventions

Twelve trials used a placebo in the control group (Xing 2013; Sharifi 2014; Barchetta 2016; Boonyagard 2016; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Komolmit 2017a; Komolmit 2017b; Dabbaghmanesh 2018; Geier 2018; Hussain 2019), whilst the remaining 15 trials used no intervention in the control group (Table 1) (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Vosoghinia 2016; Jha 2017; Sakpal 2017; Behera 2018; Hosseini 2018; Taghvaei 2018; Jeong 2019).

Co-interventions

Seven trials used pegylated-interferon and ribavirin combined with vitamin D_3 in the intervention groups versus pegylated-interferon and ribavirin in the control group (Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Esmat 2015; Vosoghinia 2016; Behera 2018; Jeong 2019). One trial used pegylated-interferon, ribavirin, and simeprevir (direct-acting antiviral agent) combined with vitamin D_3 in the intervention group versus pegylated-interferon, ribavirin, and simeprevir in the control group (Atsukawa 2016). One trial supplemented all participants with vitamin E 400 IU (Hosseini 2018). One trial in people with non-alcoholic fatty liver disease used lifestyle modification (Taghvaei 2018).

Follow-up

The mean follow-up period in all 27 trials was 7 months (range 1 to 18 months).

Excluded studies

For details of the excluded studies, see Characteristics of excluded studies.

Risk of bias in included studies

We assessed all trials at high risk of bias (had unclear or high risk of bias in one or more domains assessed) (Figure 2; Figure 3; Table 1). We did not use the test for funnel plot asymmetry because only four trials were included in the meta-analysis. The adjusted-rank correlation test (P = 0.34) and a regression asymmetry test (P = 0.48) found no significant evidence of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

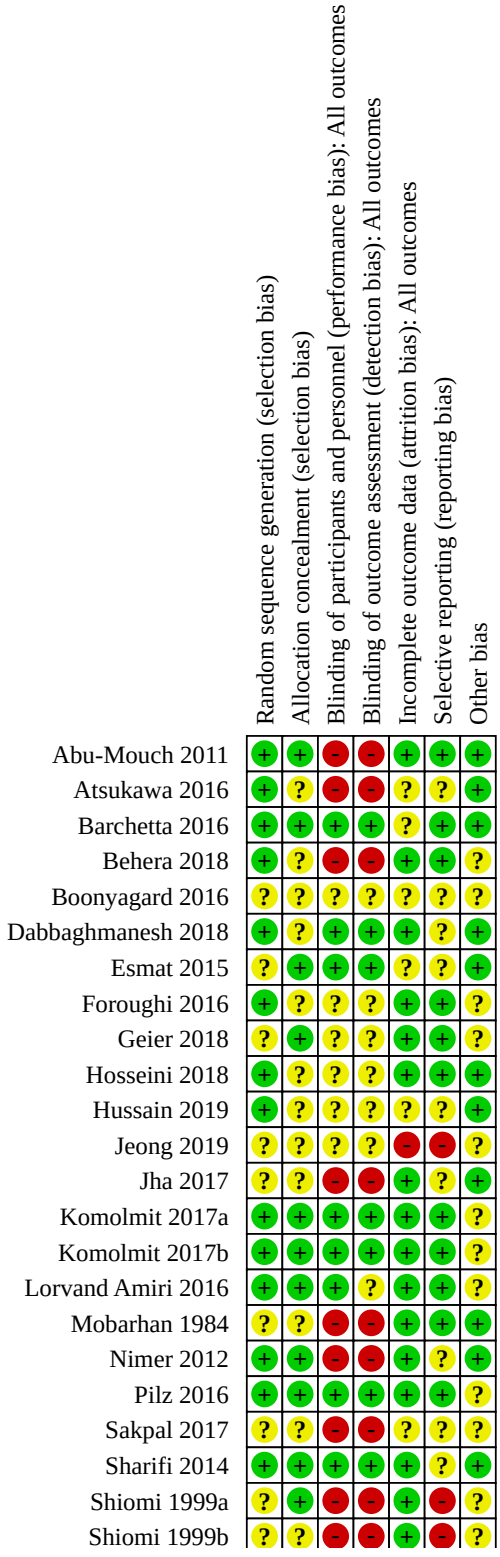


Figure 2. (Continued)

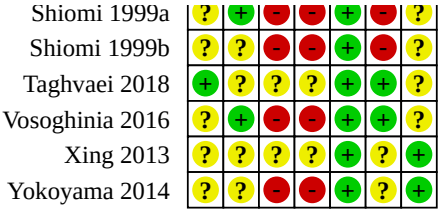
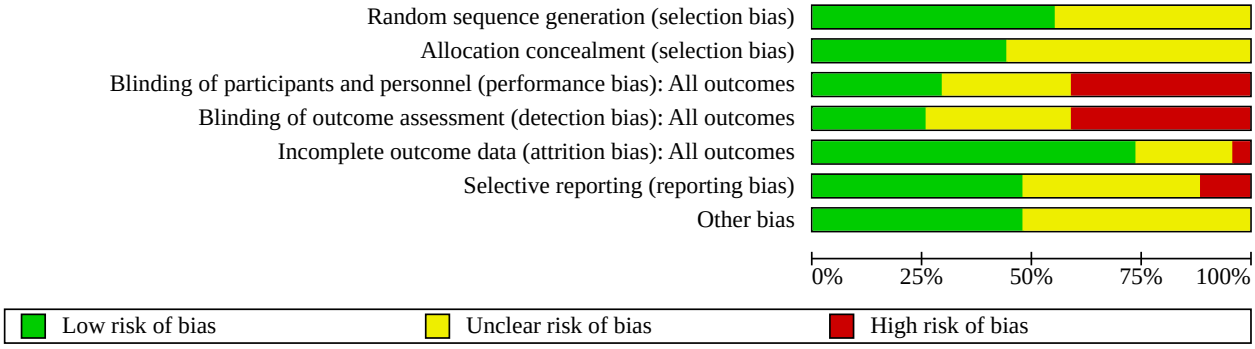


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Fifteen trials described the generation of allocation sequence adequately (Abu-Mouch 2011; Nimer 2012; Sharifi 2014; Atsukawa 2016; Barchetta 2016; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Komolmit 2017a; Komolmit 2017b; Behera 2018; Dabbaghmanesh 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019). The remaining 12 trials were described as being randomised, but the method used for sequence generation was not described or was described insufficiently.

Twelve trials described the method used to conceal allocation adequately (Shiomi 1999a; Abu-Mouch 2011; Nimer 2012; Sharifi 2014; Esmat 2015; Barchetta 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Komolmit 2017a; Komolmit 2017b; Geier 2018). The remaining 15 trials were described as being randomised, but the method used for allocation concealment was not described or was described insufficiently.

Blinding

Eight trials performed and adequately described blinding of participants and personnel (Sharifi 2014; Esmat 2015; Barchetta 2016; Lorvand Amiri 2016; Pilz 2016; Dabbaghmanesh 2018; Komolmit 2017a; Komolmit 2017b). Eleven trials did not blind participants and personnel (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Atsukawa 2016; Vosoghinia 2016; Jha 2017; Sakpal 2017; Behera 2018), whilst in eight trials the method used for blinding of participants and personnel was not described or was described insufficiently (Xing 2013; Boonyagard 2016; Foroughi 2016; Geier 2018; Hosseini 2018; Taghvaei 2018; Hussain 2019; Jeong 2019).

Seven trials performed and adequately described blinding of outcome assessors (Sharifi 2014; Esmat 2015; Barchetta 2016; Pilz 2016; Komolmit 2017a; Komolmit 2017b; Dabbaghmanesh 2018). In the remaining 19 trials the method for blinding of outcome assessors was not described or was described insufficiently.

Incomplete outcome data

Twenty trials adequately addressed incomplete outcome data (Mobarhan 1984; Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Xing 2013; Yokoyama 2014; Sharifi 2014; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Jha 2017; Komolmit 2017a; Komolmit 2017b; Behera 2018; Dabbaghmanesh 2018; Geier 2018; Hosseini 2018; Taghvaei 2018). In seven trials information was insufficient to permit an assessment of whether missing data in combination with the method used to handle missing data was likely to induce bias on the effect estimate (Esmat 2015; Atsukawa 2016; Barchetta 2016; Boonyagard 2016; Sakpal 2017; Hussain 2019; Jeong 2019).

Selective reporting

Thirteen trials reported the outcomes stated in their respective protocols (Mobarhan 1984; Abu-Mouch 2011; Barchetta 2016; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Komolmit 2017a; Komolmit 2017b; Behera 2018; Geier 2018; Hosseini 2018; Taghvaei 2018). In 11 trials it was unclear whether all predefined and clinically relevant and reasonably expected outcomes had been reported (Nimer 2012; Xing 2013; Yokoyama 2014; Sharifi 2014; Esmat 2015; Atsukawa 2016; Boonyagard 2016; Jha 2017; Sakpal 2017; Dabbaghmanesh 2018; Hussain 2019). The authors of three trials did not fully report all predefined outcomes (Shiomi 1999a; Shiomi 1999b; Jeong 2019).

Other potential sources of bias

We did not identify any clear signs of academic bias, small-trial bias, or other potential sources of bias in 13 trials (Mobarhan 1984; Abu-Mouch 2011; Nimer 2012; Xing 2013; Sharifi 2014; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Barchetta 2016; Dabbaghmanesh 2018; Hosseini 2018; Jha 2017; Hussain 2019). The remaining 14 trials may or may not have been free of other issues that could put them at risk of bias (Shiomi 1999a; Shiomi 1999b; Boonyagard 2016; Foroughi 2016; Lorvand Amiri 2016; Pilz 2016; Vosoghinia 2016; Komolmit 2017a; Komolmit 2017b; Sakpal 2017; Behera 2018; Geier 2018; Taghvaei 2018; Jeong 2019).

Effects of interventions

See: **Summary of findings 1** Vitamin D compared with placebo or no intervention for chronic liver diseases in adults

Primary outcomes

All-cause mortality

We are very uncertain about the effect of vitamin D versus placebo or no intervention on all-cause mortality (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.51 to 1.45; I^2 = 0%; 27 trials; 1979 participants; Analysis 1.1; very low-certainty evidence). We are very uncertain about the effect of vitamin D versus placebo or no intervention on all-cause mortality in people with non-alcoholic fatty liver disease (no data reported; 11 trials; 803 participants); chronic hepatitis C (RR 0.33, 95% CI 0.04 to 3.13; I^2 = 0%; 10 trials; 836 participants); liver cirrhosis (RR 0.91, 95% CI 0.53 to 1.55; I^2 = 0%; 5 trials; 265 participants); or liver transplant recipients (no data reported; 1 trial; 75 participants) (Analysis 1.1; Summary of findings 1). The certainty of evidence is very low. The mean follow-up was 7 months (range 1 to 18 months).

Subgroup analysis for overall risk of bias

All trials were at high risk of bias, therefore we did not conduct subgroup analysis.

Subgroup analysis for vested interest

Thirteen trials appeared to be free of vested interest. Twelve trials did not provide any information on clinical trial support or sponsorship. Two trials were funded by industry. The test for subgroup differences showed no significant differences in the effect of vitamin D on all-cause mortality in trials funded by industry (RR 2.69, 95% CI 0.15 to 48.64; 38 participants; 2 trials) and in trials without vested interest (RR 0.83, 95% CI 0.48 to 1.41; I^2 = 0%; 1941 participants; 25 trials) (Analysis 1.2).

Subgroup analysis according to vitamin D status at entry

The test for subgroup differences showed insignificant differences in the effect of vitamin D versus placebo or no intervention on all-cause mortality in participants with normal vitamin D status (RR 0.33, 95% CI 0.04 to 3.13; I^2 = 0%; 8 trials; 549 participants; Analysis 1.3) and with low vitamin D status (RR 0.91, 95% CI 0.53 to 1.55; I^2 = 0%; 19 trials; 1430 participants; Analysis 1.3).

Subgroup analysis according to form of vitamin D

The test for subgroup differences showed insignificant differences in the effect of different forms of vitamin D versus placebo or no intervention on all-cause mortality: vitamin D_3 (RR 0.83, 95% CI 0.48 to 1.41; I^2 = 0%; 20 trials; 1578 participants); vitamin D_2 (RR 3.00, 95% CI 0.15 to 61.74; 1 trial; 150 participants); 25-hydroxyvitamin D (RR 3.00, 95% CI 0.15 to 61.74; 1 trial; 150 participants); and 1,25 dihydroxyvitamin D (4 zero-event trials; 291 participants) (Analysis 1.4).

Sensitivity analysis for attrition bias

The authors of three trials did not report the exact numbers of participants with missing outcomes in the intervention and control groups (Boonyagard 2016; Jha 2017; Sakpal 2017). There were no losses to follow-up in 10 trials (Shiomi 1999a; Shiomi 1999b; Abu-Mouch 2011; Nimer 2012; Xing 2013; Foroughi 2016; Komolmit 2017a; Komolmit 2017b; Behera 2018; Taghvaei 2018). In the remaining 14 included trials, the authors reported the exact numbers of participants with missing outcomes in the intervention and control groups. A total of 65/663 (9.8%) participants had missing outcomes in the vitamin D groups versus 65/572 (11.4%) participants in the control groups.

Best-worst-case scenario sensitivity analysis

When we assumed that all participants lost to follow-up in the experimental intervention group survived, and all those with missing outcomes in the control group died, vitamin D supplementation significantly decreased mortality (RR 0.14, 95% CI 0.06 to 0.30; P < 0.001; I^2 = 0%; 1737 participants; 24 trials; Analysis 1.5).

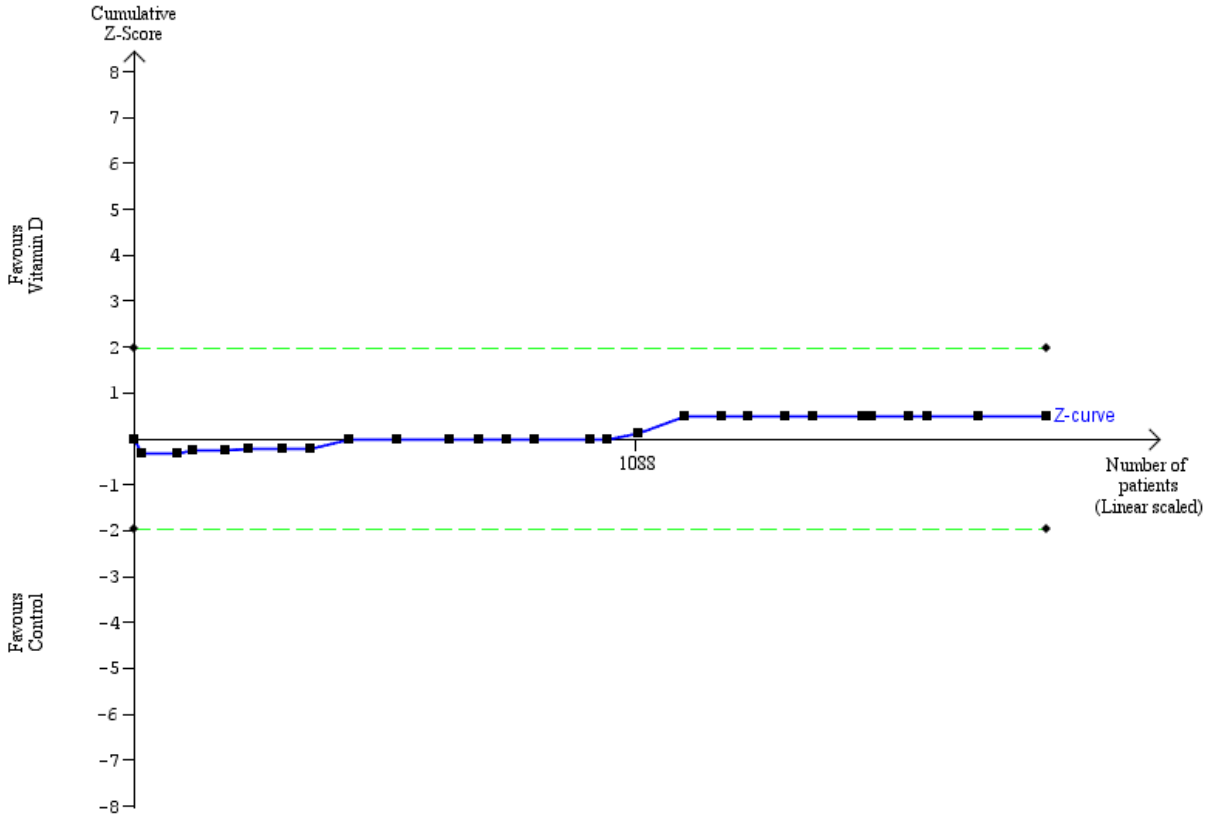
Worst-best-case scenario sensitivity analysis

When we assumed that all participants lost to follow-up in the experimental intervention group died, and all those with missing outcomes in the control group survived, vitamin D supplementation significantly increased mortality (RR 7.95, 95% CI 3.55 to 17.77; P < 0.001; I^2 = 0%; 1737 participants; 24 trials; Analysis 1.5).

Sensitivity analysis for imprecision

Trial Sequential Analysis was performed based on a mortality proportion in the control group of 2%, a relative risk reduction of 20% in the experimental intervention group, a type I error of 1.25%, and type II error of 10% (90% power). There was no diversity. The required information size was 63,116 participants. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit or harm after the 27th trial. The trial sequential monitoring boundary was ignored due to little information use (3.14%) (Figure 4). We downgraded imprecision two levels with Trial Sequential Analysis for this outcome, which was in agreement with our GRADE assessment.

Figure 4. All-cause mortality. Trial Sequential Analysis was performed based on a mortality in the control group of 2%, a relative risk reduction of 20% in the experimental intervention group, a type I error of 1.25%, and a type II error of 10% (90% power). There was no diversity. The required information size was 63,116 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundary for benefit or harm after the 27th trial. The trial sequential monitoring boundaries were ignored due to little information (3.14%). The blue line represents the cumulative Z-score of the meta-analysis. The green dotted lines represent the conventional statistical boundaries.



Liver-related mortality

The evidence of vitamin D versus placebo or no intervention on the effect of vitamin D on liver-related mortality is very uncertain (RR 1.62, 95% CI 0.08 to 34.66; 1 trial; 18 participants; very low-certainty evidence; Analysis 1.6; Summary of findings 1). The follow-up was 12 months.

Subgroup analysis according to vitamin D status at entry

Only one trial including participants with low vitamin D status reported liver-related mortality, making subgroup analysis impossible.

Sensitivity analysis for imprecision

Because of few data, we could not conduct Trial Sequential Analysis, which would only have revealed a similar need to downgrade for imprecision. We downgraded our GRADE assessment two levels for imprecision.

Serious adverse events

The evidence of vitamin D (calcitriol) versus placebo or no intervention is very uncertain on the effect of vitamin D on the risk of hypercalcaemia (RR 5.00, 95% CI 0.25 to 100.8; 1 trial; 76 participants; very low-certainty evidence; Analysis 1.7); myocardial infarction (RR 0.75, 95% CI 0.08 to 6.81; 2 trials; 86 participants; very low-certainty evidence; Analysis 1.7); thyroiditis (RR 0.33, 95% CI 0.01 to 7.91; 1 trial; 68 participants; very low-certainty evidence; Analysis 1.7); circular haemorrhoidal prolapse (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; very low-certainty evidence; Analysis 1.7); and bronchopneumonia (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; very low-certainty evidence; Analysis 1.7; Summary of findings 1). The mean follow-up was 10.5 months.

Sensitivity analysis for imprecision

Because of few data, we could not conduct Trial Sequential Analysis, which would only have revealed a similar need to downgrade imprecision. We downgraded our GRADE assessment two levels for imprecision.

Secondary outcomes

Liver-related morbidity

We found no data on liver-related morbidity.

Health-related quality of life

We found no data on health-related quality of life.

Non-serious adverse events

The evidence is very uncertain as to whether vitamin D_3 increases or decreases the risks of glossitis (RR 3.70, 95% CI 0.16 to 87.58; 1 trial; 65 participants; Analysis 1.10); depression (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); lower back pain (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); abdominal bloating (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); cold (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); constipation (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); sore throat (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); sour taste in mouth (RR 0.33, 95% CI 0.02 to 7.32; one trial; 20 participants; Analysis 1.10); contused lacerated wound (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); multiple white matter lesions (RR 0.33, 95% CI 0.02 to 7.32; 1 trial; 20 participants; Analysis 1.10); gastro-oesophageal reflux (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); abdominal menstrual cramps (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); tubular colon adenoma (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); gastric motility disturbance (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); irritable bowel syndrome (RR 5.00, 95% CI 0.27 to 92.62; 1 trial; 20 participants; Analysis 1.10); knee pain (RR 3.00, 95% CI 0.14 to 65.90; 1 trial; 20 participants; Analysis 1.10); and severe allergy (RR 5.09, 95% CI 0.25 to 103.64; 1 trial; 109 participants; Analysis 1.10) due to the overall rating of very low certainty of evidence (Summary of findings 1). The mean follow-up was seven months.

Several non-serious adverse events were reported in people with chronic hepatitis C treated with a combination of vitamin D and pegylated-interferon and ribavirin. These were similar in both vitamin D and control groups and consistent with typical interferon-ribavirin-induced systemic symptoms such as nausea, headache, insomnia, chills, myalgia, pyrexia, pruritus, mild neutropenia, mild thrombocytopenia, mild neutropenia, and mild anaemia (Abu-Mouch 2011; Nimer 2012; Yokoyama 2014; Esmat 2015; Atsukawa 2016; Behera 2018; Jeong 2019).

Failure of virological response

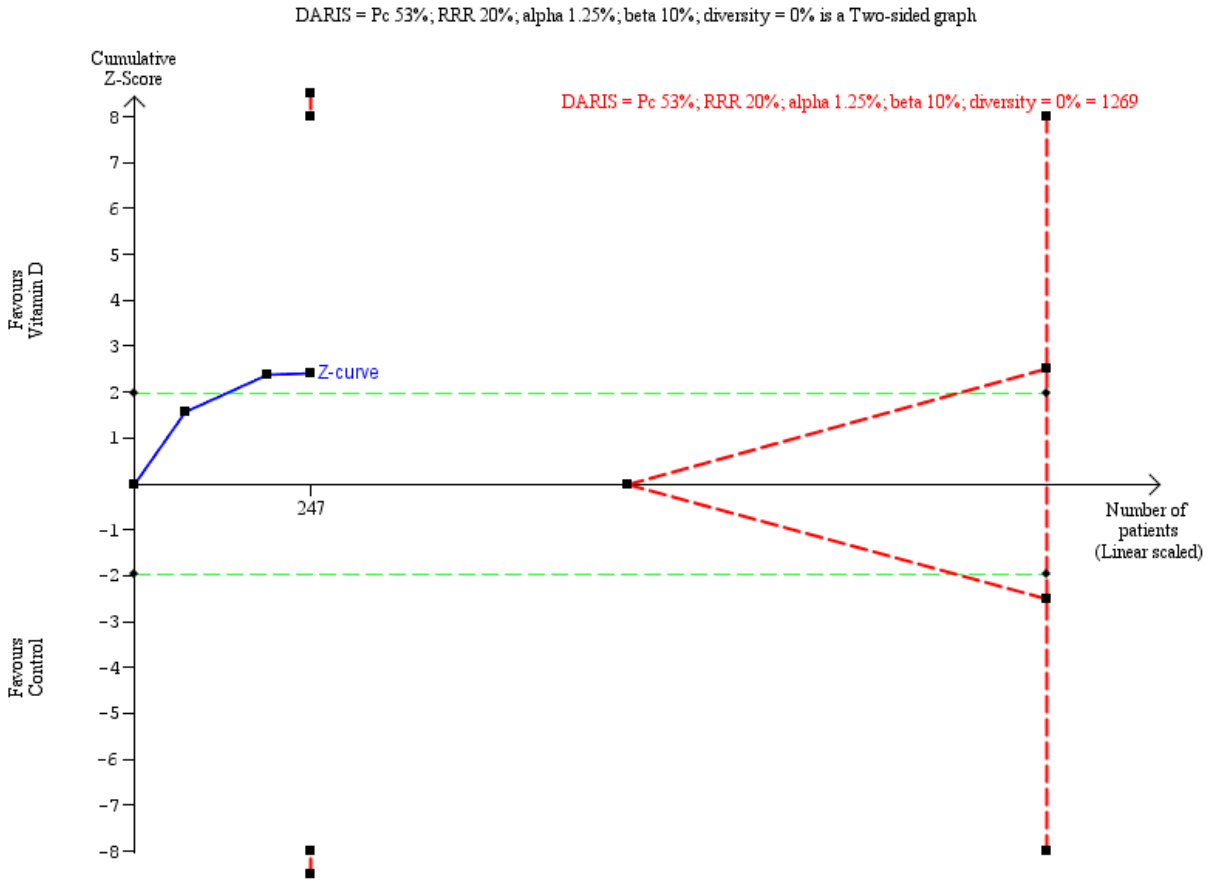
Failure of rapid virological response (at week four) in people with chronic viral hepatitis C

Vitamin D_3 versus placebo may increase or have no effect on rapid virological response in people with chronic hepatitis C, but the evidence is very uncertain (RR 0.75, 95% CI 0.60 to 0.95; P = 0.02; I^2 = 0%; 3 trials; 247 participants; very low-certainty evidence; Analysis 1.11). The mean follow-up was 16 months.

Sensitivity analysis for imprecision

Trial Sequential Analysis was conducted based on a failure of rapid virological response in the control group of 53%, a relative risk reduction (RRR) of 20% in the intervention group, a type I error of 1.25%, and type II error of 10% (90% power). There was no diversity. The required information size was 1269 participants. The cumulative Z-curve crossed the conventional monitoring boundary for benefit, but did not cross the trial sequential monitoring boundaries for benefit, futility or harm (Figure 5). We downgraded imprecision two levels with Trial Sequential Analysis, for this outcome, which was in agreement with our GRADE assessment.

Figure 5. Rapid virological response. Trial Sequential Analysis was performed based on a failure of rapid virological response in the control group of 53%, a relative risk reduction (RRR) of 20% in the intervention group, a type I error of 1.25%, and a type II error of 10% (90% power). There was no diversity. The required information size was 1269 participants. The cumulative Z-curve (blue line) crossed the conventional monitoring boundary for benefit but did not cross the trial sequential monitoring boundary for benefit (red down-sloping line). The blue line represents the cumulative Z-score of the meta-analysis. The green dotted lines represent the conventional statistical boundaries. The red inward-sloping lines represent the trial sequential monitoring boundaries.



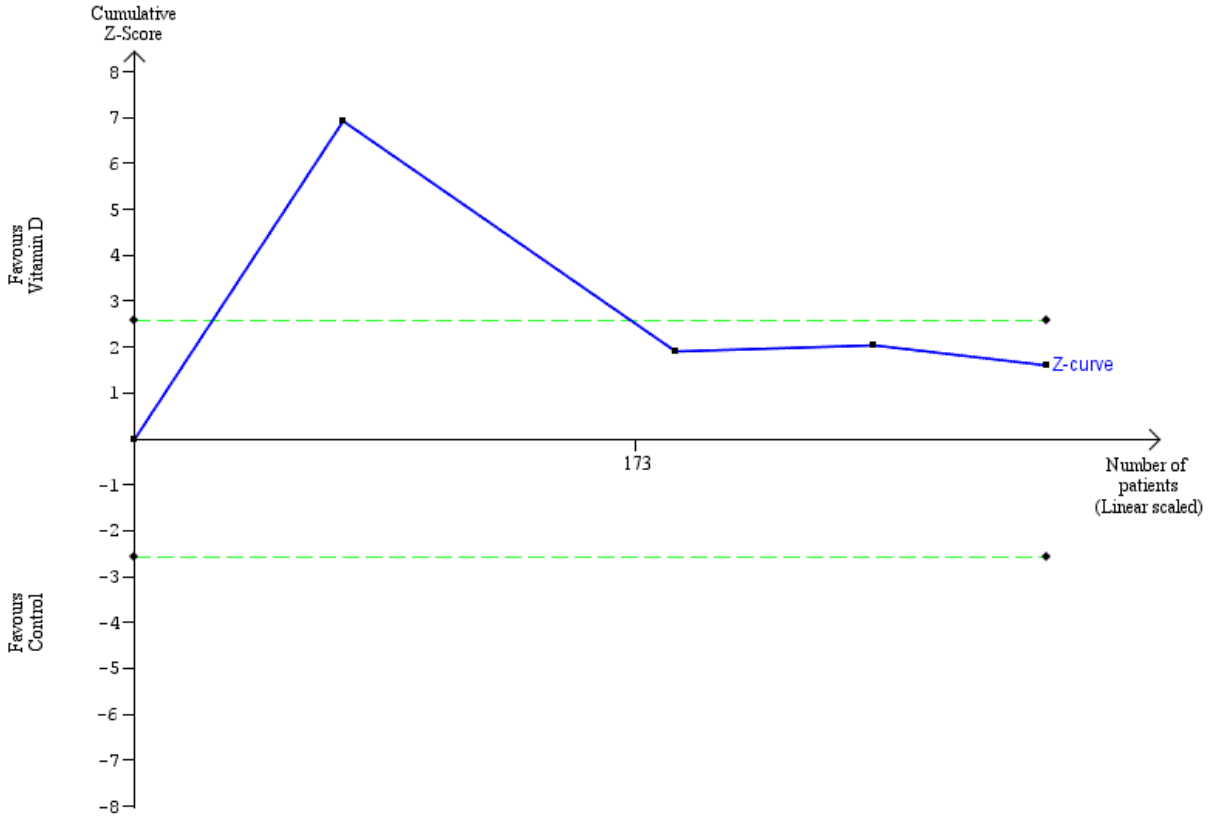
Failure of early virological response (at week 12) in people with chronic viral hepatitis C

Vitamin D_3 versus placebo may increase or have no effect on early virological response in people with chronic hepatitis C, but the evidence is very uncertain (RR 0.33, 95% CI 0.11 to 1.00; P = 0.05; I^2= 75%; 4 trials; 315 participants; very low-certainty evidence; Analysis 1.12). The mean follow-up was 13 months.

Sensitivity analysis for imprecision

Trial Sequential Analysis was performed based on a failure of early virological response in the control group of 34%, a relative risk reduction of 20% in the intervention group, a type I error of 1.25%, and type II error of 10% (90% power). The diversity was 88%. The required information size was 21,306 participants. The cumulative Z-curve (blue line) crossed the conventional monitoring boundary for benefit. The trial sequential monitoring boundary was ignored because of little information use (1.48%) (Figure 6). We downgraded two levels for imprecision with Trial Sequential Analysis for this outcome, which was in agreement with our GRADE assessment.

Figure 6. Early virological response. Trial Sequential Analysis was performed based on failure of early virological response in the control group of 34%, a relative risk reduction of 20% in the intervention group, a type I error of 1.25%, and a type II error of 10% (90% power). The diversity was 88%. The required information size was 21,306 participants. The cumulative Z-curve (blue line) crossed the conventional monitoring boundary for benefit. The trial sequential monitoring boundary was ignored due to little information (1.48%). The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries.



Failure of sustained virological response (at six months after treatment) in people with chronic viral hepatitis C

Vitamin D_3 may increase or have no effect on sustained virological response in people with chronic hepatitis C, but the evidence is very uncertain (RR 0.65, 95% CI 0.42 to 1.01; I^2 = 76%; 7 trials; 630 participants; very low-certainty evidence; Analysis 1.13; Summary of findings 1). The mean follow-up was 16 months.

Sensitivity analysis for imprecision

Trial Sequential Analysis was performed based on a failure of sustained virological response in the control group of 48%, a relative risk reduction of 20% in the intervention group, a type I error of 1.25%, and type II error of 10% (90% power). The diversity was 80%. The required information size was 7570 participants (Figure 7). We downgraded two levels for imprecision with Trial Sequential Analysis for this outcome, which was in agreement with our GRADE assessment.

Figure 7. Sustained virological response. Trial Sequential Analysis was performed based on failure of sustained virological response in the control group of 48%, a relative risk reduction (RRR) of 20% in the intervention group, a type I error of 1.25%, and a type II error of 10% (90% power). Diversity was 80%. The required information size was 7570 participants. The cumulative Z-curve (blue line) crossed the conventional monitoring boundary for benefit. However, it did not cross any of the monitoring boundaries for benefit, harm, or futility. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries. The red inward-sloping lines represent the trial sequential monitoring boundaries for benefit and harm.

Acute cellular rejection in liver transplant recipients

The evidence is very uncertain on the effect of 1,25-dihydroxyvitamin D on acute cellular rejection in liver transplant recipients, which may decrease or increase (RR 0.33, 95% CI 0.04 to 2.62; 1 trial; 75 participants; very low-certainty evidence; Analysis 1.14). The follow-up was one week.

Vitamin D status

Vitamin D supplementation versus placebo seems to increase vitamin D status of participants, but the evidence is very uncertain (MD 18.49 ng/mL, 95% CI 14.52 to 22.47; I^2 = 93%; 15 trials; 1078 participants; very low-certainty evidence; Analysis 1.15). The mean follow-up was six months.

Bone mineral density

Vitamin D seems to show an effect on bone mineral density in people with alcoholic liver cirrhosis, but the evidence is very uncertain (MD 0.15 ng/mL, 95% CI 0.04 to 0.26; 1 trial; 18 participants; very low-certainty evidence; Analysis 1.16). Follow-up was 12 months (Mobarhan 1984). Two other trials reported bone mineral density, but we could not use the data in analysis (Shiomi 1999a; Shiomi 1999b).

Biochemical indices

Worse prognosis if value result is higher than the normal range

The evidence is very uncertain on the effect of vitamin D on serum activity of aspartate aminotransferase (MD -1.75 IU/L, 95% CI -5.41 to 1.91; I^2 = 82%; 12 trials; 774 participants; Analysis 1.17); serum activity of alanine aminotransferase (MD -2.30 IU/L, 95% CI -7.60 to 3.00; I^2 = 86%; 13 trials; 855 participants; Analysis 1.18); serum activity of alkaline phosphatases (MD -0.95 IU/L, 95% CI -15.10 to 13.20; I^2 = 52%; 6 trials; 344 participants; Analysis 1.19); serum activity of gamma-glutamyl transpeptidase (MD -2.69 IU/L, 95% CI -5.26 to -0.11; I^2 = 0%; 4 trials; 227 participants; Analysis 1.20); serum concentration of bilirubin (MD 0.32 mg/dL, 95% CI 0.00 to 0.63; I^2 = 29%; 3 trials; 74 participants; Analysis 1.21); serum concentration of triglyceride (MD 11.27 mg/dL, 95% CI -10.99 to 33.53; I^2 = 87%; 5 trials; 460 participants; Analysis 1.22); serum concentration of

cholesterol (MD 3.51 mg/dL, 95% CI -2.83 to 9.85; I^2 = 0%; 4 trials; 400 participants; Analysis 1.23); and serum concentration of low-density lipoprotein (LDL) cholesterol (MD -0.97 mg/dL, 95% CI -8.70 to 6.76; I^2 = 60%; 4 trials; 400 participants; Analysis 1.24).

Worse prognosis if value result is lower than the normal range

The evidence is very uncertain on the effect of vitamin D on serum concentration of albumin (MD -1.18 g/L, 95% CI -2.96 to 0.59; I^2 = 0%; 3 trials; 74 participants; Analysis 1.25) and serum concentration of high-density lipoprotein (HDL) cholesterol (MD 1.14 mg/dL, 95% CI -0.64 to 2.92; I^2 = 0%; 4 trials; 400 participants; Analysis 1.26).

Worse prognosis if value result is lower or higher than the normal range

The evidence is very uncertain on the effect of vitamin D on serum concentration of calcium (MD 0.04 mg/dL, 95% CI -0.12 to 0.19; I^2 = 46%; 7 trials; 423 participants; Analysis 1.27); serum concentration of glucose (MD 1.44 mg/dL, 95% CI -5.05 to 7.94; I^2 = 85%; 6 trials; 469 participants; Analysis 1.28); serum concentration of phosphorus (MD 0.17 mg/dL, 95% CI -0.16 to 0.50; I^2 = 53%; 4 trials; 307 participants; Analysis 1.29); serum concentration of adiponectin (MD 1.02 µg/mL, 95% CI -0.27 to 2.30; I^2 = 62%; 4 trials; 276 participants; Analysis 1.30); serum concentration of insulin (MD 0.03 mIU/mL, 95% CI -1.15 to 1.21; I^2 = 0%; 6 trials; 428 participants; Analysis 1.31); serum concentration of parathyroid hormone (MD -15.18 pg/mL, 95% CI -38.54 to 8.18, 2 trials; 118 participants; Analysis 1.32); and serum concentration of C-reactive protein (MD -0.50 mg/L, 95% CI -0.93 to -0.07; I^2 = 86%; 4 trials; 254 participants; Analysis 1.33).

Summary of findings

We have presented our findings for the following outcomes in Summary of findings 1: all-cause mortality (mean follow-up of nine months); liver-related mortality (mean follow-up of 12 months); serious adverse events (mean follow-up of 10.5 months); liver-related morbidity (no trials); health-related quality of life (no trials); non-serious adverse events (mean follow-up of seven months); failure of sustained virological response (mean follow-up of 16 months). We downgraded the certainty of the evidence for the outcomes for which data were available to very low. For the outcomes all-cause mortality, liver-related mortality, serious adverse events, and non-serious adverse events, we downgraded the evidence because of risk of bias and imprecision; and for sustained virological response, we downgraded the evidence because of risk of bias, imprecision, inconsistency, and indirectness.

DISCUSSION

Summary of main results

Compared to the previous version of this review (Bjelakovic 2017), the number of trials included in the current review has expanded with the addition of 12 new trials (44%), adding another 945 participants (48%). The current review thus includes 27 randomised clinical trials with 1979 participants. However, our results remain largely the same. The evidence is very uncertain regarding the effect of vitamin D supplements in the form of vitamin D_3, vitamin D_2, 1,25-dihydroxyvitamin D, or 25-dihydroxyvitamin D on all-cause mortality, liver-related mortality, and serious and non-serious adverse events in people with chronic liver diseases. The trials did not present data on liver-related morbidity such as gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, ascites, or liver cancer. There were no data on health-related quality of life. It is very uncertain if vitamin D increases the number of people with sustained virological response or decreases the number of people with acute cellular rejection in liver transplant recipients. Analyses of three trials in people with chronic hepatitis C suggested that vitamin D_3 might be beneficial in increasing the number of people with rapid virological response, but the evidence is very uncertain. Vitamin D status of participants with chronic liver diseases seems to increase after supplementation with vitamin D. Vitamin D may or may not have an effect on biochemical indices, but the evidence for all biochemical indices is very uncertain.

The results of our systematic review should be interpreted with great caution because all the included trials were assessed at high risk of bias. The number of people and the trials that provided outcome data were insufficient, which adds to the risk of both type I and type II errors (Keus 2010; Wetterslev 2017). Our sensitivity analysis with Trial Sequential Analysis revealed that there was insufficient information to reach robust conclusions. In this second edition of our review, we defined what the minimal relevant difference for our continuous outcome would be if data are published. Moreover, type 1 and 2 values, diversity, control group proportions, and plausible relative risk reduction will all affect the DARIS calculated, especially as these have changed since the previous version of the review. This is in order to control risks of type 1 and type 2 errors, but will increase the requirement for trial participants. The latter may be seen as an obstacle by many.

Although vitamin D deficiency is considered to be common in people with chronic liver diseases (Chen 2014; Iruzubieta 2014; Elangovan 2017), we found no convincing evidence that vitamin D supplementation might have therapeutic impact in these individuals; however, as highlighted, the evidence is very uncertain.

Overall completeness and applicability of evidence

We included all eligible randomised clinical trials up to November 2020. We found a large number of randomised trials with a small number of participants. We found significant statistical heterogeneity in some of our analyses, such as biochemical indices. This decreases the precision and power of our analyses (Turner 2013; Higgins 2021). Our analyses revealed that outcome reporting was missing in approximately 10% of trial participants. Accordingly, our 'best-worst-case' and 'worst-best-case' analyses on all-cause mortality revealed that our results were compatible with both a large beneficial effect and a large detrimental effect of vitamin D. Although these extreme sensitivity analyses are unlikely scenarios, they reveal how missing numbers of participants can substantially change findings from showing great benefit into showing a null effect, or possibly even a harmful effect. We therefore advise critical evaluation of the evidence.

Quality of the evidence

This review followed the overall plan of our published, peer-reviewed Cochrane protocol (Bjelakovic 2015), some parts of which we revised to enhance clarity for the reader (See Differences between protocol and review). We conducted a thorough review in accordance with Cochrane methodology (Higgins 2011; Higgins 2021), and implemented findings of methodological studies (Schulz

1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018a).

We repeatedly searched several databases and contacted authors of trials and industry producing vitamin D supplements, therefore we believe it is unlikely that we have overlooked important randomised clinical trials. As stated below, we may have missed trials only reported to regulatory authorities. However, such trials are often neutral or negative (Schroll 2013). We found no evidence of publication bias (Johnson 2007). However, only about every second trial is reported (Gluud 2008), so we cannot exclude reporting biases.

We used GRADEpro GDT to construct a summary of findings table (Summary of findings 1) (GRADEpro GDT). We calculated the optimal information size when rating imprecision with Trial Sequential Analysis. The GRADE assessments showed that the certainty of evidence was very low for all-cause mortality, liver-related mortality, serious adverse events (hypercalcaemia, myocardial infarction, thyroiditis, circular haemorrhoidal prolapse, and bronchopneumonia), liver-related morbidity, health-related quality of life, non-serious adverse events, and failure of sustained virological response. All included trials were at high risk of bias.

In some of our analyses (i.e. biochemical indices) heterogeneity was substantial. This was due to the fact that biochemical indices were measured in people with different aetiology of chronic liver diseases. We also assessed the certainty of the evidence using the GRADE approach based on risk of attrition bias for imprecision, significant between-trial heterogeneity for inconsistency, and design errors for indirectness. We also conducted Trial Sequential Analysis based on the estimation of the DARIS to avoid an undue risk of random errors in a cumulative meta-analysis and to prevent premature statements of superiority of vitamin D or of lack of effect (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2011; Thorlund 2017; TSA 2017; Wetterslev 2017). We compared the results of imprecision with GRADE and with Trial Sequential Analysis. The results did not differ, which supports previous studies (Castellini 2018; Gartlehner 2019).

Potential biases in the review process

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 D on chronic liver diseases. Despite extensive speculations in the literature and a number of epidemiological studies that claimed possible beneficial effects of vitamin D in people with chronic liver diseases, only a few randomised clinical trials assessed such effects. The duration of supplementation and duration of follow-up were short in some included trials, which may make it difficult to detect any effects, beneficial or harmful. We assessed all 27 included trials at high risk of bias. Instead of reporting clinical outcomes, most of the trials based their analyses on surrogate outcomes. Such outcomes may be clinically meaningless if they have not been properly validated against clinical outcomes (Gluud 2007; Jakobsen 2017). Many of the included trials were not adequately powered. These factors corrupt the validity of our results (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b). Adverse events were insufficiently reported. It has been noted that adverse events are very often neglected in randomised trials (Ioannidis 2009). In a number of trials in people with chronic hepatitis C, vitamin D was administered in combination with pegylated-interferon and ribavirin, which made it difficult to judge the beneficial or harmful effects of vitamin D, or to judge which intervention one should assign any of the observed adverse events. Significant between-trial heterogeneity was present in some of our meta-analyses. This may emphasise the inconsistency of our findings and may additionally question some of these findings.

Most of the included trials used vitamin D_3; three trials tested vitamin D_2; four trials tested 1,25-dihydroxyvitamin D; and one trial tested 25-dihydroxyvitamin D.

We did not search the files of regulatory agencies such as the US Food and Drug Administration and European Medicines Agency, which may have biased our selection of trials (Schroll 2013; Boesen 2021). We did not conduct searches for observational studies on harms, which may have biased our findings towards benefits of the interventions with our less focus on harms (Storebø 2015; Storebø 2018).

Different types of bias could have influenced the results of our meta-analyses including selective reporting of some results in trial publications (Chan 2004; Williamson 2005; Furukawa 2007). Outcome reporting in the included trials was insufficient and inconsistent. There are several possible explanations for selective reporting of outcomes in randomised clinical trials. Trials in which the outcome was not reported may not have measured our outcomes of interest. Researchers may not have reported unexpected results or results may have not satisfied sponsors (Lesser 2007). Pharmaceutical companies provided vitamin D in two of the 27 included trials. This number may in actuality be higher because this information was not available in 11 trials. It could be that researchers have selectively reported outcomes, which may also allude to a publication bias. We are well aware of the difficulties in collecting data on outcomes in clinical trials that focus on safety and efficacy evaluations. The worst result of outcome reporting bias and suppression of some significant or non-significant findings could be the use of harmful interventions. The results of meta-analyses may underestimate the true effects of interventions when there is exaggerated outcome reporting bias. One would wish that the results of randomised clinical trials were reported in greater detail (Nordic Trial Alliance 2015). In some of the trials, instead of full reporting, we found partial or qualitative reporting. The huge human efforts of investigators and the high cost of randomised clinical trials should be justified with more rigour in their reporting. In spite of the large investment in the reviewed trials, a number of questions remain unanswered.

Other types of bias, such as academic bias, bias from trials with deficiencies in the trial design (Schulz 1995; Moher 1998; Kjaergard 2001), and small-trial bias, Siersma 2007, could possibly have influenced our results. Meta-analysis of randomised trials increases the power and precision of the estimated intervention effect, but this effect may be influenced by systematic errors or random errors and can lead to a report of false significant results (Gluud 2006; Wetterslev 2008). It is probable that the results of our meta-analysis were influenced by random errors and systematic errors.

A number of design errors may have influenced our results, the first of which is abuse of surrogate outcomes. In most of the included trials, study authors used non-validated surrogate outcomes such as biochemical indices and liver steatosis, assuming that normal

levels are beneficial. The ideal primary outcome in a randomised clinical trial is the outcome relevant to the person's quality of life or course of disease. Relying on non-validated potential surrogate outcomes is potentially dangerous when assessing new therapies (Gluud 2007; Garattini 2016). We lack validated surrogate outcome measures in hepatology. Some trials included in this review examined early, rapid, or sustained virological response as a surrogate outcome for successful treatment. However, improved early, rapid, or sustained virological response does not definitively mean significant improvement in clinical outcomes (Gluud 2007; Jakobsen 2017). The use of new interventions in hepatology should not be justified unless these have been confirmed beneficial on clinical outcomes (Gluud 2006; Jakobsen 2017). These issues could be resolved with the development and application of agreed-upon sets of outcomes, known as core outcome sets (www.comet-initiative.org). The increase in the number of hepato-biliary randomised trials will never be considered a sufficient valuable source for data if aspects of trial design, such as sample size, completeness of data reporting, duration of follow-up, and bias risk, are not improved.

Agreements and disagreements with other studies or reviews

Efforts in evaluating the benefits and harms of vitamin D supplementation in people with chronic liver diseases resulted in the absence of evidence or potentially neutral results. It is likely that vitamin D deficiency is not a pathogenetic mechanism contributing to liver damage. There is also the possibility that vitamin D deficiency is the consequence but not the cause of chronic liver diseases. Inflammatory processes involved in the pathogenesis of chronic liver diseases, as well as other chronic diseases, reduce serum vitamin D levels, which can explain their low vitamin D status (Autier 2014). Lifestyle, race, and genetic variations could also be related to vitamin D status (Skaaby 2016). Vitamin D supplementation apparently had no effect on all-cause mortality, but we are unable to exclude meaningful benefits or harms. This result may be due to the fact that the included randomised clinical trials focused on a group of people with well-compensated liver diseases at low risk of mortality.

Five trials in the current review included people with liver cirrhosis. Given the very low certainty of the evidence, we could not determine if vitamin D supplementation may decrease mortality in people with liver cirrhosis. This finding is contrary to earlier claims in the literature that vitamin D deficiency was associated with increased mortality in people with advanced cirrhosis (Putz-Bankuti 2012; Wang 2013; Stokes 2014; Finkelmeier 2015; Paternostro 2017). It seems that vitamin D status in people with liver cirrhosis is not only related to liver dysfunction (Lim 2012). In earlier years, it was thought that people with cholestatic liver disease were more likely to be vitamin D deficient. Today, it is evident that people with liver cirrhosis, non-alcoholic fatty liver disease, and chronic hepatitis C are also at risk for low vitamin D levels. Vitamin D deficiency in the last group of people is likely to be multifactorial in aetiology including decreased intake and absorption, altered activity of hepatic 25-hydroxylase, and insufficient exposure to sunlight (Lim 2012). Trials including people with liver cirrhosis reported data on biochemical indices after vitamin D supplementation. There seemed to be no significant differences between supplemented and control groups in most of the recorded values, but again we cannot be sure.

Our review did not confirm implications that vitamin D supplementation can be beneficial as an adjuvant to other drugs such as interferon or ribavirin (Luong 2012). Meta-analysis of 10 trials that included participants with chronic hepatitis C suggests that vitamin D may benefit rapid, early, and sustained virological response, but our findings are very uncertain. One study suggested noffect of vitamin D supplementation in people with advanced chronic hepatitis C (Corey 2012). Oliveira and colleagues observed no association between vitamin D and the degree of liver fibrosis in people with chronic hepatitis C (Oliveira 2017). Our results are contrary to the result of a meta-analysis that found a positive relationship between high vitamin D status and sustained virological response in people with hepatitis C virus infection (Villar 2013). Another meta-analysis observed that additional use of vitamin D has a positive effect on sustained virological response of people with chronic hepatitis C (Kim 2018). A further meta-analysis, by Kitson and colleagues, found that baseline vitamin D status was not associated with sustained virological response in people with chronic hepatitis C (Kitson 2014). However, because of paucity of data, we warn that our results may be deeply influenced by systematic and random errors. We found no randomised trials that tested vitamin D supplementation in people with chronic hepatitis B. Farnik and colleagues found that low vitamin D levels were associated with increased hepatitis B virus replication in people with chronic hepatitis B (Farnik 2013), whilst Mahamid and colleagues showed a correlation between normal vitamin D levels and spontaneous hepatitis B surface antigen clearance from serum (Mahamid 2013). Hoan and colleagues observed vitamin D deficiency in the majority of hepatitis B-infected people (Hoan 2016). A recently published systematic review and meta-analysis found that vitamin D levels were lower in people with chronic hepatitis B than in healthy controls (Hu 2019). However, whether vitamin D deficiency is the cause or a consequence of chronic hepatitis is still unknown (Bitetto 2011). We cannot judge if or to what extent the results reached in the mentioned publications are reliable or not, as we have not evaluated them methodologically.

Non-alcoholic fatty liver disease has become the most common form of chronic liver disease in high-income countries (Sayiner 2016; Younossi 2016). There is a growing interest in exploring the relationship between vitamin D deficiency and severity of non-alcoholic fatty liver disease. Eleven trials included in our review administered vitamin D to participants with non-alcoholic fatty liver disease. We were unable to extract data on clinically important outcomes from these trials. We found no significant effect of vitamin D on surrogate outcomes such as liver function tests. Our results are in accordance with the results of three recent meta-analyses (Tabrizi 2017; Mansour-Ghanaei 2019; Guo 2020), which also found no significant effect of vitamin D supplementation on biochemical indices in people with non-alcoholic fatty liver disease. Two meta-analyses of case-control and cross-sectional studies found that people with non-alcoholic fatty liver disease were more likely to be vitamin D deficient than people in the control groups, suggesting that vitamin D may play a role in the development of non-alcoholic fatty liver disease (Eliades 2013; Wang 2015). A recent systematic review of six randomised clinical trials observed improved lipid profile and inflammatory mediators after vitamin D supplementation (Hariri 2019). A systematic review and meta-analysis of observational studies showed that vitamin D status may not be associated with non-alcoholic fatty liver disease histologic severity (Jaruvongvanich 2017). We also found that vitamin D supplementation may not be beneficial in this population.

The evidence on the effect of vitamin D supplementation on liver-related morbidity and health-related quality of life is still insufficient.

Although three included randomised trials analysed the influence of vitamin D supplementation on bone mineral density in people with liver cirrhosis, we were able to use the data from only one trial (Mobarhan 1984). One systematic review and meta-analysis concluded that vitamin D supplementation for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seemed to be inappropriate (Reid 2014). Another systematic review and meta-analysis suggested that vitamin D supplementation did not prevent fractures, falls, and increase bone density in adults (Bolland 2018). Similarly, another updated systematic evidence review for the US Preventive Service Task Force found no benefit from vitamin D supplementation for the prevention of cancer and cardiovascular disease (Fortmann 2013). Bolland and colleagues found that vitamin D did not reduce skeletal, vascular, or cancer outcomes (Bolland 2014). Recently completed population-based randomised clinical trials as well as meta-analyses of randomised clinical trials found no effect of vitamin D supplementation on cancer occurrence and cardiovascular diseases (Scragg 2017; Scragg 2018; Barbarawi 2019; Keum 2019; Manson 2019; Bischoff-Ferrari 2020). Interestingly, evidence from a Cochrane Review, Bjelakovic 2014b, a meta-analysis, Keum 2019, and a large randomised clinical trial, Zhang 2019, suggest that vitamin D may reduce cancer mortality in the general population. A recent systematic review and meta-analysis of randomised clinical trials found no association between vitamin D supplementation and mortality in critically ill patients (Peng 2020).

It seems that health claims are again ahead of the evidence. The great enthusiasm for vitamin D as a cure for a myriad of diseases, reinforced by observational studies showing that healthy people have higher vitamin D status, has not been supported by evidence obtained from randomised clinical trials. It is very likely that low vitamin D status is not the cause but rather the consequence of chronic diseases (Grey 2010; Guallar 2010; Harvey 2012; Kupferschmidt 2012; Autier 2014). We now have some evidence that vitamin D status is a biomarker of health status (Skaaby 2016). It is likely that less healthy people are obese, less active, and more sunlight-deprived than healthier people, and therefore have lower vitamin D status (Lucas 2005; Bolland 2006; Grey 2010; Autier 2016; Skaaby 2016). It seems that the cautionary tale of antioxidant supplements is reiterated (Garattini 2016). The current evidence still does not support the use of vitamin D supplementation to prevent or cure chronic liver diseases. Results of ongoing randomised clinical trials may help us further in resolving the vitamin D enigma. The current evidence suggests that it is prudent to get vitamin D from sun exposure and a balanced diet.

AUTHORS' CONCLUSIONS

Implications for practice

Based on trials with very low certainty of evidence, vitamin D supplementation versus placebo or no intervention may increase or reduce all-cause mortality, liver-related mortality, serious adverse events, and non-serious adverse events in adults with chronic liver diseases. Evidence on the effect of vitamin D supplementation on liver-related morbidity such as gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, ascites, or liver cancer, and on health-related quality of life is lacking. Our conclusions are based on trials at high risk of bias, with an insufficient number of participants, and on a lack of trial data on clinically important outcomes. In addition, the analysed trials showed significant intertrial heterogeneity for some outcomes.

Implications for research

More evidence is needed before any final conclusions can be drawn on the effect of vitamin D on chronic liver diseases, especially in people with cholestatic and autoimmune liver diseases. There is also a need for trials evaluating vitamin D supplementation versus placebo or no intervention in people with chronic hepatitis C, chronic hepatitis B, and autoimmune liver diseases. More randomised clinical trials assessing a longer duration of vitamin D intervention and different forms of vitamin D with a greater number of participants, assessing clinical outcomes, seem appropriate. The effect of vitamin D 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.consort-statement.org).

ACKNOWLEDGEMENTS

We thank Marija Bjelakovic and Marko Bjelakovic for their work on the review. They were co-authors of previously published versions of this review (2015, Marija Bjelakovic; 2017, Marko Bjelakovic).

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group 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.

Peer reviewers of the first review version: Sohail Mushtaq, UK; Tony Bruns, Germany
Peer review of this update: Maria G. Grammatikopoulou, Department of Nutritional Sciences & Dietetics, International Hellenic University, Greece (peer review of the update was manged by the Cochrane Central Editorial Service).
Contact Editor: Vanja Giljaca, UK
Cochrane Abdomen and Endocrine Network Associate Editor: Rachel Richardson, UK
Cochrane Abdomen and Endocrine Network and Sign-off Editor: Cindy Farquhar, New Zealand
Copy-editor: Lisa Winer, USA

REFERENCES

References to studies included in this review

Abu-Mouch 2011 *{published data only}*

Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. *World Journal of Gastroenterology* 2011;**17**(47):5184-90.

Atsukawa 2016 *{published data only}*

Atsukawa M, Tsubota A, Shimada N, Yoshizawa K, Abe H, Asano T, et al. Effect of native vitamin D3 supplementation on refractory chronic hepatitis C patients in simeprevir with pegylated interferon/ribavirin. *Hepatology Research* 2016;**46**(5):450-8.

Barchetta 2016 *{published data only}*

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

Behera 2018 *{published data only}*

Behera MK, Shukla SK, Dixit VK, Nath P, Abhilash VB, Asati PK, et al. Effect of vitamin D supplementation on sustained virological response in genotype 1/4 chronic hepatitis C treatment-naïve patients from India. *Indian Journal of Medical Research* 2018;**148**(2):200-6.

Boonyagard 2016 *{published data only}*

Boonyagard S, Techatuvanan K. Impact of vitamin D replacement on liver enzymes in non-alcoholic fatty liver disease patients. *Hepatology (Baltimore, Md.)* 2016;**64**(S1):542.

Dabbaghmanesh 2018 *{published data only}*

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

Esmat 2015 *{published data only}*

Esmat G, El Raziky M, Elsharkawy A, Sabry D, Hassany M, Ahmed A, et al. Impact of vitamin D supplementation on sustained virological response in chronic hepatitis C genotype 4 patients treated by pegylated interferon/ribavirin. *Journal of Interferon & Cytokine Research* 2015;**35**(1):49-54.

Foroughi 2016 *{published data only}*

* Foroughi M, Maghsoudi Z, Askari G. The effect of vitamin D supplementation on blood sugar and different indices of insulin resistance in patients with non-alcoholic fatty liver disease (NAFLD). *Iranian Journal of Nursing and Midwifery Research* 2016;**21**(1):100-4.

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

Geier 2018 *{published data only}*

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

Hosseini 2018 *{published data only}*

Hosseini SM, Aliashrafi S, Ebrahimi-Mameghani M. The effect of a single intramuscular injection of cholecalciferol on the serum levels of vitamin D, adiponectin, insulin resistance, and liver function in women with non-alcoholic fatty liver disease (NAFLD): a randomized, controlled clinical trial. *Iranian Red Crescent Medical Journal* 2018;**20**(10):1-12.

Hussain 2019 *{published data only}*

Hussain M, Iqbal J, Malik SA, Waheed A, Shabnum S, Akhtar L, et al. Effect of vitamin D supplementation on various parameters in non-alcoholic fatty liver disease patients. *Pakistan Journal of Pharmaceutical Sciences* 2019;**32**(3 Special):1343-8.

Jeong 2019 *{published data only}*

Jeong JY, Jun DW, Park SJ, Sohn JH, Kim SG, Lee SW, et al. Effects of vitamin D supplements in patients with chronic hepatitis C: a randomized, multi-center, open label study. *Korean Journal of Internal Medicine* 2019;**35**(5):1074-83.

Jha 2017 *{published data only}*

Jha AK, Jha SK, Kumar A, Dayal VM, Jha SK. Effect of replenishment of vitamin D on survival in patients with decompensated liver cirrhosis: a prospective study. *World Journal of Gastrointestinal Pathophysiology* 2017;**8**(3):133-41.

Komolmit 2017a *{published data only}*

Komolmit P, Charoensuk K, Thanapirom K, Suksawatamnuay S, Thaimai P, Chirathaworn C, et al. Correction of vitamin D deficiency facilitated suppression of IP-10 and DPP IV levels in patients with chronic hepatitis C: a randomised double-blinded, placebo-control trial. *PLOS ONE* 2017;**12**(4):e0174608.

Komolmit 2017b *{published data only}*

Komolmit P, Kimtrakool S, Suksawatamnuay S, Thanapirom K, Chattrasophon K, Thaimai P, et al. Vitamin D supplementation improves serum markers associated with hepatic fibrogenesis in chronic hepatitis C patients: a randomized, double-blind, placebo-controlled study. *Scientific Reports* 2017;**7**(1):8905.

Lorvand Amiri 2016 *{published data only}*

Lorvand Amiri H, Agah S, Mousavi SN, Hosseini AF, Shidfar F. Regression of non-alcoholic fatty liver by vitamin D supplement: a double-blind randomized controlled clinical trial. *Archives of Iranian Medicine* 2016;**19**(9):631-8.

* Lorvand Amiri H, Agah S, Tolouei Azar J, Hosseini S, Shidfar F, Mousavi SN. Effect of daily calcitriol supplementation with and without calcium on disease regression in non-alcoholic fatty liver patients following an energy-restricted diet: randomized, controlled, double-blind trial. *Clinical Nutrition* 2016;**16**:31260-2.

Shidfar F, Mousavi SN, Lorvand Amiri H, Agah S, Hoseini S, Hajimiresmail SJ. Reduction of some atherogenic indices in patients with non-alcoholic fatty liver by vitamin D and calcium co-supplementation: a double blind randomized controlled clinical trial. *Iranian Journal of Pharmaceutical Research* 2019;**18**(1):496-505.

Mobarhan 1984 *{published data only}*

Mobarhan SA, Russell RM, Recker RR, Posner DB, Iber FL, Miller P. Metabolic bone disease in alcoholic cirrhosis: a comparison of the effect of vitamin D2, 25-hydroxyvitamin D, or supportive treatment. *Hepatology (Baltimore, Md.)* 1984;**4**(2):266-73.

Nimer 2012 *{published data only}*

Nimer A, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. *World Journal of Gastroenterology* 2012;**18**(8):800-5.

Pilz 2016 *{published data only}*

Pilz S, Putz-Bankuti C, Gaksch M, Spindelboeck W, Haselberger M, Rainer F, et al. Effects of vitamin D supplementation on serum 25-hydroxyvitamin D concentrations in cirrhotic patients: a randomized controlled trial. *Nutrients* 2016;**8**(5):278.

Sakpal 2017 *{published data only}*

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

Sharifi 2014 *{published data only}*

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

Sharifi N, Amani R, Hajiani E, Cheraghian B. Women may respond different from men to vitamin D supplementation regarding cardiometabolic biomarkers. *Experimental Biology & Medicine (Maywood)* 2016;**241**(8):830-8.

Shiomi 1999a *{published data only}*

Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, et al. Calcitriol for bone disease in patients with cirrhosis of the liver. *Journal of Gastroenterology and Hepatology* 1999;**14**(6):547-52.

Shiomi 1999b *{published data only}*

Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, et al. Calcitriol for bone loss in patients with primary biliary cirrhosis. *Journal of Gastroenterology* 1999;**34**(2):241-5.

Taghvaei 2018 *{published data only}*

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

Vosoghinia 2016 *{published data only}*

Vosoghinia H, Esmaeilzadeh A, Ganji A, Hosseini SM, Jamehdar SA, Salehi M, et al. Vitamin D in standard HCV regimen (PEG-Interferon plus Ribavirin), its effect on the early virologic response rate: a clinical trial. *Razavi International Journal of Medicine* 2016;**4**(2):e36632.

Xing 2013 *{published data only}*

Xing T, Qiu G, Zhong L, Ling L, Huang L, Peng Z. Calcitriol reduces the occurrence of acute cellular rejection of liver transplants: a prospective controlled study. *Pharmazie* 2013;**68**(10):821-6.

Yokoyama 2014 *{published data only}*

Yokoyama S, Takahashi S, Kawakami Y, Hayes CN, Kohno H, Kohno H, et al. Effect of vitamin D supplementation on pegylated interferon/ribavirin therapy for chronic hepatitis C genotype 1b: a randomized controlled trial. *Journal of Viral Hepatitis* 2014;**21**(5):348-56.

References to studies excluded from this review

Atsukawa 2013 *{published data only}*

Atsukawa M, Tsubota A, Shimada N, Kondo C, Itokawa N, Nakagawa A, et al. Efficacy of alfacalcidol on PEG-IFN/ribavirin combination therapy for elderly patients with chronic hepatitis C: a pilot study. *Hepatitis Monthly* 2013;**13**(12):e14872.

Benetti 2008 *{published data only}*

Benetti A, Crosignani A, Varenna M, Giussani CS, Allocca M, Zuin M, et al. Primary biliary cirrhosis is not an additional risk factor for bone loss in women receiving regular calcium and vitamin D supplementation: a controlled longitudinal study. *Journal of Clinical Gastroenterology* 2008;**42**(3):306-11.

Bitetto 2010 *{published data only}*

Bitetto D, Fabris C, Fornasiere E, Pipan C, Fumolo E, Cussigh A, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. *Transplant International* 2011;**24**(1):43-50.

Chen 2015 *{published data only}*

Chen EQ, Bai L, Zhou TY, Fe M, Zhang DM, Tang H. Sustained suppression of viral replication in improving vitamin D serum concentrations in patients with chronic hepatitis B. *Scientific Reports* 2015;**5**:15441.

Dasarathy 2017 *{published data only}*

Dasarathy J, Varghese R, Feldman A, Khiyami A, McCullough AJ, Dasarathy S. Patients with nonalcoholic fatty liver disease have a low response rate to vitamin D supplementation. *Journal of Nutrition* 2017;**147**(10):1938-46.

Fernández Fernández 2016 *{published data only}*

Fernández Fernández N, Linares Torres P, João Matias D, Jorquera Plaza F, Olcoz Goñi JL. Vitamin D deficiency in chronic liver disease, clinical-epidemiological analysis and report after vitamin D supplementation [Déficit de vitamina D en la enfermedad hepática crónica, análisis clínico epidemiológico

y tras aporte vitamínico]. *Gastroenterologia y Hepatologia* 2016;**39**(5):305-10.

Floreani 2007 *{published data only}*

Floreani A, Carderi I, Ferrara F, Rizzotto ER, Luisetto G, Camozzi V, et al. A 4-year treatment with clodronate plus calcium and vitamin D supplements does not improve bone mass in primary biliary cirrhosis. *Digestive and Liver Disease* 2007;**39**(6):544-8.

Hasanain 2018 *{published data only}*

Hasanain AF, Zayed AA, Mahdy RE, Nafee AM. Cholecalciferol for prophylaxis against antituberculosis therapy-induced liver disorders among naïve patients with pulmonary tuberculosis: a randomized, comparative study. *International Journal of Mycobacteriology* 2017;**6**:149-55.

Kitson 2016 *{published data only}*

Kitson MT, Pham A, Gordon A, Kemp W, Roberts SK. High-dose vitamin D supplementation and liver histology in NASH. *Gut* 2016;**65**(4):717-8.

Kondo 2013 *{published data only}*

Kondo Y, Kato T, Kimura O, Iwata T, Ninomiya M, Kakazu E, et al. 1(OH) vitamin D3 supplementation improves the sensitivity of the immune-response during Peg-IFN/RBV therapy in chronic hepatitis C patients - case controlled trial. *PLOS ONE* 2013;**8**(5):e63672.

Ladero 2013 *{published data only}*

Ladero JM, Torrejón MJ, Sánchez-Pobre P, Suárez A, Cuenca F, De la Orden V, et al. Vitamin D deficiency and vitamin D therapy in chronic hepatitis C. *Annals of Hepatology* 2013;**12**(2):199-204.

Long 1978 *{published data only}*

Long RG, Varghese Z, Meinhard EA, Skinner RK, Wills MR, Sherlock S. Parenteral 1,25-dihydroxycholecalciferol in hepatic osteomalacia. *British Medical Journal* 1978;**1**(6105):75-7.

Malham 2012 *{published data only}*

Malham M, Jørgensen PS, Lauridsen AL, Ott P, Glerup H, Dahlerup JF. The effect of a single oral megadose of vitamin D provided as either ergocalciferol (D_2) or cholecalciferol (D_3) in alcoholic liver cirrhosis. *European Journal of Gastroenterology & Hepatology* 2012;**24**(2):172-8.

Naderpoor 2018 *{published data only}*

Naderpoor N, Mousa A, De Courten M, Scragg R, De Courten B. The relationship between 25-hydroxyvitamin D concentration and liver enzymes in overweight or obese adults: cross-sectional and interventional outcomes. *Journal of Steroid Biochemistry and Molecular Biology* 2018;**177**:193-9.

Omori-Mizuno 2015 *{published data only}*

Omori-Mizuno Y, Nakayama N, Inao M, Funyu J, Asabe S, Tomita K, et al. Randomized study comparing vitamin D3 and 1α-hydroxyvitamin D3 in combination with pegylated interferon/ribavirin therapy for chronic hepatitis C. *Journal of Gastroenterology and Hepatology* 2015;**30**(9):1384-90.

Papapostoli 2016 *{published data only}*

Papapostoli I, Lammert F, Stokes CS. Effect of short-term vitamin D correction on hepatic steatosis as quantified by controlled attenuation parameter (CAP). *Journal of Gastrointestinal and Liver Diseases* 2016;**25**(2):175-81.

Park 2017 *{published data only}*

Park D, Kwon H, Oh SW, Joh HK, Hwang SS, Park JH, et al. Is vitamin D an independent risk factor of nonalcoholic fatty liver disease?: a cross-sectional study of the healthy population. *Journal of Korean Medical Science* 2017;**32**(1):95-101.

Rode 2010 *{published data only}*

Rode A, Fourlanos S, Nicoll A. Oral vitamin D replacement is effective in chronic liver disease [Fréquence du déficit en vitamine D et effet de la supplémentation orale au cours des maladies chroniques du foie]. *Gastroentérologie Clinique et Biologique* 2010;**34**(11):618-20.

Stokes 2016 *{published data only}*

Stokes CS, Grünhage F, Baus C, Volmer DA, Wagenpfeil S, Riemenschneider M, et al. Vitamin D supplementation reduces depressive symptoms in patients with chronic liver disease. *Clinical Nutrition (Edinburgh, Scotland)* 2016;**35**(4):950-7.

Tavakoli 2019 *{published data only}*

Tavakoli H, Rostami H, Avan A, Bagherniya M, Ferns GA, Khayyatzadeh SS. High dose vitamin D supplementation is associated with an improvement in serum markers of liver function. *Biofactors* 2019;**45**(3):335-42.

Terrier 2015 *{published data only}*

Terrier B, Lapidus N, Pol S, Serfaty L, Ratziu V, Asselah T, et al. Vitamin D in addition to peg-interferon-alpha/ribavirin in chronic hepatitis C virus infection: ANRS-HC25-VITAVIC study. *World Journal of Gastroenterology* 2015;**21**(18):5647-53.

Zhou 2019 *{published data only}*

Zhou Q, Li L, Chen Y, Zhang J, Zhong L, Peng Z, et al. Vitamin D supplementation could reduce the risk of acute cellular rejection and infection in vitamin D deficient liver allograft recipients. *International Immunopharmacology* 2019;**75**:105811.

References to ongoing studies

IRCT2016020326342N1 *{published data only}*

IRCT2016020326342N1. Effectiveness of vitamin D supplementation on severity of cirrhosis based on CHILD and MELD scores in patients with decompensate cirrhosis. en.irct.ir/trial/21847 (first received 28 February 2016).

NCT02779465 *{published data only}*

NCT02779465. Oral vitamin D treatment for the prevention of hepatocellular carcinoma (VDHCC). clinicaltrials.gov/ct2/show/NCT02779465 (first received 20 May 2016).

Additional references

Arteh 2010

Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Digestive Diseases and Sciences* 2010;**55**(9):2624-8.

Atef 2018

Atef SH. Vitamin D assays in clinical laboratory: past, present and future challenges. *Journal of Steroid Biochemistry and Molecular Biology* 2018;**175**:136-7.

Autier 2014

Autier P, Boniol M, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes & Endocrinology* 2014;**2**(1):76-89.

Autier 2016

Autier P. Vitamin D status as a synthetic biomarker of health status. *Endocrine* 2016;**51**(2):201-2.

Balshem 2011

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6. [PMID: 21208779]

Barbarawi 2019

Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiology* 2019;**4**(8):765-76.

Begg 1994

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

Bischoff-Ferrari 2009

Bischoff-Ferrari H. Vitamin D: what is an adequate vitamin D level and how much supplementation is necessary. *Best Practice & Research. Clinical Rheumatology* 2009;**23**(6):789-95.

Bischoff-Ferrari 2020

Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, Da Silva JAP, Blauth M, et al. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA* 2020;**324**(18):1855-68.

Bitetto 2011

Bitetto D, Fabris C, Falleti E, Toniutto P. Vitamin D deficiency and HCV chronic infection: what comes first. *Journal of Hepatology* 2011;**55**(4):944-5.

Bitetto 2012

Bitetto D, Fabris C, Fornasiere E, Pipan C, Fumolo E, Cussigh A, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. *Transplant International* 2012;**24**(1):43-50.

Bjelakovic 2014a

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No: CD007470. [DOI: 10.1002/14651858.CD007470.pub3]

Bjelakovic 2014b

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Krstic G, Wetterslev J, et al. Vitamin D supplementation for prevention of cancer in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No: CD007469. [DOI: 10.1002/14651858.CD007469.pub2]

Boesen 2021

Boesen K. Methodological Limitations of Psychiatric Drug Trials with a Particular Focus on Extended-Release Methylphenidate (Metodebegraensninger i Psykiatriske Laegemiddelforsøg Med et Saerligt Fokus på Methylphenidat Depotpraeparater) [PhD thesis]. University of Copenhagen, 2020.

Bolland 2006

Bolland MJ, Grey AB, Ames RW, Mason BH, Horne AM, Gamble GD, et al. Determinants of vitamin D status in older men living in a subtropical climate. *Osteoporosis International* 2006;**17**(12):1742-8.

Bolland 2014

Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes & Endocrinology* 2014;**2**(4):307-20.

Bolland 2018

Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes & Endocrinology* 2018;**6**(11):847-58.

Borenstein 2009

Borenstein M, Hedges LV, Higgins T, Rothstein HR. Introduction to Meta-Analysis. Chichester (UK): John Wiley & Sons, 2009.

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**(8):763-9.

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287-98.

Cacopardo 2012

Cacopardo B, Camma C, Petta S, Pinzone MR, Cappellani A, Zanghi A, et al. Diagnostic and therapeutical role of vitamin D in

chronic hepatitis C virus infection. *Frontiers in Bioscience (Elite Edition)* 2012;**4**:1276-86.

Castellini 2018

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**(1):110.

Chan 2004

Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**(20):2457-65.

Chen 2014

Chen EQ, Shi Y, Tang H. New insight of vitamin D in chronic liver diseases. *Hepatobiliary & Pancreatic Diseases International* 2014;**13**(6):580-5.

Chiang 2011

Chiang KC, Yeh CN, Chen MF, Chen TC. Hepatocellular carcinoma and vitamin D: a review. *Journal of Gastroenterology and Hepatology* 2011;**26**(11):1597-603.

Cholongitas 2012

Cholongitas E, Theocharidou E, Goulis J, Tsochatzis E, Akriviadis E, Burroughs K. Review article: the extra-skeletal effects of vitamin D in chronic hepatitis C infection. *Alimentary Pharmacology & Therapeutics* 2012;**35**(6):634-46.

Cohen 1960

Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960;**20**:37-46.

Corey 2012

Corey KE, Zheng H, Mendez-Navarro J, Delgado-Borrego A, Dienstag JL, Chung RT, et al. Serum vitamin D levels are not predictive of the progression of chronic liver disease in hepatitis C patients with advanced fibrosis. *PLOS ONE* 2012;**7**(2):e27144.

Davis 2007

Davis CD, Dwyer JT. The "sunshine vitamin": benefits beyond bone? *Journal of the National Cancer Institute* 2007;**99**(21):1563-5.

Dawson-Hughes 2005

Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporosis International* 2005;**16**(7):713-6.

Dawson-Hughes 2010

Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporosis International* 2010;**21**(7):1151-4.

Deeks 2021

Deeks JJ, Higgins JPT, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

DeMets 1987

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987;**6**(3):341-50.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Egger 1997

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.

Elangovan 2017

Elangovan H, Chahal S, Gunton JE. Vitamin D in liver disease: current evidence and potential directions. *Biochimica et Biophysica Acta* 2017;**1863**(4):907-16.

Eliades 2013

Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics* 2013;**38**(3):246-54.

Eliades 2015

Eliades M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease. *World Journal of Gastroenterology* 2015;**21**(6):1718-27.

Farnik 2013

Farnik H, Bojunga J, Berger A, Allwinn R, Waidmann O, Kronenberger B, et al. Low vitamin D serum concentration is associated with high levels of hepatitis B virus replication in chronically infected patients. *Hepatology (Baltimore, Md.)* 2013;**58**(4):1270-6.

Finkelmeier 2014

Finkelmeier F, Kronenberger B, Köberle V, Bojunga J, Zeuzem S, Trojan J, et al. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma - a prospective cohort study. *Alimentary Pharmacology & Therapeutics* 2014;**39**(10):1204-12.

Finkelmeier 2015

Finkelmeier F, Kronenberger B, Zeuzem S, Piiper A, Waidmann O. Low 25-hydroxyvitamin D levels are associated with infections and mortality in patients with cirrhosis. *PLOS ONE* 2015;**10**(6):e0132119.

Fortmann 2013

Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2013;**159**(12):824-34.

Furukawa 2007

Furukawa TA, Watanabe N, Omori IM, Montori VM, Guyatt GH. Association between unreported outcomes and effect size estimates in Cochrane meta-analyses. *JAMA* 2007;**297**(5):468-70.

Garattini 2016

Garattini S, Jakobsen JC, Wetterslev J, Bertelé V, Banzi R, Rath A, et al. Evidence-based clinical practice: overview of threats to the validity of evidence and how to minimise them. *European Journal of Internal Medicine* 2016;**32**:13-21.

Gartlehner 2019

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.

Geier 2011

Geier A. Shedding new light on vitamin D and fatty liver disease. *Journal of Hepatology* 2011;**55**(2):273-5.

Gluud 2006

Gluud C. The culture of designing hepato-biliary randomised trials. *Journal of Hepatology* 2006;**44**(3):607-15. [MEDLINE: 16434120]

Gluud 2007

Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *Journal of Hepatology* 2007;**46**(4):734-42.

Gluud 2008

Gluud C, Hilden J. Povl Heiberg's 1897 methodological study on the statistical method as an aid in therapeutic trials, 2008. www.jameslindlibrary.org/articles/povl-heibergs-1897-methodological-study-on-the-statistical-method-as-an-aid-in-therapeutic-trials/ (accessed 17 July 2017).

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 4 November 2020. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Grey 2010

Grey A, Bolland M. Vitamin D: a place in the sun. *Archives of Internal Medicine* 2010;**170**(13):1099-100.

Guallar 2010

Guallar E, Miller ER 3rd, Ordovas JM, Stranges S. Vitamin D supplementation in the age of lost innocence. *Annals of Internal Medicine* 2010;**152**(5):327-9.

Guañabens 2010

Guañabens N, Parés A. Liver and bone. *Archives of Biochemistry and Biophysics* 2010;**503**(1):84-94.

Guo 2020

Guo XF, Wang C, Yang T, Li S, Li KL, Li D. Vitamin D and non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Food and Function* 2020;**11**(9):7389-99.

Gutierrez 2011

Gutierrez JA, Parikh N, Branch AD. Classical and emerging roles of vitamin D in hepatitis C virus infection. *Seminars in Liver Disease* 2011;**31**(4):387-98.

Guyatt 2011a

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PMID: 21195583]

Guyatt 2011b

Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395-400. [PMID: 21194891]

Guyatt 2011c

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407-15. [PMID: 21247734]

Guyatt 2011d

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence - publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277-82. [PMID: 21802904]

Guyatt 2011e

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines: 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93. [PMID: 21839614]

Guyatt 2011f

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294-302. [PMID: 21803546]

Guyatt 2011g

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303-10. [PMID: 21802903]

Guyatt 2011h

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311-6. [PMID: 21802902]

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151-7.

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72.

Guyatt 2013c

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables - continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173-83.

Guyatt 2013d

Guyatt G, Andrews J, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology* 2013;**66**(7):719-25.

Guyatt 2017

Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *Journal of Clinical Epidemiology* 2017;**87**:14-22. [PMID: 28529188]

Han 2013

Han YP, Kong M, Zheng S, Ren Y, Zhu L, Shi H, et al. Vitamin D in liver diseases: from mechanisms to clinical trials. *Journal of Gastroenterology and Hepatology* 2013;**28**(Suppl 1):49-55.

Hariri 2019

Hariri M, Zohdi S. Effect of vitamin D on non-alcoholic fatty liver disease: a systematic review of randomized controlled clinical trials. *International Journal of Preventive Medicine* 2019;**10**(1):14.

Harvey 2012

Harvey NC, Cooper C. Vitamin D: some perspective please. *BMJ (Clinical Research Ed.)* 2012;**345**:e4695. [DOI: 10.1136/bmj.e4695]

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ (Clinical Research Ed.)* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1.

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Hilger 2014

Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. *British Journal of Nutrition* 2014;**111**(1):23-45.

Hoan 2016

Hoan NX, Khuyen N, Binh MT, Giang DP, Van Tong H, Hoan PQ, et al. Association of vitamin D deficiency with hepatitis B virus-related liver diseases. *BMC Infectious Diseases* 2016;**16**(1):507.

Holick 2007

Holick MF. Vitamin D deficiency. *New England Journal of Medicine* 2007;**357**(3):266-81.

Holick 2011

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology* 2011;**96**(7):1911-30.

Hollis 1999

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.

Hollis 2008

Hollis BW. Measuring 25-hydroxyvitamin D in a clinical environment: challenges and needs. *American Journal of Clinical Nutrition* 2008;**88**(2):507S-10S.

Hu 2019

Hu Y-C, Wang W-W, Jiang W-Y, Li C-Q, Guo J-C, Xun Y-H. Low vitamin D levels are associated with high viral loads in patients with chronic hepatitis B: a systematic review and meta-analysis. *BMC Gastroenterology* 2019;**19**(1):84.

ICH-GCP 1997

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

Ioannidis 2009

Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Archives of Internal Medicine* 2009;**169**(19):1737-9.

IOM 2011

Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press, 2011.

Iruzubieta 2014

Iruzubieta P, Terán Á, Crespo J, Fábrega E. Vitamin D deficiency in chronic liver disease. *World Journal of Hepatology* 2014;**6**(12):901-15.

Jakobsen 2014a

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

Jakobsen 2017

Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No: CD012143. [DOI: 10.1002/14651858.CD012143.pub3]

Jaruvongvanich 2017

Jaruvongvanich V, Ahuja W, Sanguankeo A, Wijarnpreecha K, Upala S. Vitamin D and histologic severity of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Digestive and Liver Disease* 2017;**49**(6):618-22.

Johnson 2007

Johnson RT, Dickersin K. Publication bias against negative results from clinical trials: three of the seven deadly sins. *Nature Clinical Practice. Neurology* 2007;**3**(11):590-1.

Keum 2019

Keum N, Lee DH, Greenwood DC, Manson JE, Giovannucci E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Annals of Oncology* 2019;**30**(5):733-43.

Keus 2010

Keus F, Wetterslev J, Gluud C, Van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. *BMC Medical Research Methodology* 2010;**10**:90.

Kim 2018

Kim H-B, Myung S-K, Lee Y-J, Park B-J. Efficacy of vitamin D supplementation in combination with conventional antiviral therapy in patients with chronic hepatitis C infection: a meta-analysis of randomised controlled trials. *Journal of Human Nutrition and Dietetics* 2018;**31**(2):168-77.

Kitson 2012

Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. *Journal of Hepatology* 2012;**57**(4):897-909.

Kitson 2014

Kitson MT, Sarrazin C, Toniutto P, Eslick GD, Roberts SK. Vitamin D level and sustained virologic response to interferon-based antiviral therapy in chronic hepatitis C: a systematic review and meta-analysis. *Journal of Hepatology* 2014;**61**(6):1247-52.

Kjaergard 2001

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

Konstantakis 2016

Konstantakis C, Tselekouni P, Kalafateli M, Triantos C. Vitamin D deficiency in patients with liver cirrhosis. *Annals of Gastroenterology* 2016;**29**(3):297-306.

Kovesdy 2013

Kovesdy Csaba P, Quarles LD. Fibroblast growth factor-23: what we know, what we don't know, and what we need to know. *Nephrology Dialysis Transplantation* 2013;**28**(9):2228-36.

Kupferschmidt 2012

Kupferschmidt K. Uncertain verdict as vitamin D goes on trial. *Science* 2012;**337**(6101):1476-8.

Kwok 2013

Kwok RM, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): is it more than just an association. *Hepatology (Baltimore, Md.)* 2013;**58**(3):1166-74.

Lange 2013

Lange CM, Miki D, Ochi H, Nischalke HD, Bojunga J, Bibert S, et al. Genetic analyses reveal a role for vitamin D insufficiency in HCV-associated hepatocellular carcinoma development. *PLOS ONE* 2013;**8**(5):e64053.

Lesser 2007

Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between funding source and conclusion among nutrition-related scientific articles. *PLOS Medicine* 2007;**4**(1):e5.

Li 2013

Li YJ, Tang YW, Shi YQ, Han S, Wang JB, Zhou XM, et al. Polymorphisms in the vitamin D receptor gene and risk of primary biliary cirrhosis: a meta-analysis. *Journal of Gastroenterology and Hepatology* 2013;**29**(4):706-15.

Lim 2012

Lim LY, Chalasani N. Vitamin D deficiency in patients with chronic liver disease and cirrhosis. *Current Gastroenterology Reports* 2012;**14**(1):67-73.

Lips 2004

Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate. *Journal of Steroid Biochemistry and Molecular Biology* 2004;**89-90**(1-5):611-4.

Lips 2006

Lips P. Vitamin D physiology. *Progress in Biophysics and Molecular Biology* 2006;**92**(1):4-8.

Lips 2010

Lips P. Worldwide status of vitamin D nutrition. *Journal of Steroid Biochemistry and Molecular Biology* 2010;**121**(1-2):297-300.

Lucas 2005

Lucas JA, Bolland MJ, Grey AB, Ames RW, Mason BH, Horne AM, et al. Determinants of vitamin D status in older women living in a subtropical climate. *Osteoporosis International* 2005;**16**(12):1641-8.

Lundh 2017

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]

Luong 2012

Luong KV, Nguyen LT. Theoretical basis of a beneficial role for vitamin D in viral hepatitis. *World Journal of Gastroenterology* 2012;**18**(38):5338-50.

Luong 2013a

Luong KV, Nguyen LT. The role of vitamin D in autoimmune hepatitis. *Journal of Clinical Medicine Research* 2013;**5**(6):407-15.

Luong 2013b

Luong KV, Nguyen LT. The role of vitamin D in primary biliary cirrhosis: possible genetic and cell signaling mechanisms. *Gastroenterology Research and Practice* 2013;**2013**:602321.

Luxon 2011

Luxon BA. Bone disorders in chronic liver diseases. *Current Gastroenterology Reports* 2011;**13**(1):40-8.

Mahamid 2013

Mahamid M, Nseir W, Abu Elhija O, Shteingart S, Mahamid A, Smamra M, et al. Normal vitamin D levels are associated with spontaneous hepatitis B surface antigen seroclearance. *World Journal of Gastroenterology* 2013;**5**(6):328-31.

Malham 2011

Malham M, Jørgensen SP, Ott P, Agnholt J, Vilstrup H, Borre M, et al. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. *World Journal of Gastroenterology* 2011;**17**(7):922-5.

Manson 2019

Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *New England Journal of Medicine* 2019;**380**(1):33-44.

Mansour-Ghanaei 2019

Mansour-Ghanaei F, Pourmasoumi M, Hadi A, Ramezani-Jolfaie N, Joukar F. The efficacy of vitamin D supplementation against nonalcoholic fatty liver disease: a meta-analysis. *Journal of Dietary Supplements* 2019;**17**(4):467-85.

Moher 1998

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

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *PLOS Medicine* 2009;**6**(7):e1000097.

Mosannen 2017

Mosannen Mozaffari H, Abbasi HA, Goshayeshi G, Esmaeelzadeh A, Bahari A, Mokhtarifar A, et al. Effect of vitamin D supplementation on chronic liver disease: systematic literature review. *Reviews in Clinical Medicine* 2017;**4**(1):14-9.

Mustafa 2013

Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of Clinical Epidemiology* 2013;**66**(7):736-42. [PMID: 23623694]

Nordic Trial Alliance 2015

Nordic Trial Alliance Working Group on Transparency and Registration. Transparency and registration in clinical research in the Nordic countries. nta.nordforsk.org/projects/nta_transparency_report.pdf (accessed 6 November 2020).

Oliveira 2017

Oliveira KD, Buss C, Tovo CV. Is there an association between vitamin D and liver fibrosis in patients with chronic hepatitis C. *Arquivos de Gastroenterologia* 2017;**54**(1):57-9.

Paternostro 2017

Paternostro R, Wagner D, Reiberger T, Mandorfer M, Schwarzer R, Ferlitsch M, et al. Low 25-OH-vitamin D levels reflect hepatic dysfunction and are associated with mortality in patients with liver cirrhosis. *Wiener Klinische Wochenschrift* 2017;**129**(1-2):8-15.

Peng 2020

Peng L, Li L, Wang P, Chong W, Li Y, Zha X, et al. Association between vitamin D supplementation and mortality in critically ill patients: a systematic review and meta-analysis of randomized clinical trials. *PLOS ONE* 2020;**15**(12):e0243768.

Petta 2010

Petta S, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology (Baltimore, Md.)* 2010;**51**(4):1158-67.

Putz-Bankuti 2012

Putz-Bankuti C, Pilz S, Stojakovic T, Scharnagl H, Pieber TR, Trauner M, et al. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. *Liver International* 2012;**32**(5):845-51.

Reid 2014

Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014;**383**(9912):146-55.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

SACN 2016

Public Health England. SACN vitamin D and health report. www.gov.uk/government/publications/sacn-vitamin-d-and-health-report (accessed 17 July 2017).

Savović 2012a

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

Savović 2012b

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

Savović 2018a

Savović J, Akl EA, Hróbjartsson A. Financial conflicts of interest in clinical research. *Intensive Care Medicine* 2018;**44**(10):1767-9.

Savović 2018b

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JPT, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane reviews: the ROBES meta-epidemiologic study. *American Journal of Epidemiology* 2018;**187**(5):1113–22.

Sayiner 2016

Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States and the rest of the world. *Clinics in Liver Disease* 2016;**20**(2):205-14.

Schroll 2013

Schroll JB, Bero L, Gøtzsche PC. Searching for unpublished data for Cochrane reviews: cross sectional study. *BMJ (Clinical Research Ed.)* 2013;**346**:f2231.

Schulz 1995

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

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Scragg 2017

Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the Vitamin D Assessment Study: a randomized clinical trial. *JAMA Cardiology* 2017;**2**(6):608-16.

Scragg 2018

Scragg R, Khaw KT, Toop L, Sluyter J, Lawes CMM, Waayer D, et al. Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the Vitamin D Assessment randomized clinical trial. *JAMA Oncology* 2018;**4**(11):e182178.

Sharifi 2019

Sharifi N, Amani R. Vitamin D supplementation and non-alcoholic fatty liver disease: a critical and systematic review of clinical trials. *Critical Reviews in Food Science and Nutrition* 2019;**59**(4):693-703.

Siersma 2007

Siersma V, Als-Nielsen B, Chen W, Hilden J, Gluud LL, Gluud C. Multivariable modelling for meta-epidemiological assessment of the association between trial quality and treatment effects estimated in randomized clinical trials. *Statistics in Medicine* 2007;**26**(14):2745-58.

Sigma Stat 2003 [Computer program]

Systat Software Inc. Sigma Stat 3.0. Systat Software Inc., 2003.

Skaaby 2014

Skaaby T, Husemoen LL, Borglykke A, Jørgensen T, Thuesen BH, Pisinger C, et al. Vitamin D status, liver enzymes, and incident liver disease and mortality: a general population study. *Endocrine* 2014;**47**(1):213-20.

Skaaby 2016

Skaaby T, Husemoen LL, Thuesen BH, Pisinger C, Hannemann A, Jørgensen T. Longitudinal associations between lifestyle and vitamin D: a general population study with repeated vitamin D measurements. *Endocrine* 2016;**51**:342-50.

StataCorp 2005 [Computer program]

College Station, TX: StataCorp LP Intercooled Stata 8.2 for Windows. College Station, TX: StataCorp LP, 2005.

Stokes 2013

Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. *Liver International* 2013;**33**(3):338-52.

Stokes 2014

Stokes CS, Krawczyk M, Reichel C, Lammert F, Grünhage F. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. *European Journal of Clinical Investigation* 2014;**44**(2):176-83.

Storebø 2015

Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia CR, Holmskov M, Skoog M, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *BMJ (Clinical Research Ed.)* 2015;**351**:h5203.

Storebø 2018

Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies.

Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No: CD012069. [DOI: 10.1002/14651858.CD012069.pub2]

Tabrizi 2017

Tabrizi R, Moosazadeh M, Lankarani KB, Akbari M, Heydari ST, Kolahdooz F, et al. The effects of vitamin D supplementation on metabolic profiles and liver function in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Diabetes & Metabolic Syndrome* 2017;**11**:S975-82.

Thorlund 2009

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):276-86.

Thorlund 2011

Thorlund K, Imberger G, Walsh M, Chu R, Gluud C, Wetterslev J, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis - a simulation study. *PLOS ONE* 2011;**6**(10):e25491.

Thorlund 2017

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/wp-content/uploads/2020/12/tsa_manual_ENG.pdf 2017 (accessed 2 September 2020).

Trépo 2013

Trépo E, Ouziel R, Pradat P, Momozawa Y, Quertinmont E, Gervy C, et al. Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease. *Journal of Hepatology* 2013;**59**(2):344-50.

TSA 2017 [Computer program]

Copenhagen Trial Unit Trial Sequential Analysis. Copenhagen Trial Unit, Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2017. ctu.dk/tsa/downloads/.

Tsiaras 2011

Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. *Acta Dermato-Venereologica* 2011;**91**(2):115-24.

Turner 2013

Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLOS ONE* 2013;**8**(3):e59202.

Van Schoor 2011

Van Schoor NM, Lips P. Worldwide vitamin D status. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2011;**25**(4):671-80.

Villar 2013

Villar LM, Del Campo JA, Ranchal I, Lampe E, Romero-Gomez M. Association between vitamin D and hepatitis C virus infection: a meta-analysis. *World Journal of Gastroenterology* 2013;**19**(35):5917-24.

Wang 2013

Wang JB, Abnet CC, Chen W, Dawsey SM, Fan JH, Yin LY, et al. Association between serum 25(OH) vitamin D, incident liver cancer and chronic liver disease mortality in the Linxian Nutrition Intervention Trials: a nested case-control study. *British Journal of Cancer* 2013;**109**(7):1997-2004.

Wang 2015

Wang X, Li W, Zhang Y, Yang Y, Qin G. Association between vitamin D and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: results from a meta-analysis. *International Journal of Clinical and Experimental Medicine* 2015;**8**(10):17221-34.

Wesley Pike 2005

Wesley Pike J, Shevde NK. The vitamin D receptor. In: Feldman D, Wesley Pike J, Glorieux FH, editors(s). Vitamin D. 2nd edition. Amsterdam: Elsevier Academic Press, 2005:167-91.

Wetterslev 2008

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.

Wetterslev 2009

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

Wetterslev 2017

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

Williamson 2005

Williamson PR, Gamble C, Altman DG, Hutton JL. Outcome selection bias in meta-analysis. *Statistical Methods in Medical Research* 2005;**14**(5):515-24.

Wood 2008

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

Younossi 2016

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease - meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology (Baltimore, Md.)* 2016;**64**(1):73-84.

Zhang 2019

Zhang Y, Fang F, Tang J, Jia L, Feng Y, Xu P, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)* 2019;**366**:l4673.

Zittermann 2014

Zittermann A, Ernst JB, Gummert JF, Börgermann J. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: a systematic review. *European Journal of Nutrition* 2014;**53**(2):367-74.

References to other published versions of this review

Bjelakovic 2015

Bjelakovic G, Nikolova D, Bjelakovic M, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No: CD011564. [DOI: 10.1002/14651858.CD011564]

Bjelakovic 2017

Bjelakovic G, Nikolova D, Bjelakovic M, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No: CD011564. [DOI: 10.1002/14651858.CD011564.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abu-Mouch 2011

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	72 participants (44% women), aged 18 to 65 years, mean age 47 years, with chronic HCV genotype 1. **Inclusion criteria:** aged 18 to 65 years; chronic HCV genotype 1 infection; no previous treatment for HCV; seronegative for HBV, HDV, and HIV infections; absolute neutrophil count > 1500/mm^3; platelet count > 90,000/mm^3; and normal haemoglobin level **Exclusion criteria:** decompensated liver disease (cirrhosis with a Child-Pugh score > 9), another cause of clinically significant liver disease, or presence of hepatocellular carcinoma
Interventions	**Intervention:** PEG-IFN-α-2b (1.5 µg/kg body weight) + oral ribavirin 1000 mg/day (for body weight < 75 kg) or 1200 mg/day (for body weight > 75 kg) and vitamin D_3 2000 IU/day (n = 36) **Control:** PEG-IFN-α-2b (1.5 µg/kg body weight) + oral ribavirin 1000 mg/day (for body weight < 75 kg) or 1200 mg/day (for body weight > 75 kg) (n = 36) For 48 weeks. All participants had ≥ 1 follow-up visit at 24 weeks after completion of treatment.
Outcomes	Outcomes reported in abstract of publication **Primary outcome:** SVR defined as undetectable HCV-RNA at 24 weeks' post-treatment **Secondary outcomes:** treatment efficacy at weeks 4 (RVR), and 12 (EVR) during therapy, and 24 weeks after cessation of therapy (SVR)
Stated aim of study	To determine whether adding vitamin D improves HCV response to antiviral therapy
Notes	All participants completed the trial. Vitamin D_3 (Vitamidyne D, Fischer Pharmaceuticals, Israel) given by oral drops for 4 weeks before initiation of antiviral treatment and after serum levels had reached > 32 ng/mL in all participants in the treatment group. Registered at ClinicalTrials.gov NCT00804752 Additional information received through personal communication with authors on 8 February 2017.

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

Abu-Mouch 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequence generation performed using computer random number generation.
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation sequence hidden in sequentially numbered, opaque, and sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported in full.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Atsukawa 2016

Study characteristics	
Methods	Open-label randomised clinical trial with parallel-group design (2 groups)
Participants	**Number of participants randomised:** 115 participants (50% women), aged 31 to 82 years, mean age 64 years, with chronic hepatitis C **Inclusion criteria:** HCV genotype 1b as determined by the conventional PCR-based method; IL28B SNP rs8099917 genotype TG or GG (designated as non-TT); HCV RNA persistently detectable in serum by the real-time PCR technique; white blood cell count of more than 2000 µL; platelet count of more than 50,000 µL; and haemoglobin levels of more than 9.0 g/dL at the time of enrolment. Patients could participate in the study regardless of whether they had received prior IFN-based therapy. Patients who had not received PEG IFN/ribavirin combination therapy were considered naive patients. **Exclusion criteria:** decompensated liver cirrhosis, evidence of other forms of liver disease, presence of malignancy and other serious medical illness, evidence of hypercalcaemia or hyperparathyroidism, positive hepatitis B surface antigen and antibody to HIV type 1, medication with Chinese herbal medicine or other type of vitamin D, past medical history of interstitial pneumonia, pregnancy or possibility of pregnancy, lactating, and past medical history of allergy to biological preparations or antiviral agents
Interventions	**Intervention:** lead-in treatment with oral native vitamin D_3 (Healthy Natural Products, Florence, KY, USA) at a dose of 2000 IU once daily for 4 weeks, followed by the addition of the vitamin D_3 to the 12-week triple therapy (PEG IFN-α-2a (Roche Group-Chugai, Tokyo, Japan), ribavirin (Chugai), and simeprevir (Janssen, Tokyo, Japan)), followed by 12 weeks of PEG IFN-α-2a and ribavirin (n = 57) **Control:** 12-week triple therapy (PEG IFN-α-2a (Roche Group-Chugai, Tokyo, Japan), ribavirin (Chugai), and simeprevir (Janssen, Tokyo, Japan)) for 12 weeks, followed by 12 weeks of PEG IFN-α-2a and ribavirin (n = 58)

Atsukawa 2016 *(Continued)*

	PEG IFN-α-2a was administered subcutaneously at a dose of 180 µg once weekly. Ribavirin was administered orally twice daily, with doses adjusted according to body weight (600 mg daily for < 60 kg, 800 mg daily for 60 to 80 kg, and 1000 mg daily for > 80 kg). Simeprevir was administered orally once daily at a dose of 100 mg. Because of the low likelihood of achieving an SVR and high likelihood of developing antiviral resistance, treatment was stopped for participants with serum HCV RNA decline from baseline of less than 3 log IU/mL at 4 weeks of treatment, detectable HCV RNA at 12 weeks of treatment, or more than 2 log IU/mL increase in HCV RNA levels from the lowest levels during treatment (defined as viral breakthrough).
Outcomes	**Primary outcome:** sustainability of undetectable viraemia 24 weeks after the end of treatment
Stated aim of study	To clarify whether native vitamin D_3 supplementation could improve SVR rate in PEG-IFN/ribavirin therapy with simeprevir for people with treatment-refractory genotype 1b HCV with the IL28B SNP rs8099917 non-TT
Notes	Study authors did not report any deaths. "No patient complained of vitamin D-related symptoms or developed signs of a vitamin D-related adverse reaction".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and outcome is likely to have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, and outcome measurement is likely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess whether missing data in combination with method used to handle missing data was likely to induce bias
Selective reporting (reporting bias)	Unclear risk	Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Barchetta 2016

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	65 participants (35% women), mean age 59 years, with NAFLD **Inclusion criteria:** men or women aged 25 to 70 years; diagnosis of type 2 diabetes according to American Diabetes Association 2009 criteria; presence of fatty liver detected by upper US and confirmed

Barchetta 2016 *(Continued)*

	by MRI in people with clinical suspicion of NAFLD (increased serum transaminase levels in absence of known hepatic chronic disease, ALT > AST, presence of multiple components of metabolic syndrome); negative tests for hepatitis B surface antigen and antibody to HCV **Exclusion criteria:** history of alcohol abuse (defined by mean daily consumption of alcohol > 30 g/day in men and > 20 g/day in women), cirrhosis, autoimmune hepatitis and other causes of liver disease (haemochromatosis, Wilson's disease), chronic enteropathies, advanced renal failure, cancer, hyper/hypoparathyroidism, known hypersensitivity to cholecalciferol or any other excipients, hypercalcaemia, hypercalciuria, nephrolithiasis, nephrocalcinosis; ongoing/recent (previous 6 months) supplementation with vitamin D, calcium, multivitamin products; treatment with agents affecting bone and calcium/vitamin D metabolism (anticonvulsants, glucocorticoids, antacids containing aluminium, cholestyramine); ultraviolet radiation exposure; pregnancy and lactation; or severe psychiatric illnesses
Interventions	**Intervention:** vitamin D_3 2000 IU/day (n = 29) **Control:** placebo (n = 36) For 24 weeks
Outcomes	**Primary outcomes:** reduction of hepatic fat fraction measured by MRI, changes in serum transaminases, CK18-M30, N-terminal procollagen III propeptide levels, and Fatty Liver Index **Secondary outcomes:** metabolic (fasting glycaemia, glycated haemoglobin, lipids, homeostasis model assessment - insulin resistance, homeostasis model assessment - beta cell function, adipose tissue insulin resistance, body fat distribution) and cardiovascular (ankle-brachial index, intima-media thickness, flow-mediated dilatation) parameters
Stated aim of study	To assess the efficacy and safety of 24-week oral high-dose vitamin D supplementation in people with type 2 diabetes and NAFLD
Notes	Registered at www.clinicaltrialsregister.eu (number 2011-003010-17). Funded by research grants from the Sapienza University Ateneo Scientific Research (authors MGC and IB) and the Italian Minister of University and Research (authors MGC and MGB). Study authors did not report any deaths. Authors were not contacted, as information on our outcomes of interest was found in the publication: “As per the safety profile, no major adverse events occurred during the study”.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by statistician using computer-generated and centrally administered procedure
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Used central and independent randomisation unit-controlled allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, clinical site staff, laboratory staff, and radiologists were all masked to treatment assignment throughout study. Treatment and placebo provided in identical vials by an experienced independent pharmacist.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that blinding could have been broken.

Barchetta 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess whether missing data in combination with method used to handle missing data was likely to introduce bias on the results
Selective reporting (reporting bias)	Low risk	Study authors reported all predefined outcomes in full.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Behera 2018

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	**Country:** India 60 participants (40% women), mean age 41 years **Inclusion criteria:** age 18 to 65 years, chronic HCV genotype 1/4, infection with detectable HCV RNA for 6 months, and no previous treatment for hepatitis C **Exclusion criteria:** advanced cirrhosis (Child-Pugh B or C), presence of HCC, HIV and hepatitis B co-infection, autoimmune liver disease, Wilson disease, haemochromatosis, α1-antitrypsin deficiency, concomitant use of medications known to affect serum vitamin D metabolism, and patients with active intravenous drug addiction
Interventions	**Intervention:** PEG-IFN alfa-2a 180 µg per week, and RBV (1000 mg/day for participants weighing < 75 kg, 1200 mg/day for participants weighing > 75 kg) and vitamin D_3 2000 IU/day (n = 28) **Control:** PEG-IFN alfa-2a 180 µg per week, and RBV (1000 mg/day for participants weighing < 75 kg, 1200 mg/day for participants weighing > 75 kg) (n = 32) For 48 weeks
Outcomes	**Primary outcomes:** rapid, early and sustained viral response
Stated aim of study	To assess the effect of vitamin D supplementation on treatment outcome in patients with genotype 1/4 chronic hepatitis C (CHC) infection
Notes	All participants completed the trial.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The computer-generated block randomization schedule was prepared using random number generator to create a list of random numbers. Stat Trek programme (https://stattrek.com) was used to derive the randomization list."
Allocation concealment (selection bias)	Unclear risk	Study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias)	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding.

Behera 2018 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	The study was registered in Clinical Trials Registry-India (CTRI/2015/07/005992).
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as competing interest bias.

Boonyagard 2016

Study characteristics	
Methods	Randomised placebo-controlled clinical trial with parallel-group design (2 groups)
Participants	**Country:** Thailand **Number of participants randomised:** 60 participants **Inclusion criteria:** NAFLD patients who have ALT elevation with vitamin D insufficiency **Exclusion criteria:** none stated
Interventions	**Intervention:** vitamin D (n = 30) **Control:** placebo (n = 30) For 20 weeks
Outcomes	**Primary outcomes:** serum ALT, inflammatory markers, and homeostasis model assessment and Fibroscan **Secondary outcomes:** none stated
Stated aim of study	To demonstrate the effect of vitamin D replacement on liver enzymes and inflammatory markers in NAFLD patients
Notes	Results were presented as an abstract. We were unable to find the address of the authors to contact them for the missing information. Study authors did not report any deaths. No information provided about adverse events.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors did not specify the method of sequence generation.

Boonyagard 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information was insufficient to assess whether missing data in combination with the method used to handle missing data was likely to induce bias on the results.
Selective reporting (reporting bias)	Unclear risk	The protocol was not available.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as competing interest bias.

Dabbaghmanesh 2018

Study characteristics	
Methods	Randomised double-blind placebo-controlled clinical trial with parallel-group design (3 groups)
Participants	**Country:** Iran **Number of participants randomised:** 106 participants (59% women), mean age 45 years **Inclusion criteria:** men and women aged between 20 and 75 years with presence of hepatic steatosis diagnosed by ultrasound **Exclusion criteria:** liver cirrhosis, with positive results for hepatitis B virus surface antigen or hepatitis C virus antibody, patients with alcohol consumption (> 10 g/day), patients with autoimmune hepatitis or other causes of chronic liver diseases such as Wilson's disease and haemochromatosis, known cancer, nephrolithiasis, nephrocalcinosis, chronic renal failure, hypercalcaemia, hypercalciuria, pregnancy, lactation, hypersensitivity to vitamin D_3, patients receiving oestrogen, tamoxifen, methotrexate, amiodarone, or tetracycline, and receiving vitamin D and calcium supplementations in previous 6 months
Interventions	**Intervention group 1:** vitamin D_3 (cholecalciferol) 50,000 IU pearl per week (n = 35) **Intervention group 2:** calcitriol 0.25 mg (1,25 dihydroxycholecalciferol) pearl per day (n = 35) **Control:** placebo (n = 36) For 12 weeks
Outcomes	**Primary outcomes:** reduction of serum ALT, AST, GGT from baseline to 12 weeks **Secondary outcomes:** improvement of metabolic component of participants including fasting plasma glucose, LDL, HDL, triglyceride, and total cholesterol

Dabbaghmanesh 2018 *(Continued)*

Stated aim of study	To investigate the role of vitamin D therapy in the amelioration of hepatic steatosis in people with NAFLD
Notes	Study authors did not report any deaths. No information provided about adverse events.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with a block size of 5 was used through a computer-based procedure.
Allocation concealment (selection bias)	Unclear risk	Study authors did not describe the method used to conceal the allocation, so the intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken. Quote: "Treatments and placebo were provided in identical packages and were given to the participants by an educated person who was blinded to the drug and patients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	The protocol was not available.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Esmat 2015

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	101 participants (25% women) aged 18 to 60 years, mean age 40 years, with chronic HCV genotype 4 **Inclusion criteria:** aged 18 to 60 years, chronic HCV infection genotype 4 for > 6 months by detectable serum quantitative HCV-RNA, naive to treatment, compensated liver disease with the following minimum haematological and biochemical criteria: haemoglobin ≥ 12 g/dL for men and ≥ 11 g/dL for women, WBC > 3500/mm^3, granulocyte count > 1500/mm^3, platelet count > 75,000/mm^3, albumin and thyroid function tests within normal limit, and antinuclear antibody ≤ 1:80. US-guided liver biopsy within 12 months prior to study entry, using a semiautomatic true-cut needle (16G) **Exclusion criteria:** other liver diseases, decompensated liver cirrhosis, hepatocellular carcinoma, liver biopsy contraindication, unsuitable for combined IFN and ribavirin treatment due to persistent haematological abnormalities, receiving medications known to affect vitamin D_3 level or metabolism (calcium, vitamin D supplementation, oestrogen, alendronate, isoniazid, thiazide diuretics, long-term antacids, calcium channel blockers, cholestyramine, anticonvulsants, and orlistat), clinically evident osteomalacia (waddling gait, bone pain, and pathological fractures), renal diseases or parathyroid diseases, and BMI > 35

Esmat 2015 *(Continued)*

Interventions	**Intervention:** vitamin D_3 15,000 IU/week + PEG-IFN-α-2b + ribavirin (n = 50) **Control:** placebo + PEG-IFN-α-2b + ribavirin (n = 51) PEG-IFN-α-2b (PegIntron, MSD) at 1.5 mg/kg subcutaneous injection once/week. Ribavirin (Rebetol, MSD) dose determined by body weight (< 75 kg 1000 mg/day; ≥ 75 kg 1200 mg/day in 2 separate oral doses after meals morning and night) for 48 weeks. Vitamin D_3 given as oral solution with juice once weekly for 48 weeks.
Outcomes	**Primary outcome:** SVR **Secondary outcome:** stage of hepatic fibrosis
Stated aim of study	To assess the role of vitamin D supplementation on response to treatment in people with chronic HCV 4 and its possible relation to stage of hepatic fibrosis
Notes	Study authors did not report any deaths. "None of the missed patients had stopped the treatment due to adverse events". Additional information received through personal communication with authors on 23 January 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Low risk	Allocation sequence hidden in sequentially numbered, opaque, and sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but we judged that outcomes were not likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but we judged that outcome measurements were not likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess whether missing data in combination with the method used to handle missing data was likely to induce bias
Selective reporting (reporting bias)	Unclear risk	Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Foroughi 2016

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	60 participants (52% women), aged 30 to 70 years, mean age 48.5 years with NAFLD

Foroughi 2016 *(Continued)*

	Inclusion criteria: NAFLD confirmed by US and normal range of ALT and AST (< 31 IU/L) **Exclusion criteria:** acute illnesses, chronic kidney disease, hyperparathyroidism, hypoparathyroidism, chronic heart failure, HCV or HBV, Wilson's syndrome, history of chronic liver diseases or disorders that affect gallbladder and bile ducts, pregnancy, history of taking any drugs affecting levels of ALT (e.g. valproic acid, tamoxifen, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, metformin, angiotensin-converting enzyme 1 and angiotensin-converting enzyme-related 1). Furthermore, participants should not have followed any special diet, and should not take oral vitamin D, calcium, or multivitamin supplements.
Interventions	**Intervention:** vitamin D_3 50,000 IU (n = 30) **Control:** placebo (n = 30) Weekly for 10 weeks
Outcomes	**Primary outcomes:** inflammatory markers, liver function, lipid profile, body composition, and liver steatosis **Secondary outcomes:** none stated
Stated aim of study	To investigate the effect of vitamin D supplementation on inflammation, liver function, and liver steatosis in people with NAFLD
Notes	All participants completed the trial. Clinical trial registered at Iranian Registry of Clinical Trials (IRCT2013060411763N8). Funded by Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported in full.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as competing interest bias.

Geier 2018

Study characteristics	
Methods	Randomised double-blind placebo-controlled clinical trial with parallel-group design (3 groups)
Participants	**Country:** Switzerland **Number of participants randomised:** 20 participants, mean age 45 years **Inclusion criteria:** increased alanine aminotransferase level (1.2-fold ULN), histological diagnosis of NASH diagnosed according to the SAF score obtained within 18 months preceding entry and decreased 25-OH vitamin D level (< 30 ng/L). The definition of NASH included non-excessive alcohol consumption as fewer than 21 standard drinks on average per week in males and fewer than 14 standard drinks on average per week in females. **Exclusion criteria:** cirrhosis, HCV RNA positivity, HBs antigen positivity, other liver disease including autoimmune hepatitis, hereditary haemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, drug-induced fatty liver disease, serious diseases limiting life expectancy, pregnancy or breastfeeding, intention to become pregnant during the course of the study, or childbearing potential in women who were not using safe contraception
Interventions	**Intervention:** 2100 IU vitamin D_3 (cholecalciferol) (n = 10) **Control:** placebo (n = 10) Orally daily for 48 weeks
Outcomes	**Primary outcomes:** change in ALT from baseline to end of treatment **Secondary outcomes:** absolute reduction of hepatic steatosis by at least 20% or by at least 1 point in NASH, serious adverse events, safety laboratory assessments, physical examination findings and vital signs
Stated aim of study	To investigate the efficacy and safety of 48-week treatment with vitamin D_3 in NASH patients
Notes	Study authors did not report any deaths. 2 serious adverse events were recorded: circular haemorrhoidal prolapse and bronchopneumonia. The study medication (vitamin D_3 2100 IU daily) and placebo were produced and provided by Antistress AG, Rapperswil-Jona, Switzerland.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study authors did not specify the method of sequence generation.
Allocation concealment (selection bias)	Low risk	A central and independent randomisation unit controlled the allocation. Quote: "Randomisation (stratified for the presence of diabetes, block size 10, not stratified by center) was performed by the Cantonal Pharmacy Zurich."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'

Geier 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	The trial was registered (NCT01571063; KEK-ZH-Nr. 2011-420).
Other bias	Unclear risk	Trial may or may not have been free of other factors that could have put it at risk of bias, such as competing interest bias.

Hosseini 2018

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	**Country:** Iran **Number of participants randomised:** 82 women, aged 18 to 50 years, mean age 34 years **Inclusion criteria:** BMI between 25 and 40 kg/m^2 with NAFLD confirmed by single ultrasonographist, vitamin D insufficiency (serum 25-hydroxyvitamin D < 30 ng/mL), not taking dietary supplements including calcium and vitamin D over the last 6 months **Exclusion criteria:** renal, hepatic, other endocrine disorders, malignancies, pregnancy and lactation, alcohol consumption, menopause condition, receiving medications influencing vitamin D metabolism or insulin
Interventions	**Intervention:** vitamin D_3 (cholecalciferol) 600,000 IU single intramuscular injection (n = 41) **Control:** no intervention (n = 41) All participants received pearl of vitamin E 400 IU/day for 1 month. Participants were followed up for 1 month.
Outcomes	**Primary outcomes:** changes in serum 25-hydroxyvitamin D, serum adiponectin, HOMA-IR, liver enzymes, and change in grade of NAFLD **Secondary outcomes:** change in anthropometric variables
Stated aim of study	To examine the effect of single intramuscular injection of 600,000 IU of cholecalciferol on serum levels of vitamin D, adiponectin, insulin resistance, and liver function status of women with NAFLD
Notes	Study authors did not report any deaths. No information provided about adverse events.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly assigned in the random blocks of four subjects using a computer Random Allocation Software, version 1, with stratification by age."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.

Hosseini 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	The trial was registered in the Iranian Registry of Clinical Trials with code number of IRCT201503163320N10.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Hussain 2019

Study characteristics	
Methods	Randomised double-blind placebo-controlled clinical trial with parallel-group design (2 groups)
Participants	**Country:** Pakistan **Number of participants randomised:** 109 (36% women), mean age 28 years **Inclusion criteria:** randomised selection based on age, sex, BMI > 28, fatty liver on sonographic findings, moderate increase in hepatic enzymes with altered serum lipid profile **Exclusion criteria:** pregnant and lactating women, smokers, type 2 diabetes, hypertension, chronic hepatitis B and C infection, alcoholic liver disease, chronic liver disease, decompensated liver disease and hepatocellular carcinoma, any history of cardiac, renal, and thyroid disorders, extremely abnormal ultrasound and liver enzymes that can indicate hereditary and autoimmune diseases of the liver
Interventions	**Intervention:** vitamin D_3 (cholecalciferol) 50,000 IU (n = 54) **Control:** placebo (n = 55) Orally, weekly for 12 weeks
Outcomes	**Primary outcomes:** body weight, BMI, insulin resistance, dyslipidaemia, hepatic enzymes, CRP, and adiponectin
Stated aim of study	To investigate the effects of oral vitamin D supplementation on body weight, BMI, insulin resistance, dyslipidaemia, hepatic enzymes, CRP, and adiponectin in NAFLD patients
Notes	Study authors did not report any deaths. No information provided about adverse events.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computed generated number was given to each patients based upon randomization."

Hussain 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess whether missing data in combination with the method used to handle missing data was likely to induce bias
Selective reporting (reporting bias)	Unclear risk	The trial was not registered. Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Jeong 2019

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	**Country:** Republic of Korea **Number of participants randomised:** 148 (49% women), aged 20 to 75 years, mean age 52 years **Inclusion criteria:** age 20 to 75 years, positive in hepatitis C virus-RNA PCR screening, normal serum calcium level before treatment, and HCV genotypes 1, 2, and 3 **Exclusion criteria:** HCC at enrolment or past history of HCC within last 1 year, decompensated cirrhosis (Child-Pugh class B or C), absolute neutrophil count < 1000/mm^3 or platelet count < 70,000/mm^3, serum creatinine level above 1.5 times to upper normal limit, present or past history of severe psychiatric diseases, parathyroid disease, uncontrolled thyroid disease, co-infection with other hepatitis virus or HIV, history of malignant diseases besides HCC within last 2 years, patients who were considered unfit to perform clinical trial, and pregnancy
Interventions	**Intervention:** PEG-IFN-α-2a 180 µg weekly plus RBV daily plus vitamin D 800 IU daily (n = 77) **Control:** PEG-IFN-α plus RBV (n = 71) Ribavirin was given orally daily in a dose of 1000 mg (body weight < 75 kg) or 1200 mg (body weight ≥ 75 kg) daily in genotype 1, or 800 mg in genotype 2 and 3. All participants were followed up 24 weeks after the completion of treatment.
Outcomes	**Primary outcomes:** rate of SVR **Secondary outcomes:** change in risk factors for SVR
Stated aim of study	To assess the role of vitamin D supplementation in response to PEG-IFN-α plus RBV treatment in naive patients with chronic hepatitis C

Jeong 2019 *(Continued)*

Notes	Study authors did not report any deaths. “Serious adverse events occurred in 10 patients, but all recovered.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors did not specify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	24 participants (33.8%) in the control group and 19 participants (24.7%) in the vitamin D group dropped out during the treatment period.
Selective reporting (reporting bias)	High risk	The study was registered at ClinicalTrials.gov (NCT01439776). No data about the early and rapid virological response
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as competing interest bias.

Jha 2017

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	**Country:** India **Number of participants randomised:** 101 (24% women), aged 18 to 70 years, mean age 45 years **Inclusion criteria:** decompensated cirrhosis of liver, Child Turcott Pugh (CTP) score ≥ 10, age between 18 years to 70 years **Exclusion criteria:** septicaemia, infection with HIV, episodes of variceal bleeding within 6 weeks, hepatocellular carcinoma or any malignancy, hepatorenal syndrome at the time of enrolment, significant cardiac and respiratory disease, pregnancy, patients being taken up for transplant, and refusal to participate in the study
Interventions	**Intervention:** vitamin D (cholecalciferol 300,000 IU) intramuscularly, single dose plus 800 IU and calcium 1000 mg daily (n = 51) **Control:** no intervention (n = 50) For 6 months

Jha 2017 *(Continued)*

Outcomes	**Primary outcomes:** all-cause mortality **Secondary outcomes:** clinical parameters, vitamin D level
Stated aim of study	To assess vitamin D levels in a cohort of patients with decompensated liver cirrhosis and the effect of vitamin D level replenishment on all-cause mortality in patients with vitamin D deficient decompensated cirrhosis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors did not specify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	The protocol was not available.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Komolmit 2017a

Study characteristics

Methods	Randomised double-blind, placebo-controlled clinical trial with parallel-group design (2 groups)
Participants	**Country:** Thailand **Number of participants randomised:** 80 (46% women), aged 18 to 70 years, mean age 52 years **Inclusion criteria:** patients with CHC **Exclusion criteria:** none stated
Interventions	**Intervention:** vitamin D_2 (ergocalciferol 60,000 to 100,000 IU (depending on vitamin D status)) (n = 40) **Control:** placebo (n = 40) Orally, weekly for 6 weeks

Komolmit 2017a *(Continued)*

	The dose of vitamin D_2 was based on the ranges of vitamin D deficiency, as follows: mild deficiency (20 to ≤ 30 ng/mL) 60,000 IU/week; moderate deficiency (10 to ≤ 20 ng/mL) 80,000 IU/week; and severe deficiency (≤ 10 ng/mL) 100,000 IU/week. Each vitamin D_2 capsule contained 20,000 units. The total dosage was divided into 2 separate doses given on Monday and Friday.
Outcomes	**Primary outcomes:** T-helper 1/2 cytokines, IP-10 and DPP-IV levels **Secondary outcomes:** vitamin D level
Stated aim of study	To assess the changes in serum levels T-helper cells associated cytokines, IP-10 and DPP-IV, without influences driven by interferon treatment, after a short-term period for correction of vitamin D deficiency in chronic hepatitis C patients
Notes	All participants completed the trial. The trial was conducted between April 2012 and April 2013.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was stratified with a 1:1 allocation using random block sizes of 4 based on computer generated method based (www.randomisation.com)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was performed by a research assistant without involvement in clinical trial. Details of the allocated group were given in sequentially numbered, opaque, sealed envelopes. After patient enrollment, the research assistant will open the envelope and inform stratified groups (A or B) to the investigators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The vitamin D_2 (Ergocalciferol) and placebo were prepared by a pharmacist in a capsule form and identical in appearance. They were prepacked in a bottle for six-week supplement and consecutively numbered for each CHC patient according to the randomised results."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values. All participants completed the trial.
Selective reporting (reporting bias)	Low risk	The trial was registered in the Thai Clinical Trials Registry, which was based on World Health Organization criteria under registration number TCTR20160429001.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could have put it at risk of bias, such as academic bias.

Komolmit 2017b

Study characteristics

Methods	Randomised double-blind, placebo-controlled clinical trial with parallel-group design (2 groups)
Participants	**Country:** Thailand

Komolmit 2017b *(Continued)*

	Number of participants randomised: 58 (38% women), aged 18 to 70 years, mean age 50 years **Inclusion criteria:** patients with CHC, naive cases or non-responder cases of CHC without decompensated cirrhosis, and serum 25-hydroxyvitamin D levels less than 30 ng/mL **Exclusion criteria:** decompensated cirrhosis, HIV infection, autoimmune diseases, active infections from other pathogens, a history of steroid or immunosuppressive therapy, or a history of interferon treatment within 12 months
Interventions	**Intervention:** vitamin D_2 (ergocalciferol 20,000 IU orally, weekly) (n = 29) **Control:** placebo (n = 29) For 6 weeks The dose of vitamin D_2 was based on the ranges of vitamin D deficiency, as follows: mild deficiency (20 to ≤ 30 ng/mL) 60,000 IU/week; moderate deficiency (10 to ≤ 20 ng/mL) 80,000 IU/week; and severe deficiency (≤ 10 ng/mL) 100,000 IU/week. Each vitamin D_2 capsule contained 20,000 units. The total dosage was divided into 2 separate doses given on Monday and Friday.
Outcomes	**Primary outcomes:** serum fibrotic markers **Secondary outcomes:** vitamin D level
Stated aim of study	To assess the dynamic changes in serum fibrogenic cytokines/enzymes in CHC patients with vitamin D deficiency after short-term supplementation with vitamin D
Notes	All participants completed the trial. The trial was conducted between February and December 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The enrolled patients were randomized into two groups with a 1:1 allocation using a random block size of 4, which was generated by computer software based on www.randomisation.com."
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was performed by a research assistant who was not involved in the clinical trial. Upon enrollment, the patients were stratified into two groups (A and B) with the details of the drugs placed in sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Vitamin D_2 and a placebo were prepared in identical capsules of the same weight by the Department of Pharmacy at King Chulalongkorn Memorial Hospital. All investigators and patients were blinded to the type of medication used until the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	The clinical trial was retrospectively registered with the Thai Clinical Trials Registry, based on World Health Organization criteria on 2 November 2016 (TCTR20161103003).

Komolmit 2017b *(Continued)*

Other bias	Unclear risk	Trial may or may not have been free of other factors that could have put it at risk of bias, such as academic bias.

Lorvand Amiri 2016

Study characteristics

Methods	Randomised clinical trial with parallel-group design (3 groups)
Participants	120 participants (38% women), aged 18 to 65 years, mean age 41 years, with NAFLD **Inclusion criteria:** BMI 25 kg/m^2 to 35 kg/m^2, serum 25-hydroxyvitamin D_3 level < 15 ng/mL, reporting a daily calcium intake 700 mg/day to 800 mg/day, and willingness to introduce a dietary change to lose weight **Exclusion criteria:** calcium intake < 700 mg/day or > 800 mg/day (in diet or as a supplement); drugs for blood glucose or lipid control; pregnancy or having given birth in the past year or planning a pregnancy in the next 6 months; lactation; weight loss ≥ 10% of body weight within the 6 months before enrolment; participation in competitive sport; abnormal thyroid hormone concentration; intake of medications that could affect body weight or energy expenditure (or both); allergy; smoking; diagnosis of chronic diseases including inflammatory diseases; heart, liver, and renal failure; cancer; acute myocardial infarction; diabetes; stroke; or serious injuries and any other conditions that were not suitable for the trial as evaluated by the physician
Interventions	**Intervention 1:** vitamin D 25 µg/day as cholecalciferol (Jalinus Arya Co, Iran) + calcium carbonate placebo (25 mg/day as lactose; Jalinus Arya Co, Iran) (n = 40) **Intervention 2:** vitamin D 25 µg/day as cholecalciferol (Jalinus Arya Co, Iran) + calcium (500 mg/day as calcium carbonate; Jalinus Arya Co, Iran) (n = 40) **Control:** placebo of calcitriol + placebo of calcium (25 mg/day as lactose; Jalinus Arya Co, Iran) (n = 40) After lunch with a glass of water for 12 weeks
Outcomes	**Primary outcomes:** weight loss, body fat, fasting plasma glucose, serum insulin concentrations, lipid profiles, and liver function tests **Secondary outcomes:** carbohydrate and lipid metabolism
Stated aim of study	To compare the effect of vitamin D supplementation with and without calcium on anthropometric measures and biochemical parameters in people with NAFLD during a weight-loss programme
Notes	Study authors did not report any deaths. No information provided about adverse events. Clinical trial registered at Iranian Registry of Clinical Trials (IRCT201408312709N29). Trial did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Additional information received through personal communication with authors on 20 January 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned using computer-generated random-numbers method by project co-ordinator.
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation controlled by a central and independent randomisation unit.

Lorvand Amiri 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Products administered by blinded research assistant to blinded participants. Shape, colour, and packaging of placebo similar to supplements in the intervention group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported in full.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as competing interest bias.

Mobarhan 1984

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (3 groups)
Participants	18 men, aged 32 to 61 years, mean age 52 years, with alcoholic cirrhosis **Inclusion criteria:** men with advanced biopsy-confirmed alcoholic cirrhosis with low levels of serum 25-hydroxyvitamin D (< 20 ng/mL) and decreased bone density (i.e. > 1.5 standard deviations below mean of healthy Baltimore men of same ages) **Exclusion criteria:** history of corticosteroid, anticonvulsant, or vitamin D intake; renal disease
Interventions	**Intervention 1:** vitamin D_2 50,000 IU 2 or 3 times weekly (n = 6) **Intervention 2:** 25-hydroxyvitamin D_3 800 IU/day to 2000 IU/day (prepared and supplied as identical soft elastic capsules (20 or 50 µg) by Upjohn Co) (n = 6) **Control:** no intervention (n = 6) For 1 year
Outcomes	Outcomes reported in abstract of publication **Primary outcomes:** bone mineral density **Secondary outcomes:** none stated
Stated aim of study	To compare the efficacy of 25-hydroxyvitamin D_3 or vitamin D_2 in correcting the bone disease of people with alcoholic cirrhosis
Notes	This study was supported by grants from Upjohn Co and the Veterans Administration.
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Mobarhan 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	All clinically relevant and reasonably expected outcomes were reported.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Nimer 2012

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	50 participants (58% women), mean age 47 years, with chronic HCV genotype 2 or 3 **Inclusion criteria:** aged 18 to 65 years; chronic genotype 2 or 3 HCV infection; no previous treatment for HCV; seronegative for HBV, hepatitis A virus, and HIV infection; absolute neutrophil count > 1500/mm^3; platelet count > 90,000/mm^3; and normal haemoglobin level. Liver biopsies not required prior to study entrance. **Exclusion criteria:** decompensated liver disease (cirrhosis with Child-Pugh score > 9), another cause of clinically significant liver disease, or presence of hepatocellular carcinoma
Interventions	**Intervention:** PEG-IFN-α-2a 180 µg weekly + oral ribavirin 800 mg/day + oral vitamin D_3 2000 IU/day (Vitamidyne D, Fischer Pharmaceuticals, Israel), given by oral drops (n = 20) **Control:** PEG-IFN-α-2a 180 µg weekly + oral ribavirin 800 mg/day (n = 30) For 24 weeks
Outcomes	Outcomes reported in abstract of publication **Primary outcome:** SVR defined as undetectable HCV-RNA at 24 weeks' post-treatment **Secondary outcomes:** treatment efficacy at weeks 4 (RVR) and 12 (EVR) during therapy, and 24 weeks after cessation of therapy (SVR)
Stated aim of study	To assess prospectively the influence of vitamin D supplementation on SVR in the treatment of people with chronic HCV with HCV genotype 2-3

Nimer 2012 *(Continued)*

Notes	All participants completed the trial. Additional information received through personal communication with authors on 8 February 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation performed using computer random number generation.
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation sequence hidden in sequentially numbered, opaque, and sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and outcomes are likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, and outcome measurements are likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Pilz 2016

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	36 participants (25% women), aged 18 to 75 years, mean age 61 years, with liver cirrhosis **Inclusion criteria:** compensated cirrhosis, 25-hydroxyvitamin D < 30 ng/mL, aged 18 to 75 years, and a negative pregnancy test in women of childbearing potential **Exclusion criteria:** presence of hepatocellular carcinoma, hypercalcaemia (plasma calcium concentrations > 2.65 mmol/L), pregnant or lactating women, drug intake as part of another clinical study, estimated glomerular filtration rate according to Modification of Diet in Renal Disease formula < 15 mL/min/1.73 m^2, any clinically significant acute disease requiring drug treatment, regular intake (in addition to study medication) of vitamin D > 800 IU daily during the last 4 weeks before study entry
Interventions	**Intervention:** vitamin D_3 2800 IU/day (Oleovit D3, Fresenius Kabi, Austria) (n = 18) **Control:** placebo daily (n = 18) For 8 weeks
Outcomes	**Primary outcome:** vitamin D status

Pilz 2016 *(Continued)*

	Secondary outcomes: liver function tests (i.e. AST, ALT, gamma glutamyl transpeptidase, and alkaline phosphatase), albumin, international normalised ratio, bilirubin, and hyaluronic acid; and parameters of mineral metabolism (i.e. parathyroid hormone, total plasma calcium, free plasma calcium, urinary midstream calcium to creatinine ratio, and plasma phosphate)
Stated aim of study	To evaluate the effects of vitamin D supplementation on 25-hydroxyvitamin D, parameters of liver function and synthesis, and hyaluronic acid as a marker of liver fibrosis
Notes	"No patient died during the study and there was no excess of adverse events in the vitamin D group." Study sponsored by the Medical University of Graz, Austria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation performed using computer random number generation.
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Central and independent randomisation unit controlled allocation. Investigators were unaware of allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and it is unlikely that blinding could have been broken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could put it at risk of bias, such as small-trial bias.

Sakpal 2017

Study characteristics

Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	**Country:** India 81 participants (32% women), aged > 12 years, mean age 38 years with NAFLD **Inclusion criteria:** patients with NAFLD aged > 12 years, non-alcoholic individuals defined as either total abstainers or individuals who consumed less than 20 g of alcohol per day, ultrasound showing features of steatosis, with or without raised ALT (> 40 IU/L), and negative viral markers (hepatitis B surface antigen and anti-hepatitis C virus), patients with raised ALT who had negative autoimmune markers (antinuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody, and an-

Sakpal 2017 *(Continued)*

	timitochondrial antibody) and normal ceruloplasmin/negative Kayser–Fleischer ring with normal iron workup (serum iron, total iron-binding capacity, ferritin, and transferrin saturation) **Exclusion criteria:** pregnant females, patients with a history of drug intake likely to cause NAFLD, patients with jejunoileal bypass or extensive small bowel resection or total parenteral nutrition at the time of liver biopsy, and those with clinical, laboratory, and imaging features of cirrhosis of liver and patients with renal, hepatic, respiratory, or congestive cardiac failure
Interventions	**Intervention:** vitamin D single intramuscular injection 600,000 IU with lifestyle modifications (n = 51) **Control:** lifestyle modifications (n = 30) Participants were treated and followed up for 6 months. Lifestyle modifications in both groups included moderate-to-vigorous exercise in the form of brisk walking, jogging, swimming, cycling, etc. for 45 to 60 min at least 5 days per week in all participants, and calorie reduction (1000 to 1200 kcal/day for overweight women and 1200 to 1600 kcal/day for overweight men and heavier or more active women) in overweight and obese subjects.
Outcomes	**Primary outcomes:** insulin resistance and serum ALT **Secondary outcomes:** serum levels of adiponectin and tumour necrosis factor-α
Stated aim of study	To evaluate the effect of vitamin D supplementation in patients with NAFLD
Notes	All participants completed the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	Trial protocol was not available.
Other bias	Unclear risk	Trial may or may not have been free of other factors that could have put it at risk of bias, such as competing interest bias.

Sharifi 2014

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	60 (51% women), aged 18 to 70 years, mean age 42 years, with NAFLD **Inclusion criteria:** diagnosis of NAFLD by US and increased serum levels of ALT (> 19 units/L for women and 30 units/L for men) **Exclusion criteria:** alcohol consumption > 20 g/day; pregnant and lactating women; hereditary haemochromatosis; Wilson's disease; α1-antitrypsin deficiency; history of jejunoileal bypass surgery or gastroplasty; using total parenteral nutrition in the past 6 months; taking hepatotoxic drugs such as calcium channel blocker, high doses of synthetic oestrogens, methotrexate, amiodarone, and chloroquine; history of hypothyroidism, Cushing's syndrome, renal failure, and kidney stones; serum calcium levels > 10.6 mg/dL; and intake of vitamin D, vitamin E, and calcium supplements during the last 6 months
Interventions	**Intervention:** vitamin D_3 50,000 IU (D-Vitin Zahravi Pharm Co, Tabriz, Iran) (n = 30) **Control:** placebo (Zahravi Pharm Co) (n = 30) Every 14 days for 4 months
Outcomes	**Primary outcomes:** changes in serum ALT and changes in insulin resistance index **Secondary outcomes:** other liver enzymes, oxidative stress, and inflammatory biomarkers
Stated aim of study	To determine the effect of vitamin D supplementation on serum liver enzymes, insulin resistance, oxidative stress, and inflammatory biomarkers in people with NAFLD
Notes	Study authors did not report any deaths. “Participants did not report any adverse or side effects such as hypercalcemia.” Study financially supported by grant (No. RDC-9105) from Vice-Chancellor for Research Affairs of Jundishapur University of Medical Sciences and approved by the Research Institute for Infectious Diseases of the Digestive System, Jundishapur University of Medical Sciences, Ahvaz, Iran.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study authors performed sequence generation using computer random number generation.
Allocation concealment (selection bias)	Low risk	An investigator with no clinical involvement in the trial packed the supplements and placebos in numbered bottles based on the random list. Another person, who was not involved in the trial and not aware of random sequences, assigned the participants to the numbered bottles of pearls.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
Incomplete outcome data (attrition bias)	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.

Sharifi 2014 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	It was unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported.
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Shiomi 1999a

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	76 participants (66% women), aged 38 to 84 years, mean age 61 years, with cirrhosis and an underlying infection of liver (HBV and HCV) **Inclusion criteria:** liver cirrhosis and an underlying infection of the liver (HBV and HCV) **Exclusion criteria:** none stated
Interventions	**Intervention:** calcitriol 0.5 µg twice daily (n = 38) **Control:** no intervention (n = 38) For 1 year
Outcomes	Outcomes reported in abstract of publication **Primary outcome:** bone mineral density of the lumbar vertebrae **Secondary outcomes:** none stated
Stated aim of study	To evaluate the efficacy of calcitriol (1,25-dihydroxyvitamin D) in the treatment of bone disease associated with cirrhosis and an underlying hepatitis viral infection
Notes	All participants completed the trial. Additional information received through personal communication with the authors on 12 February 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Low risk	Allocation sequence hidden in sequentially numbered, opaque, and sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and outcome measurement is likely to have been influenced by lack of blinding

Shiomi 1999a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	High risk	Not all predefined outcomes were reported in full.
Other bias	Unclear risk	Trial may or may not have been free of other components that could put it at risk of bias, such as competing interest bias.

Shiomi 1999b

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	34 women, aged 36 to 72 years, mean age 56 years, with primary biliary cirrhosis **Inclusion criteria:** primary biliary cirrhosis **Exclusion criteria:** none stated
Interventions	**Intervention:** calcitriol 0.5 µg twice a day (n = 17) **Control:** no intervention (n = 17) For 1 year
Outcomes	Outcomes reported in abstract of publication **Primary outcome:** bone mineral density **Secondary outcomes:** none stated
Stated aim of study	To evaluate the efficacy of calcitriol (1,25-dihydroxyvitamin D) in the treatment of bone disease associated with primary biliary cirrhosis
Notes	All participants completed the trial. Additional information received through personal communication with authors on 12 February 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Method used to conceal allocation not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessment, and outcome measurement is likely to have been influenced by lack of blinding

Shiomi 1999b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	High risk	Not all predefined outcomes reported in full.
Other bias	Unclear risk	Trial may or may not have been free of other components that could put it at risk of bias, such as competing interest bias.

Taghvaei 2018

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	40 participants (50% women), aged between 30 to 70 years, mean age 42 years with NAFLD **Inclusion criteria:** age above 18 years, increased levels of alanine aminotransferase level (more than 30 in women and 40 in men), a diagnosis of NAFLD and ruling out other causes of increased liver enzymes, and vitamin D level less than 30 ng/mL **Exclusion criteria:** the presence of liver cirrhosis, pregnancy and lactation, alcohol consumption, drug abuse, administration of vitamins in the last 6 months and during the study, weight loss more than 5% over a year before entering the study, diabetes mellitus, weight-lowering medications, hypercalcaemia, chronic kidney disease, end-stage heart and lung disease, history of hyperlipidaemia which required treatment, history of medical therapies with impact on liver enzymes such as acetaminophen, statins, azathioprine, antibiotics such as sulfonamide and penicillin, amiodarone, methotrexate, anticonvulsants, isoniazid, steroids, and herbal medicines
Interventions	**Intervention:** vitamin D_3 50,000 IU weekly plus lifestyle modification (n = 20) **Control:** lifestyle modification (n = 20) For 12 weeks. Participants were followed up for 6 months.
Outcomes	**Primary outcomes:** biochemical indices (ALT, AST, alkaline phosphatase, fasting blood sugar, triglycerides, cholesterol, LDL, creatinine, calcium, vitamin D) and level of liver steatosis on the basis of CAP score and fibrosis **Secondary outcomes:** none stated
Stated aim of study	"Investigating the effects of vitamin D on NAFLD."
Notes	All participants completed the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random allocation of the patients in each group was performed using a random number table."
Allocation concealment (selection bias)	Unclear risk	Method used to conceal allocation not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.

Taghvaei 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Subjects and all study staffs were blinded to treatment group assignments."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	The research was also registered in Iranian Registry of Clinical Trials (2015102624725n1).
Other bias	Unclear risk	Trial may or may not have been free of other components that could put it at risk of bias, such as competing interest bias.

Vosoghinia 2016

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	68 participants (13% women), mean age 42 years, with chronic HCV genotype 1, 2, 3, 4 **Inclusion criteria:** adult patients with chronic HCV infection (> 6 months) and detectable serum levels of HCV RNA (genotype 1, 2, 3, or 4) with compensated liver disease fulfilling the following criteria: absolute neutrophil count above 1500/mm^3, platelet count above 90,000/mm^3, and normal haemoglobin level **Exclusion criteria:** co-infection with hepatitis B virus or HIV, decompensated liver disease (Child-Pugh classification B or C), autoimmune or metabolic liver disease, hepatocellular carcinoma, a history of anti-HCV therapy or use of medications which alter vitamin D_3 levels or metabolism (calcium, vitamin D supplementation, oestrogen, alendronate, isoniazid, anticonvulsants, and orlistat), a history of diarrhoea or malabsorption syndromes such as coeliac and chronic pancreatitis, or those with renal or parathyroid diseases
Interventions	**Intervention:** PEG-IFN-α-2a (180 µg) + oral ribavirin (Rebetol, MSD), at dosage determined based on participant's weight and genotype, was administered for 48 weeks in participants with genotypes 1 and 4 and for 24 weeks in those with genotypes 2 and 3, and vitamin D_3 1600 IU/day (n = 34) **Control:** PEG-IFN-α-2a (180 µg) + oral ribavirin (Rebetol, MSD), at dosage determined based on participant's weight and genotype PEG-IFN-α-2a was administered for 48 weeks in participants with genotypes 1 and 4 and for 24 weeks in those with genotypes 2 and 3 (n = 34). Vitamin D_3 was administered for 12 weeks.
Outcomes	**Primary outcome:** EVR defined as undetectable HCV-RNA at 12 weeks' post-treatment
Stated aim of study	To assess the influence of vitamin D supplementation on viral response to PEG-IFN/RBV therapy

Vosoghinia 2016 *(Continued)*

Notes	The research council of Mashhad University of Medical Sciences, Mashhad, Iran financially supported this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Low risk	Participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation sequence hidden in sequentially numbered, opaque, and sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and the outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	Registered under Iranian Registry of Clinical Trials Identifier no. IRCT201408312709N29. All predefined outcomes reported in full.
Other bias	Unclear risk	Trial may or may not have been free of other components that could put it at risk of bias, such as competing interest bias.

Xing 2013

Study characteristics

Methods	Randomised clinical trial with parallel-group design (3 groups)
Participants	75 participants (17% women), aged 28 to 65 years, mean age 48 years, undergoing liver transplantation **Inclusion criteria:** primary liver transplant recipients **Exclusion criteria:** history of corticosteroid, anticonvulsant, or vitamin D intake; renal disease
Interventions	**Intervention 1:** calcitriol 0.25 µg/day + calcium gluconate (n = 25) **Intervention 2:** calcium gluconate (n = 25) **Control:** placebo (n = 25) For 1 month
Outcomes	Outcomes reported in abstract of publication **Primary outcomes:** acute cellular rejection rate at 1 month post-transplant

Xing 2013 *(Continued)*

	Secondary outcomes: none stated
Stated aim of study	To investigate the effects of calcitriol on acute cellular rejection rate of liver transplant recipients
Notes	All participants completed the trial. Study sponsored by grants from Shanghai Nature Science Fund project and Science and Technology Department of Shanghai. Additional information received through personal communication with the authors on 13 February 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Method used to conceal allocation not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

Yokoyama 2014

Study characteristics	
Methods	Randomised clinical trial with parallel-group design (2 groups)
Participants	84 participants (49% women), aged 30 to 78 years, mean age 59 years, with HCV genotype 1b **Inclusion criteria:** aged ≥ 20 years, chronically infected with HCV genotype 1 and plasma HCV RNA concentrations ≥ 100 log IU/mL **Exclusion criteria:** decompensated cirrhosis, liver cancer, HBV or HIV infection, renal insufficiency, history of heart disease or cerebral infarction, pregnancy or breastfeeding
Interventions	**Intervention:** subcutaneous injections of PEG-IFN-α-2b (1.5 µg/kg body weight) once weekly, along with weight-based oral ribavirin (600 mg/day to 1200 mg/day) + vitamin D_3 1000 IU (n = 42) **Control:** subcutaneous injections of PEG-IFN-α-2b (1.5 µg/kg body weight) once weekly, along with weight-based oral ribavirin (600 mg/day to 1200 mg/day) (n = 42)

Yokoyama 2014 *(Continued)*

	For 16 weeks
Outcomes	**Primary outcome:** undetectable HCV RNA at week 24 **Secondary outcomes:** none stated
Stated aim of study	To rigorously evaluate the antiviral effects of vitamin D supplementation in people with HCV genotype-1 infection being treated with PEG-IFN + ribavirin
Notes	No serious side effects were observed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation not described, so intervention allocations may have been foreseen before, or during, enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, and outcome is likely to have been influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment, and outcome measurement is likely to have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Unclear risk	Unclear whether all predefined and clinically relevant and reasonably expected outcomes were reported
Other bias	Low risk	Trial appeared to be free of other factors that could put it at risk of bias.

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CAP: controlled attenuation parameter
CHC: chronic hepatitis C
CRP: C-reactive protein
DPP-IV: dipeptidyl peptidase IV
EVR: early virological response
GGT: gamma-glutamyl transferase
HBs: hepatitis B surface
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HDL: high-density lipoprotein
HDV: hepatitis D virus
HOMA-IR: homeostatic model assessment for insulin resistance
IFN: interferon
IP-10: interferon gamma-induced protein 10
IU: international unit

kcal: kilocalorie
LDL: low-density lipoprotein
MRI: magnetic resonance imaging
n: number of participants
NAFLD: non-alcoholic fatty liver disease
NASH: non-alcoholic steatohepatitis
PCR: polymerase chain reaction
PEG: pegylated
RBV: ribavirin
RNA: ribonucleic acid
RVR: rapid viral response
SAF: steatosis-activity-fibrosis
SVR: sustained virological response
ULN: upper limit of normal
US: ultrasound
VD: vitamin D
WBC: white blood cell count

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

Study	Reason for exclusion
Atsukawa 2013	Not a randomised trial
Benetti 2008	Not a randomised trial
Bitetto 2010	Not a randomised trial
Chen 2015	Not a randomised trial
Dasarathy 2017	Not a randomised trial
Fernández Fernández 2016	Not a randomised trial
Floreani 2007	Not a randomised trial
Hasanain 2018	Did not fulfil inclusion criteria. This trial included antituberculosis `therapy-induced` liver disorders amongst naive patients with pulmonary tuberculosis.
Kitson 2016	Not a randomised trial
Kondo 2013	Not a randomised trial
Ladero 2013	Not a randomised trial
Long 1978	Not a randomised trial
Malham 2012	Not a randomised trial
Naderpoor 2018	Did not fulfil inclusion criteria. This trial included overweight or obese adults without chronic liver diseases.
Omori-Mizuno 2015	Not a randomised trial
Papapostoli 2016	Not a randomised trial
Park 2017	Not a randomised trial

Study	Reason for exclusion
Rode 2010	Not a randomised trial
Stokes 2016	Not a randomised trial
Tavakoli 2019	Did not fulfil inclusion criteria. This trial included adolescent girls.
Terrier 2015	Not a randomised trial
Zhou 2019	Not a randomised trial

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

IRCT2016020326342N1

Study name	Effectiveness of vitamin D supplementation on severity of cirrhosis based on CHILD and MELD scores in patients with decompensate cirrhosis
Methods	Randomised clinical trial using parallel-group design (2 groups)
Participants	**Country:** Iran **Estimated number of participants:** 80 **Inclusion criteria:** people with HIV, renal failure due to reasons other than liver failure, malabsorption such as chronic diarrhoea, coeliac disease, chronic pancreatitis; people undergoing corticosteroid treatment; pregnancy; and people with cirrhosis secondary to cholestasis such as primary biliary cirrhosis
Interventions	**Intervention:** vitamin D_3 (50,000 IU) and popular drugs using for liver cirrhosis **Control:** popular drugs using for liver cirrhosis Daily for 3 months
Outcomes	**Primary outcome:** liver function measured by Model for End-Stage Liver Disease score **Secondary outcomes:** liver function measured by Child-Turcotte-Pugh score
Starting date	March 2016
Contact information	Hossein Ali Abbasi, Emam Reza Hospital, Emam Reza Square, Ebne Sina Avenue, Mashhad, Iran hoseinabbasi1342@yahoo.com
Notes	

NCT02779465

Study name	Study of oral vitamin D treatment for the prevention of hepatocellular carcinoma in patients with chronic hepatitis B
Methods	Randomised clinical trial using parallel-group design (2 groups)
Participants	**Country:** China

NCT02779465 *(Continued)*	**Estimated number of participants:** 1500 **Inclusion criteria:** age 18 to 70 years; with chronic hepatitis B and under the oral antivirus treatment; no evidence of hepatocellular carcinoma on entry imaging study; Model for End-Stage Liver Disease score < 22; not currently participating in another intervention study; not pregnant or lactating, and willing to use effective contraception during study period; absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; and ability to provide written informed consent according to national or local regulations **Exclusion criteria:** evidence of hepatocellular carcinoma within 6 months after enrolment, serum alanine aminotransferase level > 10 times the upper limit of normal, elevated serum creatinine level, diagnosis of kidney stones, diagnosis of hyperparathyroidism or other serious disturbance of calcium metabolism in past 5 years, evidence of autoimmune hepatitis, co-infection with hepatitis C or D virus or HIV, other serious concurrent illness (e.g. alcoholism, uncontrolled diabetes, cancer), treatment with immunomodulatory agent within 6 months before screening, treatment with any investigational drug within 30 days before the study began
Interventions	**Intervention:** vitamin D_3 800 IU/day besides the antivirus treatment with nucleos(t)ide medicine **Control:** no intervention For 1 year
Outcomes	**Primary outcomes:** change in serum levels of 25-hydroxyvitamin D at baseline and at 6 and 12 months, and change in serum levels of 25-hydroxyvitamin D at 6 and 12 months compared to baseline **Secondary outcomes:** change in serum creatinine at baseline and at 6 and 12 months; change in serum creatinine at 6 and 12 months compared to baseline; change in fibrosis score at baseline and at 6 and 12 months; fibrosis score at 6 and 12 months compared to baseline; number of participants on vitamin D treatment with adverse events
Starting date	June 2016
Contact information	Yutian Chong, MD, Third Affiliated Hospital, Sun Yat-Sen University ytchongkyzy@126.com
Notes	

IU: international unit

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 1.1 All-cause mortality	27	1979	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.51, 1.45]
1.1.1 Non-alcoholic fatty liver disease	11	803	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.1.2 Chronic hepatitis C	10	836	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.3 Liver cirrhosis	5	265	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.55]
1.1.4 Liver transplant recipients	1	75	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 1.1 All-cause mortality according to vested interest	27	1979	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.51, 1.45]
1.2.1 Trials with vested interest	2	38	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.15, 48.64]
1.2.2 Trials without vested interest	25	1941	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.48, 1.41]
1.3 All-cause mortality according to vitamin D status at entry	27	1979	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.51, 1.45]
1.3.1 Normal vitamin D status	8	549	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.13]
1.3.2 Low vitamin D status	19	1430	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.55]
1.4 All-cause mortality according to form of vitamin D	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Vitamin D_3	20	1578	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.48, 1.41]
1.4.2 Vitamin D_2	3	150	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.15, 61.74]
1.4.3 1,25-dihydroxyvitamin D	4	291	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4.4 25-hydroxyvitamin D	1	12	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.15, 61.74]
1.5 All-cause mortality (best-worst-case and worst-best-case scenarios)	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Best-worst-case scenario	24	1737	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.06, 0.30]
1.5.2 Worst-best-case scenario	24	1737	Risk Ratio (M-H, Random, 95% CI)	7.95 [3.55, 17.77]
1.6 Liver-related mortality	1	18	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.08, 34.66]
1.7 Serious adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Hypercalcaemia	1	76	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 100.80]
1.7.2 Myocardial infarction	2	86	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.08, 6.81]
1.7.3 Thyroiditis	1	68	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.91]
1.7.4 Circular haemorrhoidal prolapse	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.7.5 Bronchopneumonia	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]

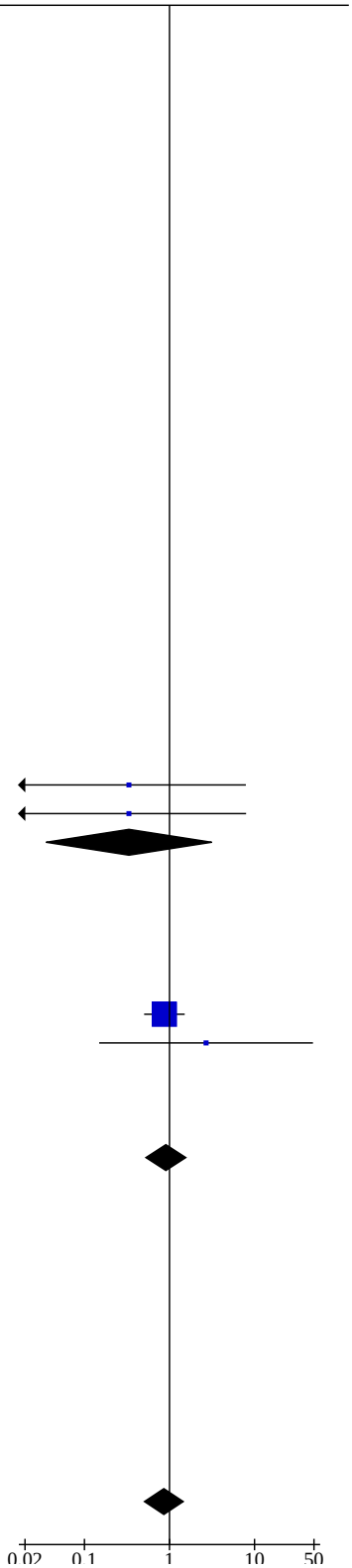
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Liver-related morbidity	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.9 Health-related quality of life	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.10 Non-serious adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 Glossitis	1	65	Risk Ratio (M-H, Random, 95% CI)	3.70 [0.16, 87.58]
1.10.2 Depression	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.3 Lower back pain	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.4 Abdominal bloating	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.5 Cold	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.6 Constipation	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.7 Sore throat	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.8 Sour taste in mouth	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.9 Contused lacerated wound	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.10 Multiple white matter lesions	1	20	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.02, 7.32]
1.10.11 Gastro-oesophageal reflux	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.12 Abdominal menstrual cramps	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.13 Tubular colon adenoma	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.14 Gastric motility disturbance	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.15 Irritable bowel syndrome	1	20	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.27, 92.62]
1.10.16 Knee pain	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
1.10.17 Severe allergy	1	109	Risk Ratio (M-H, Random, 95% CI)	5.09 [0.25, 103.64]
1.11 Failure of rapid virological response	3	247	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.60, 0.95]
1.12 Failure of early virological response	4	315	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13 Failure of sustained virological response	7	630	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.42, 1.01]
1.14 Acute cellular rejection in liver transplant recipients	1	75	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.62]
1.15 Vitamin D status (ng/mL)	15	1078	Mean Difference (IV, Random, 95% CI)	18.49 [14.52, 22.47]
1.16 Bone mineral density (g/cm)	1	18	Mean Difference (IV, Random, 95% CI)	0.15 [0.04, 0.26]
1.17 Aspartate aminotransferase (IU/L)	12	774	Mean Difference (IV, Random, 95% CI)	-1.75 [-5.41, 1.91]
1.18 Alanine aminotransferase (IU/L	13	855	Mean Difference (IV, Random, 95% CI)	-2.30 [-7.60, 3.00]
1.19 Alkaline phosphatases (IU/L)	6	344	Mean Difference (IV, Random, 95% CI)	-0.95 [-15.10, 13.20]
1.20 Gamma-glutamyl transpeptidase (IU/L)	4	227	Mean Difference (IV, Random, 95% CI)	-2.69 [-5.26, -0.11]
1.21 Bilirubin (mg/dL)	3	74	Mean Difference (IV, Random, 95% CI)	0.32 [0.00, 0.63]
1.22 Triglyceride (mg/dL)	5	460	Mean Difference (IV, Random, 95% CI)	11.27 [-10.99, 33.53]
1.23 Cholesterol (mg/dL)	4	400	Mean Difference (IV, Random, 95% CI)	3.51 [-2.83, 9.85]
1.24 LDL cholesterol (mg/dL)	4	400	Mean Difference (IV, Random, 95% CI)	-0.97 [-8.70, 6.76]
1.25 Albumin (g/L)	3	74	Mean Difference (IV, Random, 95% CI)	-1.18 [-2.96, 0.59]
1.26 HDL cholesterol (mg/dL)	4	400	Mean Difference (IV, Random, 95% CI)	1.14 [-0.64, 2.92]
1.27 Calcium (mg/dL)	7	423	Mean Difference (IV, Random, 95% CI)	0.04 [-0.12, 0.19]
1.28 Glucose (mg/dL)	6	469	Mean Difference (IV, Random, 95% CI)	1.44 [-5.05, 7.94]
1.29 Phosphorus (mg/dL)	4	307	Mean Difference (IV, Random, 95% CI)	0.17 [-0.16, 0.50]
1.30 Adiponectin (µg/mL)	4	276	Mean Difference (IV, Random, 95% CI)	1.02 [-0.27, 2.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.31 Insulin (mIU/mL)	6	428	Mean Difference (IV, Random, 95% CI)	0.03 [-1.15, 1.21]
1.32 Parathyroid hormone (pg/mL)	2	118	Mean Difference (IV, Random, 95% CI)	-15.18 [-38.54, 8.18]
1.33 C-reactive protein (mg/L)	4	254	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.93, -0.07]

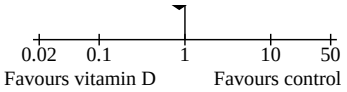
Analysis 1.1. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 1: 1.1 All-cause mortality

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Non-alcoholic fatty liver disease						
Barchetta 2016	0	29	0	36		Not estimable
Boonyagard 2016	0	30	0	30		Not estimable
Dabbaghmanesh 2018	0	70	0	36		Not estimable
Foroughi 2016	0	30	0	30		Not estimable
Geier 2018	0	10	0	10		Not estimable
Hosseini 2018	0	41	0	41		Not estimable
Hussain 2019	0	54	0	55		Not estimable
Lorvand Amiri 2016	0	80	0	40		Not estimable
Sakpal 2017	0	51	0	30		Not estimable
Sharifi 2014	0	30	0	30		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Subtotal (95% CI)		**445**		**358**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 Chronic hepatitis C						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	0	57	0	58		Not estimable
Behera 2018	0	28	0	32		Not estimable
Esmat 2015	0	50	0	51		Not estimable
Jeong 2019	0	77	0	71		Not estimable
Komolmit 2017a	0	40	0	40		Not estimable
Komolmit 2017b	0	29	0	29		Not estimable
Nimer 2012	0	20	0	30		Not estimable
Vosoghinia 2016	0	34	1	34	2.7%	0.33 [0.01 , 7.91]
Yokoyama 2014	0	42	1	42	2.7%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**413**		**423**	**5.5%**	**0.33 [0.04 , 3.13]**
Total events:	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.1.3 Liver cirrhosis						
Jha 2017	16	51	18	50	91.2%	0.87 [0.50 , 1.51]
Mobarhan 1984	2	12	0	6	3.3%	2.69 [0.15 , 48.64]
Pilz 2016	0	18	0	18		Not estimable
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Subtotal (95% CI)		**136**		**129**	**94.5%**	**0.91 [0.53 , 1.55]**
Total events:	18		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.1.4 Liver transplant recipients						
Xing 2013	0	25	0	50		Not estimable
Subtotal (95% CI)		**25**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1019**		**960**	**100.0%**	**0.86 [0.51 , 1.45]**
Total events:	18		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						



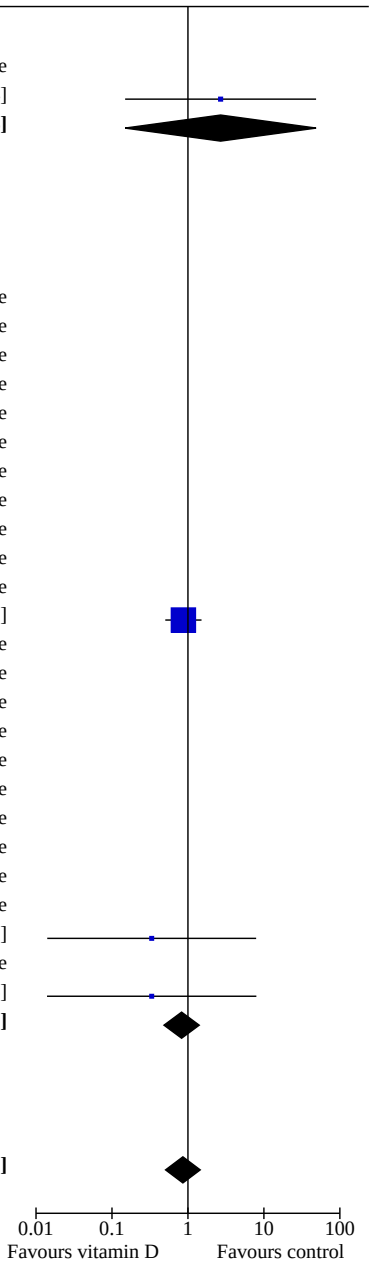
Analysis 1.1. (Continued)

Total events:	18		20				
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%							
Test for overall effect: Z = 0.57 (P = 0.57)							
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%							



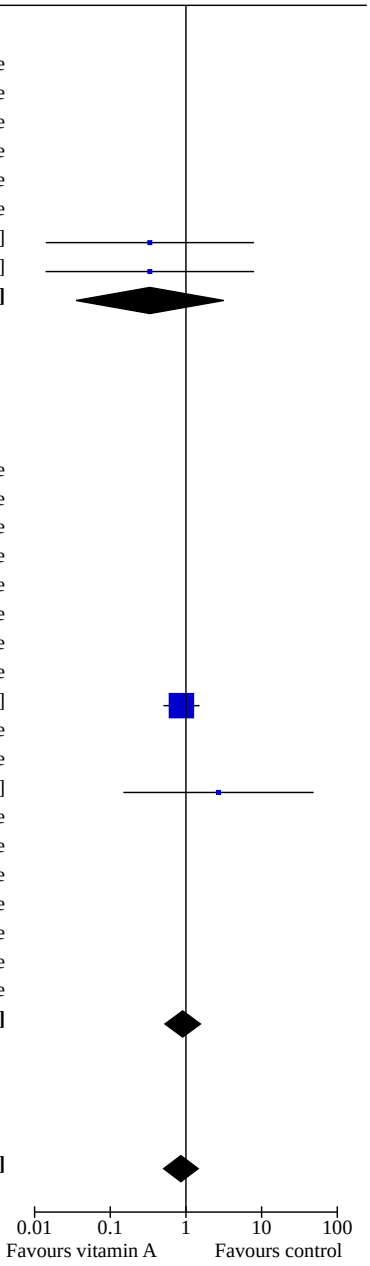
Analysis 1.2. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 2: 1.1 All-cause mortality according to vested interest

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Trials with vested interest						
Geier 2018	0	10	0	10		Not estimable
Mobarhan 1984	2	12	0	6	3.3%	2.69 [0.15 , 48.64]
Subtotal (95% CI)		**22**		**16**	**3.3%**	**2.69 [0.15 , 48.64]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.2.2 Trials without vested interest						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	0	57	0	58		Not estimable
Barchetta 2016	0	29	0	36		Not estimable
Behera 2018	0	28	0	32		Not estimable
Boonyagard 2016	0	30	0	30		Not estimable
Dabbaghmanesh 2018	0	70	0	36		Not estimable
Esmat 2015	0	50	0	51		Not estimable
Foroughi 2016	0	30	0	30		Not estimable
Hosseini 2018	0	41	0	41		Not estimable
Hussain 2019	0	54	0	55		Not estimable
Jeong 2019	0	77	0	71		Not estimable
Jha 2017	16	51	18	50	91.2%	0.87 [0.50 , 1.51]
Komolmit 2017a	0	40	0	40		Not estimable
Komolmit 2017b	0	29	0	29		Not estimable
Lorvand Amiri 2016	0	80	0	40		Not estimable
Nimer 2012	0	20	0	30		Not estimable
Pilz 2016	0	18	0	18		Not estimable
Sakpal 2017	0	51	0	30		Not estimable
Sharifi 2014	0	30	0	30		Not estimable
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Vosoghinia 2016	0	34	1	34	2.7%	0.33 [0.01 , 7.91]
Xing 2013	0	25	0	50		Not estimable
Yokoyama 2014	0	42	1	42	2.7%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**997**		**944**	**96.7%**	**0.83 [0.48 , 1.41]**
Total events:	16		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**1019**		**960**	**100.0%**	**0.86 [0.51 , 1.45]**
Total events:	18		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%						



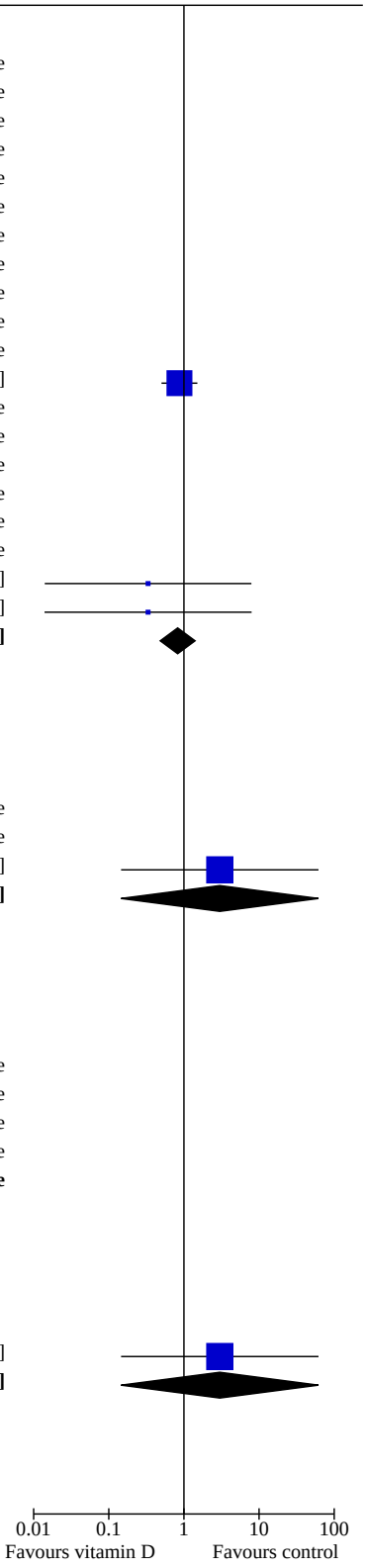
Analysis 1.3. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 3: All-cause mortality according to vitamin D status at entry

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Normal vitamin D status						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	0	57	0	58		Not estimable
Behera 2018	0	28	0	32		Not estimable
Geier 2018	0	10	0	10		Not estimable
Komolmit 2017a	0	40	0	40		Not estimable
Nimer 2012	0	20	0	30		Not estimable
Vosoghinia 2016	0	34	1	34	2.7%	0.33 [0.01 , 7.91]
Yokoyama 2014	0	42	1	42	2.7%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**267**		**282**	**5.5%**	**0.33 [0.04 , 3.13]**
Total events:	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.3.2 Low vitamin D status						
Barchetta 2016	0	29	0	36		Not estimable
Boonyagard 2016	0	30	0	30		Not estimable
Dabbaghmanesh 2018	0	70	0	36		Not estimable
Esmat 2015	0	50	0	51		Not estimable
Foroughi 2016	0	30	0	30		Not estimable
Hosseini 2018	0	41	0	41		Not estimable
Hussain 2019	0	54	0	55		Not estimable
Jeong 2019	0	77	0	71		Not estimable
Jha 2017	16	51	18	50	91.2%	0.87 [0.50 , 1.51]
Komolmit 2017b	0	29	0	29		Not estimable
Lorvand Amiri 2016	0	80	0	40		Not estimable
Mobarhan 1984	2	12	0	6	3.3%	2.69 [0.15 , 48.64]
Pilz 2016	0	18	0	18		Not estimable
Sakpal 2017	0	51	0	30		Not estimable
Sharifi 2014	0	30	0	30		Not estimable
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Xing 2013	0	25	0	50		Not estimable
Subtotal (95% CI)		**752**		**678**	**94.5%**	**0.91 [0.53 , 1.55]**
Total events:	18		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**1019**		**960**	**100.0%**	**0.86 [0.51 , 1.45]**
Total events:	18		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%						



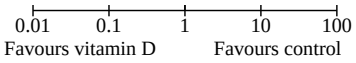
Analysis 1.4. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 4: All-cause mortality according to form of vitamin D

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Vitamin D 3						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	0	57	0	58		Not estimable
Barchetta 2016	0	29	0	36		Not estimable
Behera 2018	0	28	0	32		Not estimable
Dabbaghmanesh 2018	0	70	0	36		Not estimable
Esmat 2015	0	50	0	51		Not estimable
Foroughi 2016	0	30	0	30		Not estimable
Geier 2018	0	10	0	10		Not estimable
Hosseini 2018	0	41	0	41		Not estimable
Hussain 2019	0	54	0	55		Not estimable
Jeong 2019	0	77	0	71		Not estimable
Jha 2017	16	51	18	50	94.3%	0.87 [0.50 , 1.51]
Lorvand Amiri 2016	0	80	0	40		Not estimable
Nimer 2012	0	20	0	30		Not estimable
Pilz 2016	0	18	0	18		Not estimable
Sakpal 2017	0	51	0	30		Not estimable
Sharifi 2014	0	30	0	30		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Vosoghinia 2016	0	34	1	34	2.8%	0.33 [0.01 , 7.91]
Yokoyama 2014	0	42	1	42	2.8%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**828**		**750**	**100.0%**	**0.83 [0.48 , 1.41]**
Total events:	16		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.4.2 Vitamin D 2						
Komolmit 2017a	0	40	0	40		Not estimable
Komolmit 2017b	0	29	0	29		Not estimable
Mobarhan 1984	1	6	0	6	100.0%	3.00 [0.15 , 61.74]
Subtotal (95% CI)		**75**		**75**	**100.0%**	**3.00 [0.15 , 61.74]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.4.3 1,25-dihydroxyvitamin D						
Dabbaghmanesh 2018	0	70	0	36		Not estimable
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Xing 2013	0	25	0	50		Not estimable
Subtotal (95% CI)		**150**		**141**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.4 25-hydroxyvitamin D						
Mobarhan 1984	1	6	0	6	100.0%	3.00 [0.15 , 61.74]
Subtotal (95% CI)		**6**		**6**	**100.0%**	**3.00 [0.15 , 61.74]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Chi² = 1.32, df = 2 (P = 0.52), I² = 0%						



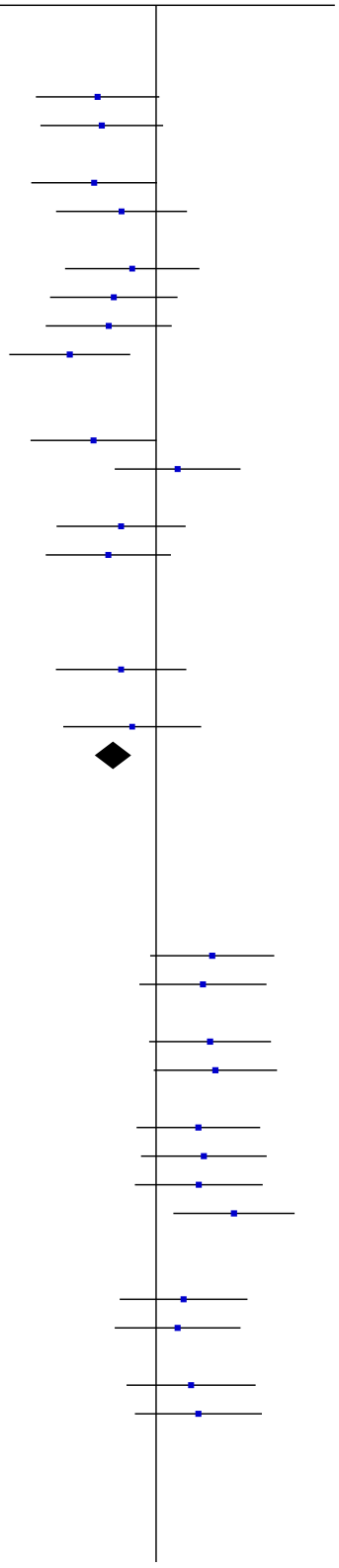
Analysis 1.4. (Continued)

Test for subgroup differences: Chi² = 1.32, df = 2 (P = 0.52), I² = 0%



Analysis 1.5. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 5: All-cause mortality (best-worst-case and worst-best-case scenarios)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Best-worst-case scenario						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	0	57	7	58	7.6%	0.07 [0.00 , 1.16]
Barchetta 2016	0	29	7	36	7.7%	0.08 [0.00 , 1.38]
Behera 2018	0	28	0	32		Not estimable
Dabbaghmanesh 2018	0	70	4	36	7.3%	0.06 [0.00 , 1.05]
Esmat 2015	0	50	2	51	6.8%	0.20 [0.01 , 4.14]
Foroughi 2016	0	30	0	30		Not estimable
Geier 2018	0	10	1	10	6.4%	0.33 [0.02 , 7.32]
Hosseini 2018	0	41	3	41	7.1%	0.14 [0.01 , 2.68]
Hussain 2019	0	54	4	55	7.3%	0.11 [0.01 , 2.05]
Jeong 2019	0	77	24	71	7.9%	0.02 [0.00 , 0.30]
Komolmit 2017a	0	40	0	40		Not estimable
Komolmit 2017b	0	29	0	29		Not estimable
Lorvand Amiri 2016	0	80	4	40	7.3%	0.06 [0.00 , 1.02]
Mobarhan 1984	2	12	0	6	7.3%	2.69 [0.15 , 48.64]
Nimer 2012	0	20	0	30		Not estimable
Pilz 2016	0	18	2	18	7.0%	0.20 [0.01 , 3.89]
Sharifi 2014	0	30	4	30	7.4%	0.11 [0.01 , 1.98]
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Vosoghinia 2016	0	34	2	34	6.8%	0.20 [0.01 , 4.02]
Xing 2013	0	25	0	50		Not estimable
Yokoyama 2014	0	42	1	42	6.1%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**887**		**850**	**100.0%**	**0.14 [0.06 , 0.30]**
Total events:	2		65			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.35$, df = 13 (P = 0.82); $I^2 = 0\%$						
Test for overall effect: Z = 4.97 (P < 0.00001)						
1.5.2 Worst-best-case scenario						
Abu-Mouch 2011	0	36	0	36		Not estimable
Atsukawa 2016	6	57	0	58	8.0%	13.22 [0.76 , 229.42]
Barchetta 2016	3	29	0	36	7.6%	8.63 [0.46 , 160.68]
Behera 2018	0	28	0	32		Not estimable
Dabbaghmanesh 2018	11	70	0	36	8.2%	11.99 [0.73 , 197.77]
Esmat 2015	7	50	0	51	8.0%	15.29 [0.90 , 260.86]
Foroughi 2016	0	30	0	30		Not estimable
Geier 2018	3	10	0	10	8.0%	7.00 [0.41 , 120.16]
Hosseini 2018	4	41	0	41	7.8%	9.00 [0.50 , 161.98]
Hussain 2019	3	54	0	55	7.5%	7.13 [0.38 , 134.78]
Jeong 2019	19	77	0	71	8.3%	36.00 [2.21 , 585.40]
Komolmit 2017a	0	40	0	40		Not estimable
Komolmit 2017b	0	29	0	29		Not estimable
Lorvand Amiri 2016	3	80	0	40	7.5%	3.54 [0.19 , 66.97]
Mobarhan 1984	2	12	0	6	7.7%	2.69 [0.15 , 48.64]
Nimer 2012	0	20	0	30		Not estimable
Pilz 2016	2	18	0	18	7.3%	5.00 [0.26 , 97.37]
Sharifi 2014	3	30	0	30	7.6%	7.00 [0.38 , 129.93]
Shiomi 1999a	0	38	0	38		Not estimable
Shiomi 1999b	0	17	0	17		Not estimable
Taghvaei 2018	0	20	0	20		Not estimable
Vosoghinia 2016	0	34	0	34		Not estimable
Xing 2013	0	25	0	50		Not estimable

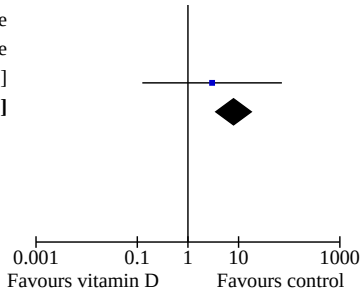


Analysis 1.5. (Continued)

Vosoghinia 2016	0	34	0	34		Not estimable
Xing 2013	0	25	0	50		Not estimable
Yokoyama 2014	1	42	0	42	6.4%	3.00 [0.13 , 71.61]
Subtotal (95% CI)		**887**		**850**	**100.0%**	**7.95 [3.55 , 17.77]**
Total events:	67		0			

Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 12 (P = 0.99); I² = 0%

Test for overall effect: Z = 5.05 (P < 0.00001)



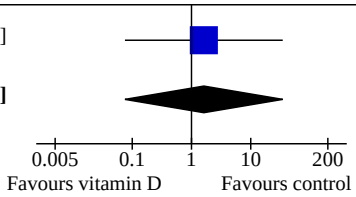
Analysis 1.6. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 6: Liver-related mortality

	Vitamin D		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Mobarhan 1984	1	12	0	6	100.0%	1.62 [0.08 , 34.66]	
Total (95% CI)		**12**		**6**	**100.0%**	**1.62 [0.08 , 34.66]**	
Total events:	1		0				

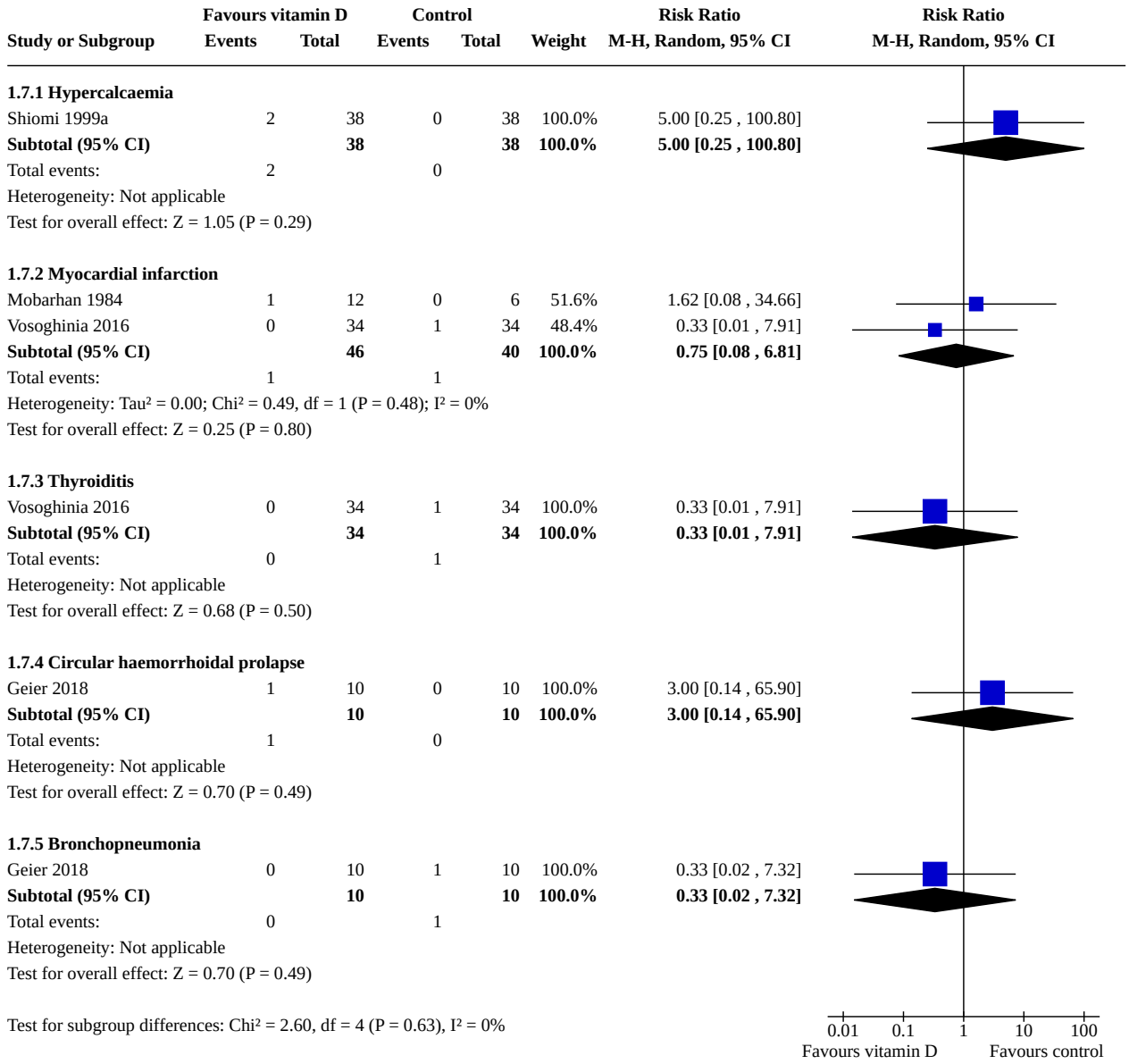
Heterogeneity: Not applicable

Test for overall effect: Z = 0.31 (P = 0.76)

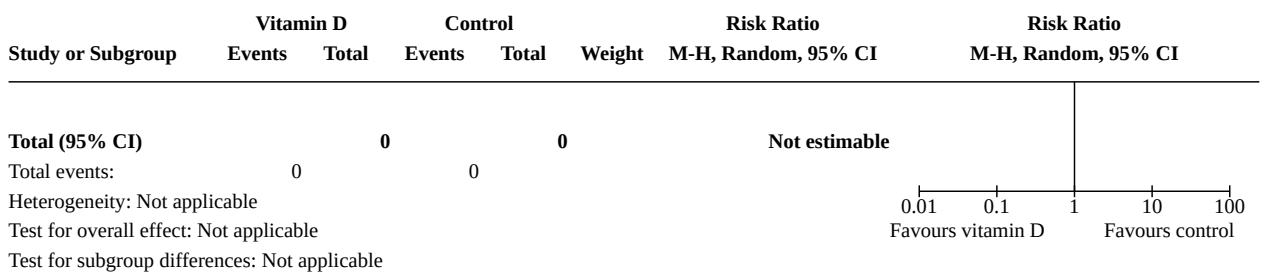
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 7: Serious adverse events

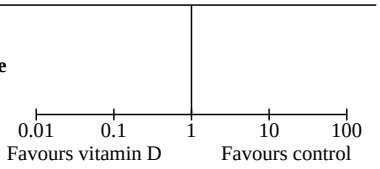


Analysis 1.8. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 8: Liver-related morbidity



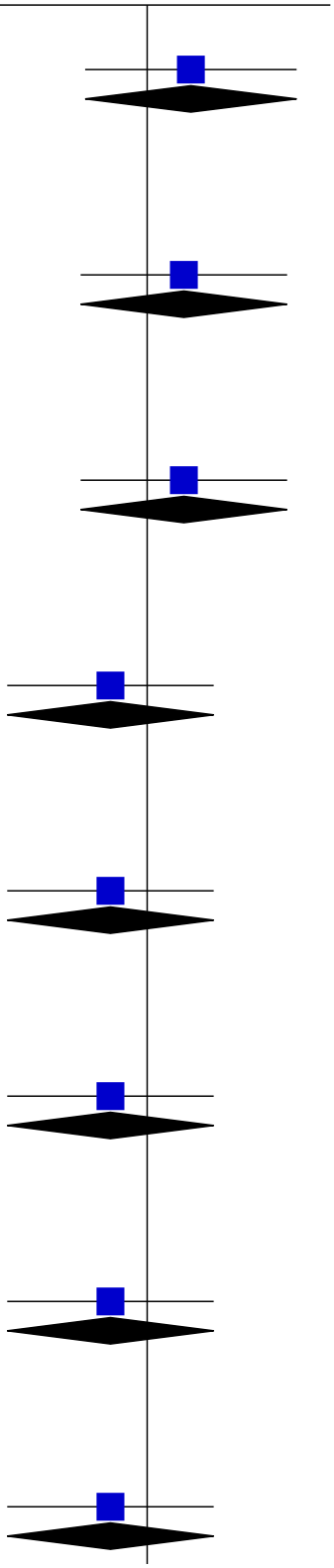
Analysis 1.9. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 9: Health-related quality of life

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



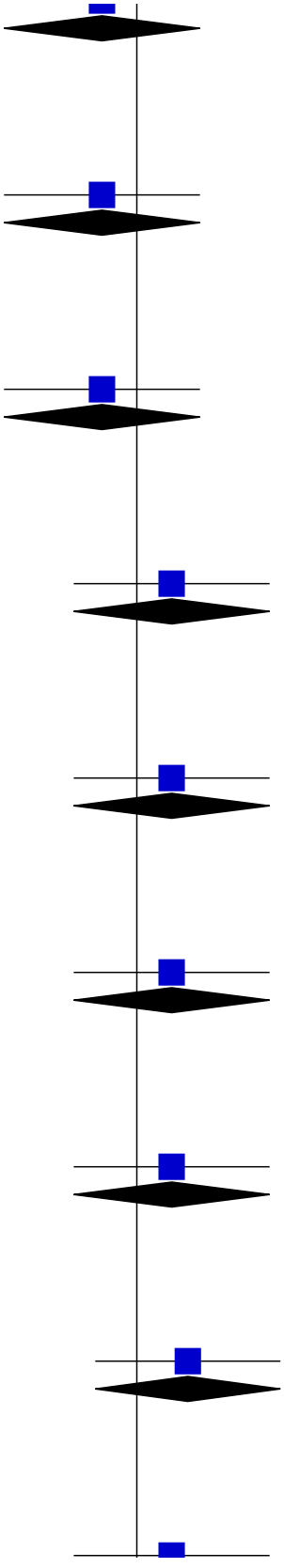
Analysis 1.10. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 10: Non-serious adverse events

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Glossitis						
Barchetta 2016	1	29	0	36	100.0%	3.70 [0.16 , 87.58]
Subtotal (95% CI)		**29**		**36**	**100.0%**	**3.70 [0.16 , 87.58]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.10.2 Depression						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.3 Lower back pain						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.4 Abdominal bloating						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.5 Cold						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.6 Constipation						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.7 Sore throat						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.8 Sour taste in mouth						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			



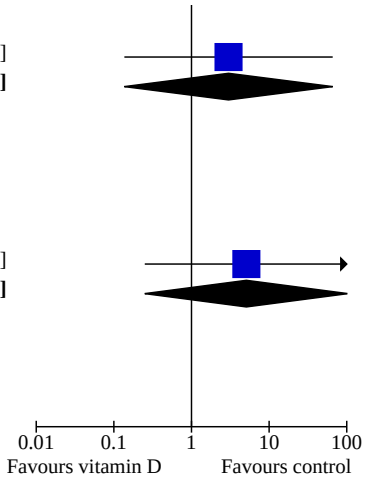
Analysis 1.10. (Continued)

Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.9 Contused lacerated wound						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.10 Multiple white matter lesions						
Geier 2018	0	10	1	10	100.0%	0.33 [0.02 , 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02 , 7.32]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.11 Gastro-oesophageal reflux						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.12 Abdominal menstrual cramps						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.13 Tubular colon adenoma						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.14 Gastric motility disturbance						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.15 Irritable bowel syndrome						
Geier 2018	2	10	0	10	100.0%	5.00 [0.27 , 92.62]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**5.00 [0.27 , 92.62]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.10.16 Knee pain						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]



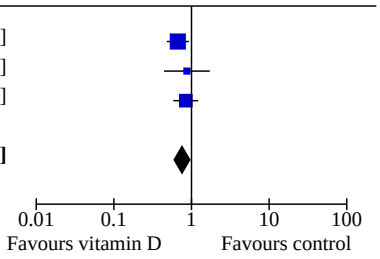
Analysis 1.10. (Continued)

1.10.16 Knee pain						
Geier 2018	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.10.17 Severe allergy						
Hussain 2019	2	54	0	55	100.0%	5.09 [0.25 , 103.64]
Subtotal (95% CI)		**54**		**55**	**100.0%**	**5.09 [0.25 , 103.64]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi² = 9.21, df = 16 (P = 0.90), I² = 0%						



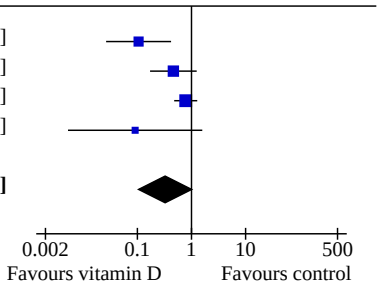
Analysis 1.11. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 11: Failure of rapid virological response

	Vitamin D		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Abu-Mouch 2011	20	36	30	36	49.6%	0.67 [0.48 , 0.92]	
Atsukawa 2016	12	57	14	58	11.5%	0.87 [0.44 , 1.72]	
Behera 2018	17	28	23	32	39.0%	0.84 [0.58 , 1.22]	
Total (95% CI)		**121**		**126**	**100.0%**	**0.75 [0.60 , 0.95]**	
Total events:	49		67				
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%							
Test for overall effect: Z = 2.41 (P = 0.02)							
Test for subgroup differences: Not applicable							



Analysis 1.12. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 12: Failure of early virological response

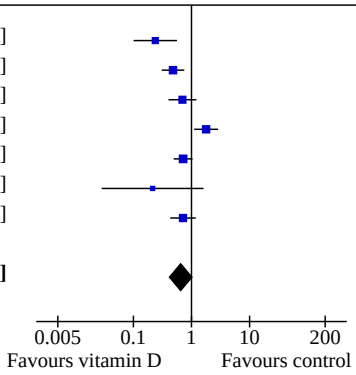
	Vitamin D		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Abu-Mouch 2011	2	36	19	36	24.2%	0.11 [0.03 , 0.42]	
Atsukawa 2016	5	57	11	58	29.3%	0.46 [0.17 , 1.25]	
Behera 2018	13	28	19	32	35.4%	0.78 [0.48 , 1.28]	
Vosoghinia 2016	0	34	5	34	11.0%	0.09 [0.01 , 1.58]	
Total (95% CI)		**155**		**160**	**100.0%**	**0.33 [0.11 , 1.00]**	
Total events:	20		54				
Heterogeneity: Tau² = 0.87; Chi² = 11.77, df = 3 (P = 0.008); I² = 75%							
Test for overall effect: Z = 1.95 (P = 0.05)							
Test for subgroup differences: Not applicable							



Analysis 1.13. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 13: Failure of sustained virological response

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abu-Mouch 2011	5	36	21	36	11.7%	0.24 [0.10 , 0.56]
Atsukawa 2016	17	57	36	58	17.2%	0.48 [0.31 , 0.75]
Behera 2018	11	28	18	32	15.8%	0.70 [0.40 , 1.21]
Esmat 2015	28	50	16	51	16.8%	1.78 [1.11 , 2.87]
Jeong 2019	28	77	36	71	18.2%	0.72 [0.49 , 1.04]
Nimer 2012	1	20	7	30	3.9%	0.21 [0.03 , 1.61]
Yokoyama 2014	15	42	21	42	16.4%	0.71 [0.43 , 1.18]
Total (95% CI)		**310**		**320**	**100.0%**	**0.65 [0.42 , 1.01]**
Total events:	105		155			

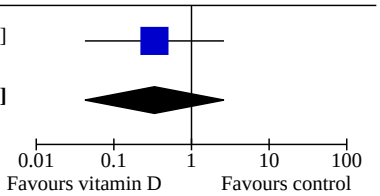
Heterogeneity: Tau² = 0.24; Chi² = 25.24, df = 6 (P = 0.0003); I² = 76%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 14: Acute cellular rejection in liver transplant recipients

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Xing 2013	1	25	6	50	100.0%	0.33 [0.04 , 2.62]
Total (95% CI)		**25**		**50**	**100.0%**	**0.33 [0.04 , 2.62]**
Total events:	1		6			

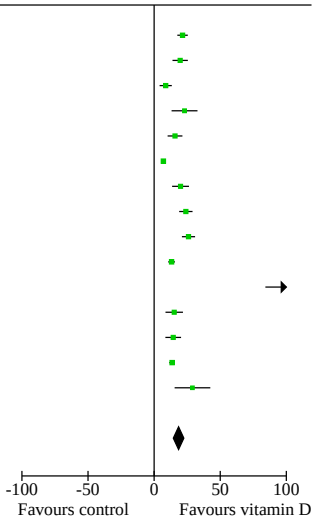
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 15: Vitamin D status (ng/mL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Atsukawa 2016	43.1	13.1	57	21.6	7.8	58	7.7%	21.50 [17.55 , 25.45]
Barchetta 2016	35.9	11.5	29	16.2	12.3	36	7.1%	19.70 [13.90 , 25.50]
Dabbaghmanesh 2018	27.55	17.1	70	18.8	7	36	7.5%	8.75 [4.14 , 13.36]
Geier 2018	39	13	10	16	9	10	5.5%	23.00 [13.20 , 32.80]
Hosseini 2018	24.9	17.4	41	9.1	5.6	41	7.1%	15.80 [10.20 , 21.40]
Hussain 2019	24.5	3.8	54	17.5	3.5	55	8.2%	7.00 [5.63 , 8.37]
Jha 2017	29	21.9	51	9.02	7.7	50	6.9%	19.98 [13.60 , 26.36]
Komolmit 2017a	45.9	15.4	40	21.9	5.3	40	7.3%	24.00 [18.95 , 29.05]
Komolmit 2017b	45.6	12.6	29	19.6	5.3	29	7.4%	26.00 [21.02 , 30.98]
Lorvand Amiri 2016	24.2	6.3	80	11	7	40	8.0%	13.20 [10.63 , 15.77]
Mobarhan 1984	131	56.7	12	12	17	6	1.1%	119.00 [84.15 , 153.85]
Pilz 2016	33.8	10.3	18	18.6	9.9	18	6.8%	15.20 [8.60 , 21.80]
Sharifi 2014	34.4	16.2	30	19.95	3.5	30	7.0%	14.45 [8.52 , 20.38]
Taghvaei 2018	34.4	4.3	20	20.8	2.5	20	8.1%	13.60 [11.42 , 15.78]
Vosoghinia 2016	52	38	34	23	13	34	4.2%	29.00 [15.50 , 42.50]
Total (95% CI)			**575**			**503**	**100.0%**	**18.49 [14.52 , 22.47]**

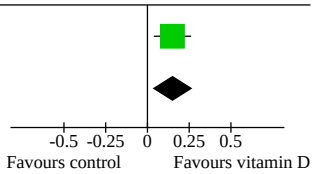
Heterogeneity: Tau² = 49.34; Chi² = 193.09, df = 14 (P < 0.00001); I² = 93%
Test for overall effect: Z = 9.13 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 16: Bone mineral density (g/cm)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Mobarhan 1984	0.8	0.1	12	0.65	0.12	6	100.0%	0.15 [0.04 , 0.26]
Total (95% CI)			**12**			**6**	**100.0%**	**0.15 [0.04 , 0.26]**

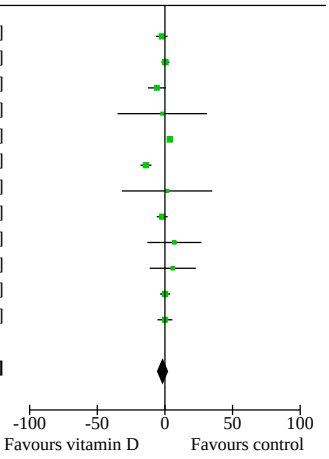
Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 17: Aspartate aminotransferase (IU/L)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	20.7	7.6	29	23	10	36	11.4%	-2.30 [-6.58 , 1.98]
Dabbaghmanesh 2018	24.9	6.6	70	24.5	7.7	36	12.4%	0.40 [-2.55 , 3.35]
Foroughi 2016	21.5	6.8	30	27.4	17.3	30	9.4%	-5.90 [-12.55 , 0.75]
Geier 2018	56	48	10	58	23	10	1.1%	-2.00 [-34.99 , 30.99]
Hosseini 2018	19.9	5.7	41	16.2	4.3	41	12.9%	3.70 [1.51 , 5.89]
Hussain 2019	46	10.5	54	60	11	55	11.6%	-14.00 [-18.04 , -9.96]
Komolmit 2017b	83.7	68.9	29	82.1	60.8	29	1.1%	1.60 [-31.84 , 35.04]
Lorvand Amiri 2016	26.6	8.6	80	28.6	11.4	40	11.7%	-2.00 [-6.00 , 2.00]
Mobarhan 1984	44	27.2	12	37	16	6	2.7%	7.00 [-13.02 , 27.02]
Pilz 2016	51	25.7	18	45.2	26.5	18	3.4%	5.80 [-11.25 , 22.85]
Sharifi 2014	21.4	7	30	21.3	7.8	30	11.9%	0.10 [-3.65 , 3.85]
Taghvaei 2018	29.5	10.9	20	29.5	6.3	20	10.4%	0.00 [-5.52 , 5.52]
Total (95% CI)			**423**			**351**	**100.0%**	**-1.75 [-5.41 , 1.91]**

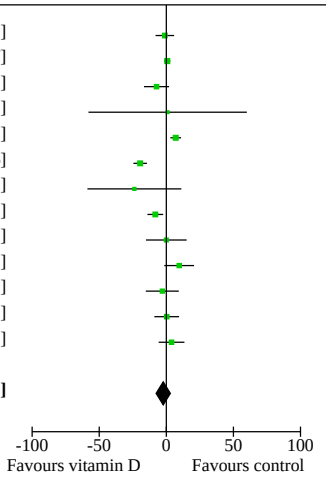
Heterogeneity: Tau² = 25.76; Chi² = 62.46, df = 11 (P < 0.00001); I² = 82%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 18: Alanine aminotransferase (IU/L

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	28.8	13.6	29	29.9	14.7	36	9.5%	-1.10 [-8.00 , 5.80]
Dabbaghmanesh 2018	17.2	6.1	70	16.5	5.4	36	11.1%	0.70 [-1.57 , 2.97]
Foroughi 2016	29.5	14.6	30	36.8	21.6	30	8.4%	-7.30 [-16.63 , 2.03]
Geier 2018	96	77	10	95	56	10	0.8%	1.00 [-58.01 , 60.01]
Hosseini 2018	23.7	11.2	41	16.7	6.6	41	10.7%	7.00 [3.02 , 10.98]
Hussain 2019	54.5	14.5	54	74	12.2	55	10.3%	-19.50 [-24.54 , -14.46]
Komolmit 2017b	78	60.3	29	101.8	74.9	29	1.9%	-23.80 [-58.80 , 11.20]
Lorvand Amiri 2016	39.1	13.5	80	47.3	16.4	40	10.0%	-8.20 [-14.08 , -2.32]
Mobarhan 1984	22	11.8	12	22	17	6	5.9%	0.00 [-15.15 , 15.15]
Pilz 2016	39.2	18.5	18	29.6	15.3	18	7.6%	9.60 [-1.49 , 20.69]
Sakpal 2017	59	32	51	62	24	30	7.1%	-3.00 [-15.28 , 9.28]
Sharifi 2014	27.5	14.8	30	27.2	21	30	8.5%	0.30 [-8.89 , 9.49]
Taghvaei 2018	43.6	19.3	20	39.7	10.4	20	8.3%	3.90 [-5.71 , 13.51]
Total (95% CI)			**474**			**381**	**100.0%**	**-2.30 [-7.60 , 3.00]**

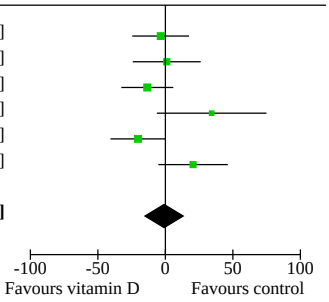
Heterogeneity: Tau² = 64.34; Chi² = 83.37, df = 12 (P < 0.00001); I² = 86%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 19: Alkaline phosphatases (IU/L)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Dabbaghmanesh 2018	181.5	54.1	70	185	51.4	36	19.1%	-3.50 [-24.54 , 17.54]
Geier 2018	80	32	10	79	25	10	16.1%	1.00 [-24.17 , 26.17]
Hosseini 2018	157.7	46.9	41	171.1	41.9	41	20.5%	-13.40 [-32.65 , 5.85]
Pilz 2016	126.5	84.5	18	92.2	24.1	18	8.9%	34.30 [-6.29 , 74.89]
Sharifi 2014	195.3	51.4	30	215.6	24.56	30	19.6%	-20.30 [-40.68 , 0.08]
Taghvaei 2018	201.4	49.8	20	180.9	31.1	20	15.8%	20.50 [-5.23 , 46.23]
Total (95% CI)			**189**			**155**	**100.0%**	**-0.95 [-15.10 , 13.20]**

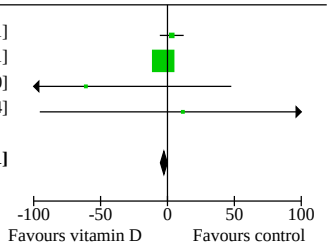
Heterogeneity: Tau² = 157.62; Chi² = 10.42, df = 5 (P = 0.06); I² = 52%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 20: Gamma-glutamyl transpeptidase (IU/L)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	30.3	18.3	29	27.1	18.1	36	8.4%	3.20 [-5.71 , 12.11]
Dabbaghmanesh 2018	25.9	10.9	70	29.1	2.6	36	91.5%	-3.20 [-5.89 , -0.51]
Geier 2018	87	74	10	148	159	10	0.1%	-61.00 [-169.70 , 47.70]
Pilz 2016	151.6	187.4	18	140.1	135.9	18	0.1%	11.50 [-95.44 , 118.44]
Total (95% CI)			**127**			**100**	**100.0%**	**-2.69 [-5.26 , -0.11]**

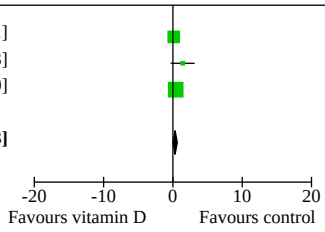
Heterogeneity: Tau² = 0.00; Chi² = 2.99, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 21: Bilirubin (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Geier 2018	0.76	0.47	10	0.64	0.41	10	41.2%	0.12 [-0.27 , 0.51]
Mobarhan 1984	2.6	2.9	12	1.2	0.7	6	3.2%	1.40 [-0.33 , 3.13]
Pilz 2016	1.1	0.5	18	0.7	0.4	18	55.6%	0.40 [0.10 , 0.70]
Total (95% CI)			**40**			**34**	**100.0%**	**0.32 [0.00 , 0.63]**

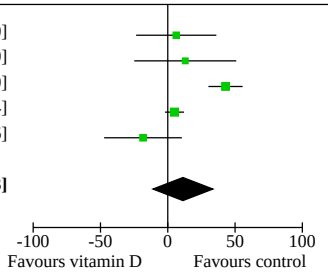
Heterogeneity: Tau² = 0.02; Chi² = 2.80, df = 2 (P = 0.25); I² = 29%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 22: Triglyceride (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	127.2	69.4	29	120.9	48.4	36	17.7%	6.30 [-23.50 , 36.10]
Dabbaghmanesh 2018	179.1	84.4	70	166.1	99	36	14.8%	13.00 [-24.90 , 50.90]
Foroughi 2016	188	31.2	30	145.1	16.9	30	24.0%	42.90 [30.20 , 55.60]
Hussain 2019	175	16.5	54	170	20.8	55	25.3%	5.00 [-2.04 , 12.04]
Lorvand Amiri 2016	177.5	65	80	195.9	81	40	18.1%	-18.40 [-47.26 , 10.46]
Total (95% CI)			**263**			**197**	**100.0%**	**11.27 [-10.99 , 33.53]**

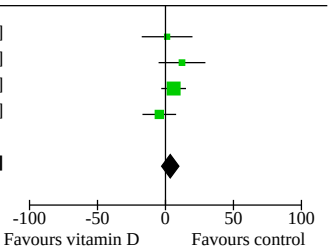
Heterogeneity: Tau² = 496.11; Chi² = 30.94, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 23: Cholesterol (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	168.9	39	29	167.7	37.1	36	11.5%	1.20 [-17.46 , 19.86]
Dabbaghmanesh 2018	207.75	40.9	70	195.6	43.8	36	13.6%	12.15 [-5.07 , 29.37]
Hussain 2019	250	20.5	54	244	27.5	55	48.6%	6.00 [-3.09 , 15.09]
Lorvand Amiri 2016	191.15	34	80	195.7	31.9	40	26.3%	-4.55 [-16.93 , 7.83]
Total (95% CI)			**233**			**167**	**100.0%**	**3.51 [-2.83 , 9.85]**

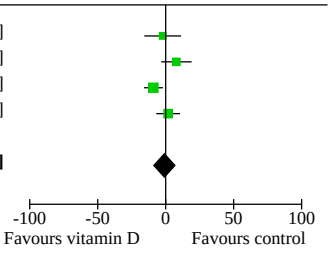
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 24: LDL cholesterol (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	85.6	29.8	29	87.8	24.7	36	18.5%	-2.20 [-15.72 , 11.32]
Dabbaghmanesh 2018	100.4	23.5	70	92.5	29.8	36	22.5%	7.90 [-3.28 , 19.08]
Hussain 2019	143	20.4	54	152	16.5	55	31.5%	-9.00 [-15.97 , -2.03]
Lorvand Amiri 2016	117.9	27.6	80	116.1	20.2	40	27.6%	1.80 [-6.90 , 10.50]
Total (95% CI)			**233**			**167**	**100.0%**	**-0.97 [-8.70 , 6.76]**

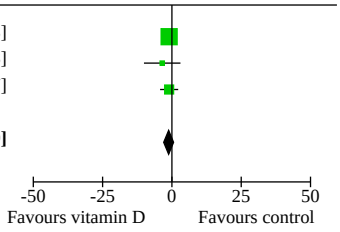
Heterogeneity: Tau² = 36.69; Chi² = 7.59, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 0.25 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 25: Albumin (g/L)

Study or Subgroup	Favours control Mean	SD	Total	Favours vitamin D Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Geier 2018	41	2	10	42	3	10	63.2%	-1.00 [-3.23 , 1.23]
Mobarhan 1984	34.5	6.1	12	38	7	6	7.3%	-3.50 [-10.08 , 3.08]
Pilz 2016	39	5	18	40	5	18	29.6%	-1.00 [-4.27 , 2.27]
Total (95% CI)			**40**			**34**	**100.0%**	**-1.18 [-2.96 , 0.59]**

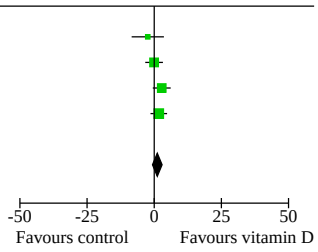
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 26: HDL cholesterol (mg/dL)

Study or Subgroup	Vitamin D Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	48	9	29	50.4	15.4	36	8.8%	-2.40 [-8.40 , 3.60]
Dabbaghmanesh 2018	38.35	7.3	70	38.4	8.6	36	29.3%	-0.05 [-3.34 , 3.24]
Hussain 2019	37.8	8.2	54	35	9.5	55	28.6%	2.80 [-0.53 , 6.13]
Lorvand Amiri 2016	39.9	6.3	80	38.2	8.9	40	33.3%	1.70 [-1.38 , 4.78]
Total (95% CI)			**233**			**167**	**100.0%**	**1.14 [-0.64 , 2.92]**

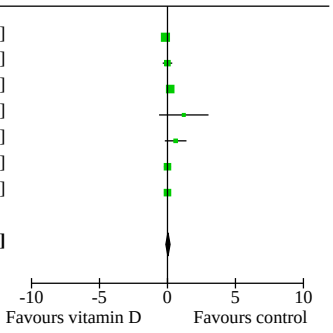
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 27: Calcium (mg/dL)

Study or Subgroup	Vitamin D Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dabbaghmanesh 2018	9.25	0.42	70	9.4	0.4	36	25.5%	-0.15 [-0.31 , 0.01]
Geier 2018	9.6	0.4	10	9.6	0.4	10	12.4%	0.00 [-0.35 , 0.35]
Hosseini 2018	9.6	0.5	41	9.4	0.4	41	22.6%	0.20 [0.00 , 0.40]
Jha 2017	6.7	5	51	5.5	4.3	50	0.7%	1.20 [-0.62 , 3.02]
Mobarhan 1984	9.4	1	12	8.8	0.7	6	3.3%	0.60 [-0.20 , 1.40]
Pilz 2016	9.1	0.4	18	9.1	0.4	18	17.6%	0.00 [-0.26 , 0.26]
Sharifi 2014	9.2	0.4	30	9.2	0.6	30	17.8%	0.00 [-0.26 , 0.26]
Total (95% CI)			**232**			**191**	**100.0%**	**0.04 [-0.12 , 0.19]**

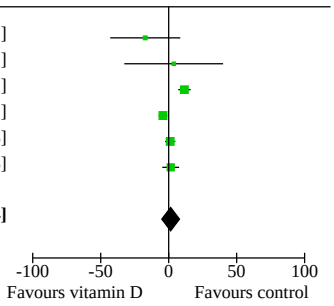
Heterogeneity: Tau² = 0.02; Chi² = 11.06, df = 6 (P = 0.09); I² = 46%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 28: Glucose (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Dabbaghmanesh 2018	111.75	45.8	70	129	71.7	36	5.1%	-17.25 [-43.01 , 8.51]
Geier 2018	113.5	43.2	10	109.8	39.6	10	2.8%	3.70 [-32.62 , 40.02]
Hosseini 2018	97.1	9.7	41	85.5	11.1	41	23.0%	11.60 [7.09 , 16.11]
Lorvand Amiri 2016	85.2	8.7	80	89.4	8.2	40	24.3%	-4.20 [-7.38 , -1.02]
Sakpal 2017	100.1	9	51	99	8	30	23.8%	1.10 [-2.68 , 4.88]
Sharifi 2014	93.8	10.1	30	92.3	14	30	21.0%	1.50 [-4.68 , 7.68]
Total (95% CI)			**282**			**187**	**100.0%**	**1.44 [-5.05 , 7.94]**

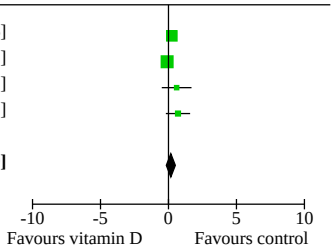
Heterogeneity: Tau² = 42.50; Chi² = 33.47, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 29: Phosphorus (mg/dL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Dabbaghmanesh 2018	4.35	0.9	70	4.1	0.7	36	37.0%	0.25 [-0.06 , 0.56]
Hosseini 2018	3.9	0.4	41	4	0.6	41	44.2%	-0.10 [-0.32 , 0.12]
Jha 2017	3.3	2.7	51	2.7	2.9	50	7.9%	0.60 [-0.49 , 1.69]
Mobarhan 1984	4	1.1	12	3.3	0.8	6	11.0%	0.70 [-0.19 , 1.59]
Total (95% CI)			**174**			**133**	**100.0%**	**0.17 [-0.16 , 0.50]**

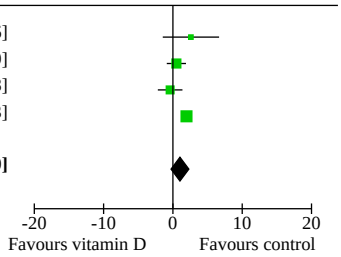
Heterogeneity: Tau² = 0.05; Chi² = 6.36, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.30. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 30: Adiponectin (µg/mL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	15.3	10.1	29	12.7	5.3	36	8.1%	2.60 [-1.46 , 6.66]
Geier 2018	3.5	2	10	3	1	10	29.4%	0.50 [-0.89 , 1.89]
Hosseini 2018	8.7	4	41	9.1	4.2	41	24.1%	-0.40 [-2.18 , 1.38]
Hussain 2019	10.4	2.35	54	8.44	1.72	55	38.4%	1.96 [1.19 , 2.73]
Total (95% CI)			**134**			**142**	**100.0%**	**1.02 [-0.27 , 2.30]**

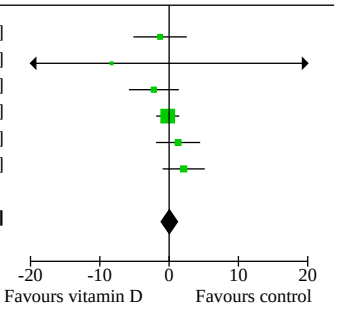
Heterogeneity: Tau² = 0.96; Chi² = 7.91, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 31: Insulin (mIU/mL)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	12.6	6.5	29	13.9	9.3	36	9.4%	-1.30 [-5.15 , 2.55]
Geier 2018	71.3	68.2	10	79.6	62.8	10	0.0%	-8.30 [-65.76 , 49.16]
Hosseini 2018	14.7	6.5	41	16.9	9.8	41	10.7%	-2.20 [-5.80 , 1.40]
Lorvand Amiri 2016	15.9	5.8	80	16.1	3.4	40	51.0%	-0.20 [-1.85 , 1.45]
Sakpal 2017	10	7.9	51	8.7	6.5	30	13.8%	1.30 [-1.88 , 4.48]
Sharifi 2014	14.1	6.3	30	12	5.7	30	15.0%	2.10 [-0.94 , 5.14]
Total (95% CI)			**241**			**187**	**100.0%**	**0.03 [-1.15 , 1.21]**

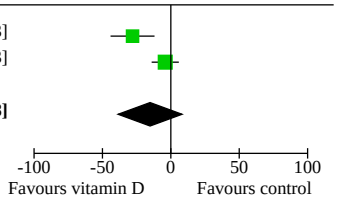
Heterogeneity: Tau² = 0.00; Chi² = 4.48, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 1.32. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 32: Parathyroid hormone (pg/mL)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hosseini 2018	62.5	38.7	41	90.5	35.5	41	46.4%	-28.00 [-44.07 , -11.93]
Pilz 2016	38.5	15.1	18	42.6	15.3	18	53.6%	-4.10 [-14.03 , 5.83]
Total (95% CI)			**59**			**59**	**100.0%**	**-15.18 [-38.54 , 8.18]**

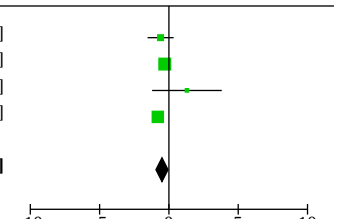
Heterogeneity: Tau² = 239.14; Chi² = 6.15, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.33. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 33: C-reactive protein (mg/L)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barchetta 2016	0.8	1.1	29	1.4	2.6	36	14.4%	-0.60 [-1.54 , 0.34]
Foroughi 2016	0.8	0.3	30	1.1	0.1	30	42.5%	-0.30 [-0.41 , -0.19]
Geier 2018	4.1	3.9	10	2.8	1.1	10	2.8%	1.30 [-1.21 , 3.81]
Hussain 2019	2.3	0.4	54	3.1	0.6	55	40.3%	-0.80 [-0.99 , -0.61]
Total (95% CI)			**123**			**131**	**100.0%**	**-0.50 [-0.93 , -0.07]**

Heterogeneity: Tau² = 0.11; Chi² = 21.42, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Characteristics of included trials (I)

Study ID	Protocol	Design	Groups	Bias risk	Blinding	Partici-pants (n)	Women (%)	Mean age (years)
Abu-Mouch 2011	Yes	Parallel group	2	High	NI	72	44	47
Atsukawa 2016	No	Parallel group	2	High	NI	115	50	64
Barchetta 2016	Yes	Parallel group	2	High	PL	65	35	59
Behera 2018	Yes	Parallel group	2	High	NI	60	40	41
Boonyagard 2016	No	Parallel group	2	High	PL	60	-	-
Dabbaghmanesh 2018	Yes	Parallel group	2	High	PL	106	59	45
Esmat 2015	No	Parallel group	2	High	NI	101	25	40
Foroughi 2016	Yes	Parallel group	2	High	PL	60	52	48
Geier 2018	Yes	Parallel group	2	High	PL	20	-	44
Hosseini 2018	Yes	Parallel group	2	High	NI	82	100	34
Hussain 2019	No	Parallel group	2	High	PL	109	36	28
Jeong 2019	Yes	Parallel group	2	High	NI	148	49	52
Jha 2017	No	Parallel group	2	High	NI	101	24	45
Komolmit 2017a	Yes	Parallel group	2	High	PL	80	46	52
Komolmit 2017b	Yes	Parallel group	2	High	PL	58	38	50
Lorvand Amiri 2016	Yes	Parallel group	3	High	PL	120	38	41
Mobarhan 1984	No	Parallel group	3	High	NI	18	0	61
Nimer 2012	No	Parallel group	2	High	NI	50	58	47
Pilz 2016	Yes	Parallel group	2	High	PL	36	25	61

Table 1. Characteristics of included trials (I) *(Continued)*

Sakpal 2017	No	Parallel group	2	High	NI	81	32	38
Sharifi 2014	No	Parallel group	2	High	PL	60	51	60
Shiomi 1999a	No	Parallel group	2	High	NI	76	66	61
Shiomi 1999b	No	Parallel group	2	High	NI	34	100	56
Taghvaei 2018	Yes	Parallel group	2	High	NI	40	50	42
Vosoghinia 2016	Yes	Parallel group	2	High	NI	68	13	42
Xing 2013	No	Parallel group	3	High	PL	75	17	48
Yokoyama 2014	No	Parallel group	2	High	NI	84	49	59

n: number of participants
NI: no intervention
PL: placebo

Table 2. Characteristics of included trials (II)

Study ID	Participants	Outcome measures	Sponsor	Country
Abu-Mouch 2011	Chronic hepatitis C genotype 1	Sustained virological response	No information	Israel
Atsukawa 2016	Chronic hepatitis C genotype 1	Sustained virological response	No information	Japan
Barchetta 2016	NAFLD	Liver steatosis, liver function	No	Italy
Behera 2018	Chronic hepatitis C genotype 1, 4	Sustained virological response	No	India
Boonyagard 2016	NAFLD	Biochemical indices, HOMA, FibroScan measurement	No information	Thailand
Dabbaghmanesh 2018	NAFLD	Biochemical indices	No	Iran
Esmat 2015	Chronic hepatitis C genotype 4	Sustained virological response	No information	Egypt
Foroughi 2016	NAFLD	Liver steatosis, liver function	No	Iran
Geier 2018	NAFLD (NASH)	Liver steatosis, liver function	Yes	Switzerland
Hosseini 2018	NAFLD	Serum 25-hydroxyvitamin D, adiponectin, HOMA-IR, liver enzymes, and change in grade of NAFLD	No	Iran
Hussain 2019	NAFLD	Body weight, BMI, insulin resistance, dyslipidaemia, hepatic enzymes, CRP, and adiponectin	No information	Pakistan
Jeong 2019	Chronic hepatitis C genotype 1, 2, 3	Sustained virological response	No information	Republic of Korea
Jha 2017	Liver cirrhosis	Mortality	No information	India
Komolmit 2017a	Chronic hepatitis C	Serum levels of T-helper cells associated cytokines	No	Thailand
Komolmit 2017b	Chronic hepatitis C	Serum fibrotic markers	No	Thailand
Lorvand Amiri 2016	NAFLD	Liver function, body fat	No	Iran
Mobarhan 1984	Liver cirrhosis	Bone mineral density	Yes	USA
Nimer 2012	Chronic hepatitis C genotype 2 or 3	Sustained virological response	No information	Israel
Pilz 2016	Liver cirrhosis	Vitamin D status, liver function	No	Austria
Sakpal 2017	NAFLD	Insulin resistance and serum ALT	No	India

Table 2. Characteristics of included trials (II) *(Continued)*

Sharifi 2014	NAFLD	Liver function, insulin resistance index	No	Iran
Shiomi 1999a	Liver cirrhosis	Bone mineral density	No information	Japan
Shiomi 1999b	Primary biliary cirrhosis	Bone mineral density	No information	Japan
Taghvaei 2018	NAFLD	Biochemical indices, liver steatosis	No information	Iran
Vosoghinia 2016	Chronic hepatitis C genotype 1, 2, 3, 4	Early virological response	No	Iran
Xing 2013	Liver transplant recipients	Acute cellular rejection rate	No	China
Yokoyama 2014	Chronic hepatitis C genotype 1	Sustained virological response	No information	Japan

ALT: alanine aminotransferase
BMI: body mass index
CRP: C-reactive protein
HOMA-IR: homeostatic model assessment for insulin resistance
NAFLD: non-alcoholic fatty liver disease
NASH: non-alcoholic steatohepatitis

Table 3. Characteristics of included studies (III)

Study ID	Vitamin				Calcium (mg)	Route	Regimen	Treatment (weeks)	Follow-up (weeks)	Co-intervention
	D_3 (IU)	D_2 (IU)	25(OH)D (IU)	$1,25(OH)_2D$ (µg)						
Abu-Mouch 2011	2000	-	-	-	-	Orally	Daily	48	72	PEG-IFN, RBV
Atsukawa 2016	2000	-	-	-	-	Orally	Daily	16	24	PEG-IFN, RBV, SP
Barchetta 2016	2000	-	-	-	-	Orally	Daily	24	24	-
Behera 2018	2000	-	-	-	-	Orally	Daily	48	48	PEG-IFN, RBV
Boonyagard 2016	-	-	-	-	-	Orally	Daily	20	20	
Dabbaghmanesh 2018	50,000	-	-	0.25	-	Orally	Weekly and daily	12	12	
Esmat 2015	2143	-	-	-	-	Orally	Weekly	48	72	PEG-IFN, RBV
Foroughi 2016	7143	-	-	-	-	Orally	Weekly	10	10	-
Geier 2018	2100	-	-	-	-	Orally	Daily	48	48	
Hosseini 2018	600,000	-	-	-	-	Intramuscularly	Single dose	Single dose	4	Vitamin E 400 IU/day
Hussain 2019	50,000	-	-	-	-	Orally	Weekly	12	12	
Jeong 2019	800	-	-	-	-	Orally	Daily	24, 48	48, 72	PEG-IFN, RBV
Jha 2017	300,000; 800	-	-	-	1000	Intramuscularly and orally	Single dose; daily	24	24	

Table 3. Characteristics of included studies (III) *(Continued)*

Komolmit 2017a	-	60,000; 80,000; 100,000	-	-	-	Orally	Weekly	6	6	
Komolmit 2017b	-	60,000; 80,000; 100,000	-	-	-	Orally	Weekly	6	6	
Lorvand Amiri 2016	1000	-	-	-	500	Orally	Daily	10	12	-
Mobarhan 1984	-	17,857	2400	-	-	Orally	Daily	52	52	-
Nimer 2012	2000	-	-	-	-	Orally	Daily	24	48	PEG-IFN, RBV
Pilz 2016	2800	-	-	-	-	Orally	Daily	8	8	-
Sakpal 2017	600,000	-	-	-	-	Intramuscularly	Single dose	Single dose	24	
Sharifi 2014	3571	-	-	-	-	Orally	Twice a week	16	16	-
Shiomi 1999a	-	-	-	1	-	Orally	Daily	52	52	-
Shiomi 1999b	-	-	-	1	-	Orally	Daily	52	52	-
Taghvaei 2018	50,000	-	-	-	-	Orally	Weekly	12	72	Lifestyle modification
Vosoghinia 2016	1600	-	-	-	-	Orally	Daily	12	12	PEG-IFN, RBV
Xing 2013	-	-	-	0.25	1000	Orally	Daily	4	4	-
Yokoyama 2014	1000	-	-	-	-	Orally	Daily	16	24	PEG-IFN, RBV

$1,25(OH)_2D$: calcitriol
25(OH)D: calcidiol
IU: international unit
PEG-IFN: pegylated-interferon

RBV: ribavirin
SP: simeprevir

APPENDICES

Appendix 1. Search strategies

Database	Search performed	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	November 2020	(vitamin D* OR calciferol) AND (liver OR hepat* OR cirrhosis OR fibrosis)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2020; Issue 11	#1 MeSH descriptor: [Vitamin D] explode all trees #2 vitamin d or calciferol #3 #1 or #2 #4 MeSH descriptor: [Liver Diseases] explode all trees #5 liver or hepat* or cirrhosis or fibrosis #6 #4 or #5 #7 #3 and #6
MEDLINE Ovid	1946 to November 2020	1. exp Vitamin D/ 2. (vitamin d or calciferol).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Liver Diseases/ 5. (liver or hepat* or cirrhosis or fibrosis).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analysis).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 9. 7 and 8
Embase Ovid	1974 to November 2020	1. exp vitamin D/ 2. (vitamin d or calciferol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 3. 1 or 2 4. exp liver disease/ 5. (liver or hepat* or cirrhosis or fibrosis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

(Continued)

		6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 9. 7 and 8
LILACS (Bireme)	1982 to November 2020	(vitamin D OR calciferol) [Words] and (liver OR hepat$ OR cirrhosis OR fibrosis) [Words]
Science Citation Index Expanded (Web of Science)	1900 to November 2020	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(liver OR hepat* OR cirrhosis OR fibrosis) #1 TS=(vitamin D OR calciferol)
Conference Proceedings Citation Index - Science (Web of Science)	1990 to November 2020	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(liver OR hepat* OR cirrhosis OR fibrosis) #1 TS=(vitamin D OR calciferol)

WHAT'S NEW

Date	Event	Description
7 October 2021	Amended	A few improvements made to sentences in text

HISTORY

Protocol first published: Issue 3, 2015
Review first published: Issue 11, 2017

Date	Event	Description
24 November 2020	New search has been performed	The most recent search for this review was performed on 24 November 2020. One included trial (Shidfar 2019) moved to principal reference (Lorvand Amiri 2016), and one new trial included (Taghvaei 2018).
24 November 2020	New citation required but conclusions have not changed	We added data from 12 trials.

CONTRIBUTIONS OF AUTHORS

MB: took the lead in updating the review, performed data extraction, and drafted the review update.
DN: revised the protocol, performed data extraction, commented on and revised the review.
GB: initiated the review; drafted the protocol; performed the literature search, data extraction, and statistical analyses; updated and revised the review.
CG: revised the protocol, acted as arbiter for disagreements, and commented on and revised the review.

DECLARATIONS OF INTEREST

MB: none known.
DN is the Managing Editor of the Cochrane Hepato-Biliary Group. However, the peer review process was dealt with through staff within the Cochrane Central Editorial Service Team.
GB: none known.
CG: none known.

SOURCES OF SUPPORT

Internal sources

- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark

  Working place

External sources

- Ministry of Education, Science and Technological Development of Republic of Serbia (Grant No: 451-03-9/2021-14/200113), Serbia

  Salary
- Medical Faculty, University of Nis, Internal project 66, Serbia

  No monetary support
- Serbian Academy of Sciences and Arts - branch in Nis Project O-26-20, Serbia

  No monetary support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We updated the Methods section of the protocol part of the review, as follows.
  - We removed the sentence "We included such studies only for assessment of harms." from the first two risk of bias domains.
  - Types of outcome measures. We modified and changed the order of outcomes. In addition, we merged secondary and exploratory outcomes due to updated editorial recommendations.
  - We added subgroup analysis according to participant's vitamin D status at entry, comparing participants with normal vitamin D levels at entry to those with decreased levels, and comparing different forms of vitamin D (vitamin D_3, vitamin D_2, 25-dihydroxyvitamin D, and 1,25-dihydroxyvitamin D).
  - We increased the number of biochemical indices to mirror the expanding number of outcomes assessed in the included trials.
  - Data synthesis. In our Trial Sequential Analysis, the diversity-adjusted required information size was based on the event proportion in the control group; assumption of a plausible relative risk reduction of 20%; a risk of type I error of 1.25% for the first seven outcomes; a risk of type II error of 10%; and the observed diversity of the included trials in the meta-analysis (Jakobsen 2014a; Wetterslev 2017). We reduced the relative risk reduction from 28% in our primary analysis to 20% in the current update given that the higher number seems unrealistic, and we could not find any evidence supporting it. The alpha level in our review update has decreased to 1.25% in order to account for multiplicity, assuming seven outcomes in the summary of findings table (Jakobsen 2014a).
  - We used Trial Sequential Analysis as sensitivity analysis to assess imprecision.
- Milica Bjelakovic joined the team of authors during the preparation of the review update.

NOTES

Cochrane Reviews can be expected to have a high percentage of overlap in the Methods section due to the use of standardised methods. In addition, overlap may be observed across some of our protocols and reviews, as they share at least three common authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Dietary Supplements; *Hepatitis C, Chronic; Quality of Life; Vitamin D

MeSH check words

Adult; Female; Humans; Male; Middle Aged