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Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD009422.

DOI: [10.1002/14651858.CD009422.pub4](https://doi.org/10.1002/14651858.CD009422.pub4).

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[Intervention Review]

Vitamin E supplementation in people with cystic fibrosis

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2020.

Citation: Okebukola PO, Kansra S, Barrett J. Vitamin E supplementation in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No.: CD009422. DOI: [10.1002/14651858.CD009422.pub4](https://doi.org/10.1002/14651858.CD009422.pub4).

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ABSTRACT

Background

People with cystic fibrosis are at an increased risk of fat-soluble vitamin deficiency, including vitamin E. Vitamin E deficiency can cause a host of conditions such as haemolytic anaemia, cerebellar ataxia and cognitive difficulties. Vitamin E supplementation is widely recommended for people with cystic fibrosis and aims to ameliorate this deficiency. This is an updated version of the review.

Objectives

To determine the effects of any level of vitamin E supplementation on the frequency of vitamin E deficiency disorders in people with cystic fibrosis.

Search methods

We searched the Cochrane Group's Cystic Fibrosis Trials Register and also searched international online trial registries for any ongoing clinical trials that were not identified during our register search.

Date of last search of the Register: 11 August 2020.

Date of last search of international online trial registries: 20 July 2020.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials comparing any preparation of vitamin E supplementation to placebo or no supplement, regardless of dosage or duration.

Data collection and analysis

Two authors extracted outcome data from each study (published information) and assessed the risk of bias of each included study. They assessed the quality of the evidence using GRADE.

Main results

Four studies with a total of 141 participants were included in the review, two of these were in children (aged six months to 14.5 years), and two did not specify participants' age. All studies used different formulations and doses of vitamin E for various durations of treatment (10 days to six months). Two studies compared the supplementation of fat-soluble as well as water-soluble formulations to no supplementation in different arms of the same study. A third study compared a water-soluble formulation to a placebo; and in the fourth study a fat-soluble formulation of vitamin E was assessed against placebo.

There was limited detail about randomisation and blinding in the included studies which compromises the quality of the evidence base for the review. The heterogeneous mix of the formulations with differing bioavailabilities among these studies also limits the generalisability of the data to the wider cystic fibrosis population.

None of the studies in either comparison report the review's primary outcomes of vitamin E total lipid ratio or the incidence of vitamin E-specific deficiency disorders, or the secondary outcomes lung function or quality of life.

Water-soluble vitamin E

Water-soluble vitamin E may improve serum vitamin E levels compared with control at six months, one study (45 participants), mean difference (MD) 19.74 umol/L (95% confidence interval (CI) 13.48 to 26.00) (low-quality evidence). Similar results were also seen at one month, two studies (32 participants), MD 17.66 umol/L (95% CI 10.59 to 24.74) and at three months, one study (45 participants), MD 11.61 umol/L (95% CI 4.77 to 18.45). Only one study (45 participants) reported weight (secondary outcome of growth and nutritional status) at one and six months, but showed no difference between treatment and control at either time point.

Fat-soluble vitamin E

Two studies (36 participants) reported higher levels of serum vitamin E at one month with fat-soluble vitamin E compared with control, MD 13.59 umol/L (95% CI 9.52 to 17.66); however, at three months one study (36 participants) showed no difference between treatment and control. No studies in this comparison reported on growth or nutritional status.

Authors' conclusions

Vitamin E supplementation may lead to an improvement in vitamin E levels in people with cystic fibrosis, although evidence we assessed was low quality. No data on other outcomes of interest were available to allow conclusions about any other benefits of this therapy.

In future, larger studies are needed, especially in people already being treated with enteric-coated pancreatic enzymes and supplemented with vitamin E, to look at more specific outcome measures such as vitamin E status, lung function and nutritional status. Future studies could also look at the optimal dose of vitamin E required to achieve maximal clinical effectiveness.

PLAIN LANGUAGE SUMMARY

Vitamin E supplementation in people with cystic fibrosis

Review question

We wanted to know what effects, if any, vitamin E supplementation (at any dose) has on how often people with cystic fibrosis have health problems due to vitamin E deficiency.

Background

Approximately 85% to 90% of people with cystic fibrosis do not produce enough enzymes in their pancreas and are not able to absorb fat when digesting food; they are also likely to have problems absorbing the fat-soluble vitamins A, D, E and K. If levels of vitamin E are too low, this may cause blood disorders and problems with the nervous system, with memory and with thinking skills.

Search date

We last searched for evidence on 20 July 2020.

Study characteristics

We identified four studies including 141 participants; two of these were in children (aged six months to 14.5 years) and two did not specify the age of the participants. Those taking part in the studies received different forms of vitamin E supplements (either water-soluble or fat-soluble), placebo (a substance containing no medication) or no supplements. Three studies stated that the treatment for each person was chosen at random, but one study only said the people were split into different groups.

Key results

Water-soluble vitamin E

Evidence from one study (45 participants) showed that supplementation may increase vitamin E levels in the blood after six months. Similar results were seen at the earlier time points of one month (two studies, 32 participants) and three three months (one study, 45 participants). Only one study (45 participants) reported weight at one and six months, but showed no difference between supplementation and placebo at either time point.

Fat-soluble vitamin E

Two studies (36 participants) reported higher levels of serum vitamin E after one month of fat-soluble vitamin E supplements compared with no treatment, but a different study (36 participants) did not find any difference between supplementation and no treatment after three months.

None of the studies in either comparison reported results for our planned outcomes of vitamin E total lipid ratio, the incidence of vitamin E-specific deficiency disorders, lung function or quality of life.

As the studies used different forms of supplements and different doses, it was difficult to combine the results and apply them to the wider cystic fibrosis population. The results showed that vitamin E supplementation may lead to an improvement in vitamin E levels in people with cystic fibrosis, but the quality of the evidence was low.

Future studies should look at more specific outcomes such as vitamin E status, lung function and nutritional status, especially in people already receiving treatment with pancreatic enzymes and vitamin E supplements. They could also look at the best level of vitamin E supplements needed to be most clinically effective.

Quality of the evidence

We judged the evidence to be low quality for the following reasons. We do not think that any of the people taking part in the studies could tell whether they received the supplements or the placebo, so that would not have affected the results; although they would have known if they were taking supplements or not taking anything. We could not tell from the information we have whether most of the studies were designed so all people had an equal chance of being in any of the groups. We also could not tell if anyone would have been able to guess in advance which group they would be in. It was also not clear if there were results reported for everyone taking part in the studies and the reasons why anyone might have dropped out of the studies. We do not know if these facts will affect our confidence in the results.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: water-soluble vitamin E compared with control for cystic fibrosis

Water-soluble vitamin E compared with control for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: 10 mg/kg/day of oral vitamin E tocopherol (d-l alpha-tocopheryl acetate) in water-miscible solution

Comparison: no supplementation ([Harries 1969](#); [Wong 1988](#)) or placebo ([Levin 1961](#))

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No supplementation or placebo	Water-soluble oral vitamin E				
Vitamin E total lipid ratio	This outcome was not measured.					
Vitamin E levels in serum: umol/L Follow-up: 6 months	The mean serum level of vitamin E in the control group was 4.6 umol/L.	The mean serum level of vitamin E in the intervention group was 19.74 umol/L higher (13.48 umol/L higher to 26.00 umol/L higher).	MD 19.74 (13.48 to 26.00).	45 (1)	⊕⊕⊕⊕ low^{a,b}	Only 1 study reported this outcome at the 6-month time point (Levin 1961). 2 further studies reported serum levels of vitamin E at 1 month and found a statistically significant result in favour of the supplemental group, MD 17.66 (95% CI 10.59 to 24.74) (Harries 1969 ; Wong 1988).
Neuropathy due to vitamin E deficiency	This outcome was not measured.					
Retinopathy due to vitamin E deficiency	This outcome was not measured.					
BMI	This outcome was not measured.					
Height	This outcome was not measured.					

FEV₁ % predicted:
change from baseline

This outcome was not measured.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

BMI: body mass index; **CI**: confidence interval; **FEV₁**: forced expiratory volume in 1 second; **MD**: mean difference.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

- a. Downgraded once because of indirectness in the data. The single study reporting at 6 months included only children and therefore the effect on adults is unknown.
b. Downgraded once due to imprecision resulting from small numbers of participants (n = 45).

Summary of findings 2. Summary of findings: fat-soluble vitamin E compared with control for cystic fibrosis

Fat-soluble vitamin E compared with control for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: fat-soluble vitamin E 10 mg/kg/day in 2 trials ([Harries 1969](#); [Wong 1988](#)); participants < 20 kg = 600 IU/Day < 20 kg; participants > 20 kg = 1200 IU/day in 1 trial ([Keljo 2000](#))

Comparison: no supplementation ([Harries 1969](#); [Wong 1988](#)) or placebo ([Keljo 2000](#))

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No supplementation or placebo	Fat-soluble oral vitamin E				
Vitamin E total lipid ratio	This outcome was not measured post-intervention.					
Vitamin E levels in serum: umol/l	None of the trials measured this outcome at the 6-month time point.					2 studies reported serum levels of vitamin E at 1 month and found a statistically significant

Follow-up: six months		<p>icant result in favour of the supplemental group, MD 13.59 (95% CI 9.52 to 17.66) (Harries 1969; Wong 1988).</p> <p>1 study reported serum levels of vitamin E at 3 months and found no statistically significant difference between intervention and control, MD 6.40 (95% CI -1.45 to 14.25) (Keljo 2000).</p>
Neuropathy due to vitamin E deficiency	This outcome was not measured.	
Retinopathy due to vitamin E deficiency	This outcome was not measured.	
BMI	This outcome was not measured.	
Height	This outcome was not measured.	
FEV ₁ % predicted: change from baseline	This outcome was not measured.	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

BMI: body mass index; **CI**: confidence interval; **FEV₁** : forced expiratory volume in 1 second; **MD**: mean difference.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is caused by a genetic defect in the CF transmembrane conductance regulator (CFTR) protein in exocrine glands (e.g. the pancreas, airways, lungs, liver, salivary glands, reproductive tract and sweat glands) (Goss 2004; Kerem 2005; Welsh 2001). The disease is clinically characterized by thick, sticky secretions which impair numerous body systems, primarily the digestive and respiratory tracts. Within the respiratory system, CFTR dysfunction leads to a breakdown in mucociliary clearance, mucous retention, infection and inflammation. These in turn result in respiratory signs and symptoms including cough, copious production of sputum, difficulty in breathing, decreased lung function and respiratory tract infections most importantly due to *Pseudomonas aeruginosa* (Aaron 2004; Kozłowska 2008; Linnane 2008). Within the digestive system, pancreatic secretions are reduced with low volumes of fluid and bicarbonate in people with CF. This causes duct obstruction and retention and activation of secreted proenzymes in pancreatic ducts leading to destruction and fibrosis of the pancreas itself. This process begins in utero and continues after birth, leading to exocrine pancreatic insufficiency. Pancreatic insufficiency (decreased pancreatic enzyme release), failure of CFTR-mediated intestinal bicarbonate secretion, deranged bile acid function and inactivation of enzymes by hyperacidity in the upper intestine all contribute to malabsorption (Taylor 2010).

Approximately 85% to 90% of people with CF are pancreatic insufficient and have impaired fat absorption. These individuals are also prone to malabsorption of the fat soluble vitamins A, D, E and K and require pancreatic enzyme replacement therapy (PERT). Low vitamin E levels in people with CF put them at an increased risk of the detrimental effects of vitamin E deficiency. Vitamin E deficiency disorders are rare (Dodge 2006; Sinaasappel 2002; Welsh 2001). They include, but are not limited to, cerebellar ataxia, peripheral neuropathy, myopathy, pigmented retinopathy and visual field constriction with loss of vision (Ueda 2009). Sensory motor neuropathy, which manifests as loss of reflexes and generalized weakness, may occur late in the course of vitamin E deficiency (Suskind 2009). Vitamin E deficiency can also manifest as cognitive impairment (Koscik 2005) and haemolytic anemias (Swann 1998; Wilfond 1994).

Current guidelines on the treatment of CF support PERT in individuals with pancreatic enzyme insufficiency, including fat-soluble vitamin supplementation, which includes vitamin E (Dodge 2006; Sinaasappel 2002). Recommendations include a dosage of 100 IU to 400 IU per day for all individuals with CF (Sinaasappel 2002).

Description of the intervention

Vitamin E is a generic term for a group of eight fat-soluble compounds, the tocopherols and tocotrienols, of which α -tocopherol has the highest biological activity (Suskind 2009). It functions as an antioxidant that protects cell membranes from oxidative damage (Peters 1996); its deficiency may worsen the burden of oxidative stress that results from constant inflammation, especially in respiratory and digestive systems which occurs in CF (Brigelius-Flohé 2009). In addition to its antioxidant properties, vitamin E also helps improve nerve conduction (Cynamon 1988),

maintain the structural integrity of the haemoglobin membrane (Swann 1998) and, along with vitamin A, plays a role in vision (Bines 2005). The specific mechanism of action for most of its effects is still relatively unknown (Brigelius-Flohé 2009).

Normal vitamin E blood levels generally range from about 23 $\mu\text{mol/L}$ to 46 $\mu\text{mol/L}$. Plasma levels of 80 $\mu\text{mol/L}$ and above are considered excessive (Biesalski 2009). However, vitamin E circulates in the blood bound to lipoproteins and, as a consequence, more accurate assessment of status should be assessed using the vitamin E to total lipid ratio, which has a sensitivity of 95% and a specificity of 99% for detecting vitamin E deficiency (Thurnham 1986). Normal ratios of α -tocopherol to total lipid are greater than 0.6 mg and greater than 0.8 mg α -tocopherol per gram total lipid in children and adults respectively. In a study in a non-CF population, 47% of low vitamin E levels were normal and 58% with elevated plasma vitamin E were normal or low when re-evaluated using vitamin E to total lipid ratio (Winbauer 1999).

Oral and parenteral multivitamin and vitamin E supplements have previously been used to ameliorate vitamin E deficiencies (Aparicio 2001; Peters 1996; Swann 1998; Ueda 2009; Winklhofer-Roob 1996). In CF, this supplementation is usually oral and used in conjunction with PERT. Oral vitamin E may be in the form of chewable or non-chewable tablets, liquids or powders (Mayo Clinic 2009). Treatment is usually begun as soon as the serum vitamin E levels are investigated and is often life-long. Even in large doses, treatment has few adverse effects (Aparicio 2001), which were therefore not specifically measured in this review.

How the intervention might work

Vitamin E supplementation aims to correct the deficiency of this vitamin in the body.

Why it is important to do this review

Routine fat-soluble multivitamin supplementation has become the accepted standard of care in management of people with CF (Bell 2002; Bines 2005; Sinaasappel 2002). The general recommendation of the UK Cystic Fibrosis Trust Nutrition Working Group is regular estimation of serum vitamin E (in addition to lipid ratio) levels to guide vitamin E supplementation of up to 100 mg to 200 mg daily depending on the age of the individual (UK Cystic Fibrosis Trust 2002). This is an updated version of a previous review (Okebukola 2011; Okebukola 2014; Okebukola 2017).

OBJECTIVES

To determine the effects of supplementation of vitamin E (whether this was over and above the usual supplements or the only vitamin E supplement given) on vitamin E deficiency or frequency of vitamin E deficiency disorders in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised controlled trials (including cluster-randomised trials).

Types of participants

All individuals with a diagnosis of CF who have not received a lung transplant. Diagnosis of CF should be based on a positive sweat test or genetic testing or both, plus one or more characteristic clinical features, a history of CF in a sibling, or a positive newborn screening test (Farrell 2008).

Vitamin E supplements are prescribed routinely only to people with CF who are pancreatic insufficient; people who are pancreatic sufficient are supplemented only when levels are found to be suboptimal from blood test results (usually in an antioxidant role). These are very different sets of individuals and vitamin E is supplemented for entirely different reasons. We therefore planned to analyse studies with people who were pancreatic insufficient separately from those studies with people who were pancreatic sufficient.

Types of interventions

Any preparation of vitamin E supplementation compared to placebo or no supplement, regardless of dosage or duration. This supplement could be over the usual amount of vitamin being given, or the only vitamin E supplement.

Types of outcome measures

Primary outcomes

1. Vitamin E total lipid ratio
2. Vitamin E levels in serum
3. Incidence of vitamin E-specific deficiency disorders
 - a. peripheral neuropathy
 - b. retinopathy
 - c. myopathy and ataxia
 - d. cognitive impairment
 - e. haemolytic anemias

Secondary outcomes

1. Growth and nutritional status
 - a. weight
 - b. height
 - c. body mass index (BMI) percentile
2. Lung function tests
 - a. forced expiratory volume at one second (FEV₁) (% predicted or L)
 - b. forced vital capacity (FVC) (% predicted or L)
3. Quality of life (QoL) (using validated tools, e.g. the Cystic Fibrosis Questionnaire- Revised (CFQ-R) (Quittner 2009) and Cystic Fibrosis Quality of Life Questionnaire (CFQoL) (Gee 2000))

Search methods for identification of studies

There are no restrictions regarding language or publication status.

Electronic searches

We identified relevant studies from the Group's CF Trials Register using the term: vitamin E.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the *Cochrane Library*),

weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group [website](#).

Date of last search: 11 August 2020.

We searched the online international trial registers ([ISRCTN](#) and [www.clinicaltrials.gov](#)) for any ongoing clinical trials; we planned to search the WHO International Clinical Trials Registry Platform ([apps.who.int/trialsearch/](#)) for the 2020 update; however, due to the Covid-19 pandemic this resource was not available. The details of the search terms and resources are found in the appendices ([Appendix 1](#)).

Date of last search: 20 July 2020.

Searching other resources

We contacted manufacturers of vitamin E supplements for the results of studies that have been completed but not yet published, other ongoing or published studies. Where it was possible, we also contacted authors of included studies to obtain further information.

Data collection and analysis

Selection of studies

Two authors (PO and SK) independently reviewed titles and abstracts of all articles yielded from the literature search to identify potentially relevant studies. We assessed the full-texts of these identified studies for inclusion using pre-formulated screening criteria; and resolved disagreements by consensus. Due to a change in the author team between publication of the protocol and work commencing on the full review, only two authors selected studies instead of three as was indicated in the protocol.

Data extraction and management

Two authors (PO and SK) independently extracted pre-determined variables into electronic data collection forms. As indicated above, due to a change in the author team, only two authors independently extracted data instead of three as was planned in the protocol. We resolved disagreements by discussion and reached a consensus. In addition to extracting data for all outcome variables, we also recorded the following data when available.

Study details

- year of study
- study setting
- study design (cross-over, cluster or parallel, single centre or multicentre)
- source of funding
- whether sample size was calculated
- sample size (number enrolled or randomised versus the number analysed)
- method of sequence generation

- method of allocation concealment
- who was blinded and for which outcomes

Participant details

- age of participants
- sex of participants
- severity of disease
- inclusion and exclusion criteria
- pancreatic sufficient versus pancreatic insufficient
- record of PERT
- pre- or post-lung transplant
- presence or absence of diabetes mellitus
- numbers of dropouts and reasons for withdrawal from study (clinical, side effects, refusal, other)

Intervention details

- intervention formulation (i.e. capsule, solution, powder)
- dose of intervention
- frequency of administration
- duration of therapy
- concurrent medication(s)

Where available, we planned to extract data relevant for outcomes at one month, up to three months, up to six months, up to 12 months and annually thereafter. However, we were only able to extract data at one month, up to three months, up to six months. We also converted the units from md/dL to umol/L which is the SI unit.

We originally planned to present all formulations of vitamin E supplements combined, but have since decided it is more clinically appropriate to present the water-soluble formulations separately from the fat-soluble formulations.

As stated above, vitamin E supplements are prescribed routinely only to people who are pancreatic insufficient; those who are pancreatic sufficient are supplemented only when levels are found to be suboptimal. We therefore planned to analyse studies with people who are pancreatic insufficient separately from studies with people who are pancreatic sufficient. However, as the included studies did not present sufficient information to allow us to do this, we have presented all data combined.

Assessment of risk of bias in included studies

Two authors independently judged the risk of bias of each included study, following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We assessed the following domains as having a low, unclear or high risk of bias.

1. Randomisation (low risk - random number table, computer-generated lists or similar methods; unclear risk - described as randomised, but no details given; high risk - e.g. alternation, the use of case record numbers, and dates of birth or day of the week)
2. Concealment of allocation (low risk - e.g. list from a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes; unclear risk - not described; high risk - if allocation

sequence was known to, or could be deciphered by the investigators who assigned participants or if the study was quasi-randomised)

3. Blinding (of participants, personnel and outcome assessors)
4. Incomplete outcome data (whether investigators used an intention-to-treat analysis)
5. Selective outcome reporting
6. Other sources of bias

Measures of treatment effect

We reported the results from continuous outcomes as mean differences (MD) in change scores between groups and their 95% confidence intervals (CIs), as planned. Where only endpoint data were available, we planned to use the MD between endpoint scores, but no study reported endpoint data. All studies reported standard deviations (SD), which we used in the analysis. No studies reported standard errors (SEs).

We had planned to report the results from dichotomous outcomes using odds ratios (OR) and 95% CIs. However, all the data were reported as continuous outcomes. We did not include adverse effects as an outcome of interest and no studies reported data on relevant adverse event outcomes.

Initially, we had planned that where both change scores and endpoint data were available, we would combine both using the MD method in RevMan, being careful to use the appropriate SD (of both endpoint data and or change from baseline change) for each study. The differences were reported as MD in RevMan (RevMan 2011). However, we did not combine change scores and endpoint data as standardised mean differences (SMDs).

We planned to use the SMD and 95% CIs and calculate pooled effects, if studies reported outcomes using different measurement scales, but this was unnecessary as all the studies reported using the same measurement system. We did, however, convert all measurements to the SI unit (umol/L).

Unit of analysis issues

If we had found any cross-over studies, we intended to calculate the mean treatment differences where possible and enter these using the fixed-effect generic inverse variance (GIV) analysis in RevMan, to provide summary weighted differences and 95% CIs (RevMan 2011). For any cross-over studies we identify in future updates of this review, if we believe there is a carryover effect which will outlast any washout period included in the study or where second period data is unavailable, we will include only data from the first arm in the meta-analysis (Elbourne 2002). Following peer review comments, we updated our planned methods and for multi-arm studies, we now plan to include data from both arms, in line with the current guidance in the *Cochrane Handbook of Systematic Reviews* (Higgins 2011b).

Dealing with missing data

We planned to make up to three attempts to contact corresponding authors for studies in which there are missing data. If this was not productive, we planned to impute the missing data (SDs, standard errors (SEs) or other parameters) with replacement values based on statistical analysis as recommended in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We planned to treat these as if they were observed, under the assumption that

these data are not missing at random. We contacted the authors of the Keljo study to obtain some of the missing data which were used in the abstract. The authors replied and sent us the complete unpublished study (Keljo 2000). We also planned to conduct a sensitivity analysis to test the effects of imputing missing data, but did not need to do this as we obtained the missing data directly from the authors.

Assessment of heterogeneity

If we had been able to combine sufficient data from multiple studies, we intended to describe any heterogeneity between the study results and test this to see if it reached statistical significance using the χ^2 test. We considered heterogeneity to be significant when the P value is less than 0.10. We also planned to use the I^2 statistic (Higgins 2003), where heterogeneity is categorized such that a value around 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and over 70% to 100% is considerable heterogeneity as described in the *Cochrane Handbook of Systematic Reviews* (Higgins 2011c)

Assessment of reporting biases

We intended to analyse included studies for selective reporting by comparing study protocols with final reports to identify outcomes measured but not reported. Where protocols were not available, we cross-referenced the 'Methods' section of the study report with the 'Results' section to assess whether study authors comment on all the outcomes they say they measured. We did not identify clinically important outcomes that were omitted in the included studies. We also attempted to reduce publication bias by searching unpublished sources and grey literature in addition to published sources.

Data synthesis

If possible, we planned to enter data into meta-analyses, combining all dose regimens and include the 95% CI, estimated using a fixed-effect model. We also planned to utilise the random-effects model whenever we had identified moderate or substantial heterogeneity (I^2 greater than 50%).

Subgroup analysis and investigation of heterogeneity

We intended to study the following subgroups to investigate any heterogeneity that we might have identified, but were not able to do so due to a lack of data:

1. children (under 18 years) and adults (18 years of age and over);
2. method of diagnosis of CF (screened versus non-screened);
3. presence versus absence of co-morbid conditions like diabetes mellitus.

Sensitivity analysis

We also planned to use the following sensitivity analyses to assess the impact of the potentially important factors on the overall outcomes, but were not able to do so due to a lack of data:

1. analysis using a random-effects model;
2. per protocol analysis;
3. high versus low risk of bias for each domain assessed;
4. analysis with or without imputed data.

Summary of findings tables

In a post hoc change from protocol, the review authors have presented two summary of findings tables, one for water-soluble vitamin E versus control and one for fat-soluble vitamin E versus control (Summary of findings 1; Summary of findings 2).

We have reported the following outcomes in both tables at six months.

1. Vitamin E total lipid ratio
2. Vitamin E levels in serum
3. Neuropathy due to vitamin E deficiency
4. Retinopathy due to vitamin E deficiency
5. BMI
6. Height
7. FEV₁ % predicted (change from baseline)

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

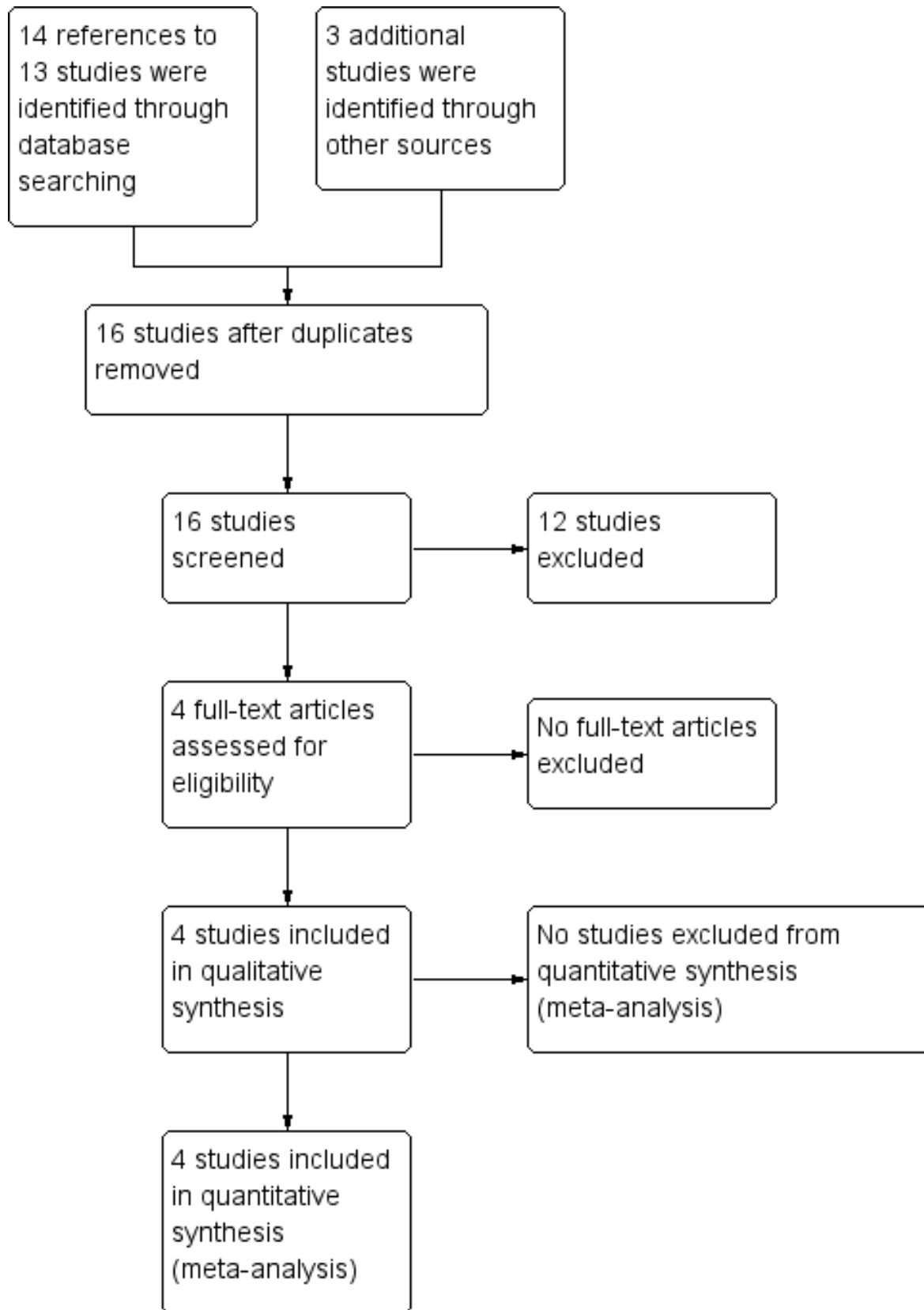
RESULTS

Description of studies

Results of the search

We identified 14 references to 13 studies from the search of our databases outlined above. We identified two additional studies from searching other databases (the [ISRCTN](http://www.isrctn.com) website and www.clinicaltrials.gov). As illustrated in the PRISMA diagram, 15 studies were included for screening (Figure 1). Of the 15 studies, four were included and 11 were excluded; the reasons for their exclusion are discussed below.

Figure 1. Study flow diagram



We contacted the manufacturers of vitamin E supplements; however, they responded that they did not have any information about any unpublished or ongoing studies.

Included studies

Four studies ($n=141$) were included (Harries 1969; Levin 1961; Keljo 2000; Wong 1988). Two of these were only available as abstracts, which limited the amount of detail available for the review (Keljo 2000; Wong 1988); however, we were able to obtain additional information from the authors of the Keljo study. The fourth study is a full paper, but has only been published as part of conference proceedings and not in a journal (Harries 1969). Two of these studies are from the 1960s when PERT would not have been widely available and the management strategies for CF quite different from present times.

There were insufficient studies included to conduct subgroup analyses or sensitivity analyses.

Trial characteristics

Three of the four studies were described as randomised (Harries 1969; Levin 1961; Keljo 2000) and the fourth study was a controlled clinical study with no reference to randomisation during allocation of participants to study arms (Wong 1988). However, we assumed that the authors performed some form of randomisation. All studies were of parallel design; two consisted of two arms (Keljo 2000; Levin 1961) and two of three arms (Harries 1969; Wong 1988). All were single-centre studies; two were conducted in the USA (Keljo 2000; Levin 1961), one was conducted in Canada (Wong 1988) and the fourth study was conducted in the UK (Harries 1969). Study duration ranged from between 10 and 14 days (Wong 1988) to six months (Levin 1961).

Participants

All studies were of similar size, the number of participants ranged from 22 (Wong 1988) to 49 (Levin 1961). Two studies recruited children only (Harries 1969; Levin 1961) and two studies did not specify if participants were children or adults or a mix of both (Keljo 2000; Wong 1988). Both paediatric studies gave details on the age of their participants: range six months to 14.5 years (Harries 1969); and mean (SD) age of participants in the treatment group 113.1 (65.12) months and in the placebo group 113.5 (63.99) months (Levin 1961). Only one study gave any details of the gender split of participants (26 males, 19 females) (Levin 1961). Two studies reported that participants had dropped out (Harries 1969; Levin 1961), but only one gave specific reasons for this (Levin 1961). In the remaining two studies there seemed to be drop outs from the study, but these were not clearly discussed (Keljo 2000; Wong 1988). Disease status varied between studies; one study described participants as having been stabilized with a study-specific disease severity score of 2.22 in the treatment group and 2.10 in the placebo group (where 1 is good condition and 5 is very severe illness) (Levin 1961). A second study described participants as having mild pulmonary disease (Keljo 2000). A third study recruited participants admitted to hospital for a pulmonary exacerbation (Wong 1988) and the remaining study did not comment on disease status (Harries 1969). None of the studies explicitly stated whether the participants were pancreatic sufficient or insufficient.

Interventions

Two studies compared fat-soluble and water-miscible supplements of vitamin E to no supplementation; both these studies used the dose of 10 mg/kg/day for the supplements (Harries 1969; Wong 1988). The water-miscible formulation Harries used contained the surface active agent cremaphor EI and glycerine (Harries 1969). Wong used an oral water-soluble vitamin E preparation (Aqasol E) (Wong 1988). A further study compared the same dose of water-miscible vitamin E supplement to placebo (Levin 1961). The remaining study compared a vegetable oil placebo to RRR alpha-tocopherol which was given to participants weighing less than 20 kg at a dose of 600 IU/day and to participants weighing more than 20 kg at a dose of 1200 IU/day (Keljo 2000).

Two studies stated that participants continued to receive pancreatic enzyme supplementation during the study (Harries 1969; Wong 1988). One study stated participants continued to receive their standard vitamin supplements ADEKs[®] (Keljo 2000).

Outcomes

Only the measurement of serum vitamin E levels was common to all four included studies (Harries 1969; Keljo 2000; Levin 1961; Wong 1988). Other outcomes measured in the blood included peroxide red blood cell (RBC) haemolysis (Harries 1969), serum glutamic oxalacetic transaminase (Levin 1961), tumour necrosis factor (TNF) alpha and interleukin-6 levels (Keljo 2000) and alpha tocopherol to cholesterol ratio (Wong 1988). In addition, Levin reported on weight gain, muscle strength and subjective improvement (Levin 1961).

Excluded studies

A total of 11 studies were excluded from this review. Eight studies were excluded as they compared various vitamin E formulations, but not to a placebo or no supplement arm, and therefore not meeting the selection criteria for the review (Homola 2017; Jacquemin 2009; Munck 2010; Nasr 1993; Papas 2007; Winklhofer-Roob 1992; Winklhofer-Roob 1996; Wood 2003). A further study was excluded because it described the use of vitamin E with placebo compared to vitamin E with ursodeoxycholic acid in a single participant, therefore the only difference in treatment was ursodeoxycholic acid (Thomas 1995). One study was excluded because it was not randomised or quasi-randomised (Sagel 2011). In the final study, which is still ongoing, tocotrienol is being used as a genetic modifier in people with CF (Kerem 2009). One of the arms of the study entails supplementation with tocotrienol followed by a washout period; however, this study was excluded because it is not a study of vitamin E supplementation compared to placebo or control.

Risk of bias in included studies

Two of the included studies were published as short abstracts, hence the information available about the design and robustness was limited (Keljo 2000; Wong 1988). However, one of the authors provided additional information by sending us the unpublished manuscript which contained further details (Keljo 2000). Clear information was available for the remaining two studies (Harries 1969; Levin 1961).

Allocation

In three of the included studies the risk of bias from sequence generation was unclear (Harries 1969; Keljo 2000; Wong 1988). Two

of these were described as randomised, but gave no details of the randomisation process (Harries 1969; Keljo 2000); the third merely stated that participants were divided into one of three groups (Wong 1988). In the final study, there was a clear description of the randomisation process using labelled cards being placed in sealed envelopes and then each child accepted into the study group was assigned an envelope; we judged this to have a low risk of bias for sequence generation (Levin 1961).

Three of the studies did not discuss concealment of allocation and are judged to have an unclear risk of bias (Harries 1969; Keljo 2000; Wong 1988) the fourth study used sealed envelopes to conceal the allocation sequence and is judged to have a low risk of bias (Levin 1961).

Blinding

In two studies, vitamin E supplementation is compared to no supplementation, so these studies cannot be blinded (Harries 1969; Wong 1988). Since we are reporting on objective outcome measurements, the absence of blinding is unlikely to increase the risk of bias in these studies and we have judged them to have a low risk of bias. Another study was double-blinded and used a vegetable oil placebo, we therefore judged it to have a low risk of performance and detection bias (Keljo 2000). In the study by Levin, the participants and the testers are described as being blinded; serum tocopherol levels were also not known to the examiners (Levin 1961). We felt overall that it had a low risk of bias.

Incomplete outcome data

Two studies reported that participants had dropped out (Harries 1969; Levin 1961). Only one of these gave specific reasons for these withdrawals and the attrition is balanced among the two groups; hence we judged this study to have a low risk of bias (Levin 1961). In the study by Harries, vitamin E levels at the end of one month of supplementation were not available for one participant in the fat-soluble group and two in the water-miscible supplementation group (Harries 1969). An intention-to-treat analysis was not used; however, these missing data are unlikely to have a clinically significant impact on the results and we therefore judged the study to have a low risk of bias (Harries 1969).

In the study by Wong, the initial number of participants allocated to each group is not clear and hence it is difficult to judge the number of dropouts across each group (Wong 1988). In view of this insufficient reporting we judged it have an unclear risk of bias due to incomplete outcome data (Wong 1988). In the remaining study, there appeared to be dropouts, but these were not clearly discussed and we judged this study to also have an unclear risk of bias (Keljo 2000).

Selective reporting

No study protocol was available to inform the risk of reporting bias in any of the four studies (Harries 1969; Keljo 2000; Levin 1961; Wong 1988). All studies report results for the outcomes stated in their 'Methods' sections. In the absence of a protocol and no apparent risk of bias, we judge the overall risk of bias to be unclear in three studies (Harries 1969; Levin 1961; Wong 1988). The authors of the Keljo study sent us the full study article on request, but the full article did not elucidate the methods of randomisation and did not fully report the results of the control group, which gives it a high risk for bias (Keljo 2000).

Other potential sources of bias

There is no information on how the diagnosis of CF was reached in any of the included studies or whether participants were pancreatic sufficient or insufficient, which may introduce a potential risk of bias. We therefore conclude a unclear risk of other potential bias for all studies. However, in the earlier studies the participants would not have had their pancreatic insufficiency treated with effective pancreatic enzymes as enteric-coated preparations were not available. Instead, they would have been treated with a low-fat diet to control symptoms of fat malabsorption. In addition, the dosages used in the Keljo study are higher than current international recommendations of: age up to 12 months, 40 IU to 80 IU; age one to three years, 50 IU to 150 IU; age four to seven years, 150 IU to 300 IU; and age eight years to adult, 150 IU to 500 IU (Sinaasappel 2002).

Effects of interventions

See: **Summary of findings 1** Summary of findings: water-soluble vitamin E compared with control for cystic fibrosis; **Summary of findings 2** Summary of findings: fat-soluble vitamin E compared with control for cystic fibrosis

The effects of interventions are summarised in the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided (Summary of findings 1; Summary of findings 2).

Water-soluble vitamin E versus control

Three studies (n = 101) reported on this comparison (Levin 1961; Harries 1969; Wong 1988).

Primary outcomes

1. Vitamin E: total lipid ratio

None of the studies using this comparison reported on this outcome.

2. Vitamin E levels in serum

Three studies of water-soluble vitamin E preparations reported on this outcome (Levin 1961; Harries 1969; Wong 1988). Data are available from two studies (n = 32) at the one-month time point (Harries 1969; Wong 1988) and show a statistically significant result in favour of the supplemented group, MD 17.66 (95% CI 10.59 to 24.74) (Analysis 1.1). Levin (n = 45) reported statistically significant improvement in vitamin E levels at three months, MD 11.61 (95% CI 4.77 to 18.45) and six months, MD 19.74 (95% CI 13.48 to 26.00) (low-quality evidence) (Analysis 1.1).

3. Incidence of vitamin E-specific deficiency disorders

None of the studies include reported peripheral neuropathy, retinopathy, myopathy and ataxia, or cognitive impairment in either the supplemented or the placebo group. The studies did not report on clinical occurrence of haemolytic anaemia in either group.

Secondary outcomes

1. Growth and nutritional status

a. Weight

Levin (n = 45) reported an increase in weight in both the placebo and supplemented arms from the baseline to the one-month and six-month mark. However, the improvement in weight, which although was higher in the placebo group, was not statistically significant between groups at one month, MD -2.80 kg (95% CI -8.98 to 3.38) or after six months, MD -3.60 kg (95% CI -13.36 to 6.16) ([Analysis 1.2](#)).

b. Height

None of the included studies reported any changes in height as an outcome measure.

c. BMI percentile

None of the studies reported BMI percentile as an outcome measure.

2. Lung function tests

None of the studies measured and reported lung function (FEV₁ or FVC, either as % predicted or L).

3. QoL

None of the included studies reported on QoL.

Fat-soluble vitamin E versus control

Three studies (n = 101) reported on this comparison ([Harries 1969](#); [Keljo 2000](#); [Wong 1988](#)).

Primary outcomes

1. Vitamin E: total lipid ratio

A single study measured alpha tocopherol to cholesterol ratio at baseline, but did not report post-intervention levels ([Wong 1988](#)).

2. Vitamin E levels in serum

Three studies of fat-soluble vitamin E preparations reported on this outcome ([Harries 1969](#); [Keljo 2000](#); [Wong 1988](#)). At up to one month data were combined for two studies (n = 36) and showed a statistically significant result in favour of supplementation, MD 13.59 (95% CI 9.52 to 17.66). Data were also available at up to three months for a single study (36 participants), but were not statistically significant, MD 6.40 (95% CI -1.45 to 14.25) ([Analysis 2.1](#)).

3. Incidence of vitamin E-specific deficiency disorders

None of the studies include reported peripheral neuropathy, retinopathy, myopathy and ataxia, or cognitive impairment in either the supplemented or the placebo group. The studies did not report on clinical occurrence of haemolytic anaemia in either group.

Secondary outcomes

1. Growth and nutritional status

None of the included studies reported any changes in weight, height or BMI percentile as an outcome measure.

2. Lung function tests

None of the studies measured and reported lung function (FEV₁ or FVC, either as % predicted or L).

3. QoL

None of the included studies reported on QoL.

DISCUSSION

People with CF who are pancreatic insufficient are at an increased risk of malabsorption of fat-soluble vitamins. Vitamin E supplementation, usually in combination with PERT, is universally recommended for people with CF who are pancreatic insufficient. We attempted to evaluate the effect of vitamin E supplementation compared with placebo in improving vitamin E levels and rectifying this deficiency in people with CF. We also wanted to assess the effect of vitamin E supplementation on the avoidance of vitamin E deficiency, growth, nutrition and respiratory status in people with CF.

A state of vitamin E deficiency, as characterised by low levels of the vitamin, has been shown to be associated with problems such as haemolysis and cognitive difficulties. Vitamin E supplementation may have additional beneficial effects as an antioxidant and possibly also an anti-inflammatory role. It was not in the remit of this review to explore the latter role.

Summary of main results

Four studies with a total of 141 participants were included in the review ([Harries 1969](#); [Keljo 2000](#); [Levin 1961](#); [Wong 1988](#)). All studies used different formulations and doses of vitamin E for various durations of treatment. There were three eligible trials comparing fat-soluble vitamin supplementation to control ([Harries 1969](#); [Keljo 2000](#); [Wong 1988](#)), two of these studies also used water-miscible formulations ([Harries 1969](#); [Wong 1988](#)). One further study compared a water-miscible formulation to control ([Levin 1961](#)). The duration of supplementation in the studies also differed from 10 days ([Wong 1988](#)) to six months ([Levin 1961](#)). Vitamin E supplementation is usually undertaken in conjunction with PERT, as was case in at least three of the four included studies ([Harries 1969](#); [Keljo 2000](#); [Wong 1988](#)).

Fat-soluble vitamin E supplementation

Two studies (n = 32) evaluating fat-soluble supplementation indicated improvements in vitamin E levels in serum at one month ([Harries 1969](#); [Wong 1988](#)); a third study (n = 45) also found higher levels of serum vitamin E in the supplemented group at three and six months, but the evidence was low-quality ([Levin 1961](#)). Only one study (n = 45) assessed our secondary outcome of nutritional status and reported an increase in weight in both supplemented and no treatment groups at one and six months, but there was no difference between groups at either time point ([Levin 1961](#)).

Water-miscible vitamin E supplementation

Three studies reporting the use of water-soluble supplements ([Harries 1969](#); [Keljo 2000](#); [Wong 1988](#)). At one month, two studies (n = 36) showed higher levels of serum vitamin E in the supplemented group ([Harries 1969](#); [Wong 1988](#)). At three months, a single study (n = 36) in which participants were receiving the usual vitamin E supplements did not find any difference between

supplements or placebo in serum vitamin E levels (Keljo 2000). It is, however, difficult to definitively draw the conclusion that additional supplementation (over the usual amount) does not lead to a statistically significant improvement since the dosage of vitamin E supplementation may impact the results.

None of the studies in either comparison report the review's primary outcomes of vitamin E total lipid ratio or the incidence of vitamin E-specific deficiency disorders; however, baseline (untreated) vitamin E levels were low in all participants in three of the four included studies and these continued to be so in the placebo or no supplementation groups (Harries 1969; Levin 1961; Wong 1988). None of the included studies in either comparison looked at improvements in lung function or cognition following supplementation; and hence it is difficult to draw any conclusions about the effect of vitamin E on these parameters. It is also instructive that none of the studies reported on many of the review outcomes and none of them had a common set of outcomes. It may thus be necessary to consider developing a core set of outcomes for research in this area.

Overall completeness and applicability of evidence

Vitamin E levels were the primary outcome measures in only two of the four included studies (Harries 1969; Wong 1988). One of these studies also reported the alpha tocopherol to cholesterol ratio at baseline, which is also a valid measure of vitamin E levels; however, this study did not report alpha tocopherol to cholesterol ratios post-intervention (Wong 1988). None of the studies detail the basis for diagnosis of CF or pancreatic insufficiency. Varying formulations of vitamin E supplementation were used in the studies; three used fat-soluble formulations (Harries 1969; Keljo 2000; Wong 1988) and three used water-miscible formulations (Harries 1969; Levin 1961; Wong 1988). Bioavailability of vitamin E formulations can be variable. Comparison between various formulations was not in the remit of our review; however, this can potentially impact the serum vitamin levels thereby impacting the generalizability of the data. It is also possible that duration of supplementation may be a limitation to overall applicability as the longest study only lasted six months. Some of the included studies were conducted more than 50 years ago, when PERT was not available. Since PERT helps in fat (and fat-soluble vitamin) absorption, the routine use of PERT will affect vitamin E levels in clinical practice.

Quality of the evidence

Two of these studies were published as short abstracts only (Keljo 2000; Wong 1988). Assessment of one of these was limited (Wong 1988), but the author of the second abstract provided us with additional data (Keljo 2000). One study was available as a full paper, but only presented at a conference and not published in a peer-reviewed journal (Harries 1969). In the remaining three papers, the methods of randomisation and blinding are detailed only in one paper (Levin 1961). In one paper there is no presentation of standard deviation (SD) of the effect in the control group introducing a risk of bias (Keljo 2000).

We were only able to assess limited evidence from each comparison (fat-soluble supplementation versus control and water-miscible supplementation versus control) using the GRADE criteria (Summary of findings 1; Summary of findings 2). The limitations of the available data due to imprecision and inconsistency compromise the quality of the evidence base for

the review. Furthermore, indirectness (the study assessed only included children so the effects on adults are unknown) restricts the applicability of the evidence.

Potential biases in the review process

The two authors individually appraised all the studies and the risk of any further biases, other than those detailed in risk of bias tables, is very unlikely. None of the authors have any conflicts of interest to declare.

Agreements and disagreements with other studies or reviews

Vitamin E deficiency in CF is reported to cause haemolytic anaemia (Wilfond 1994). None of the participants in the included studies were reported to have this complication. The exact relationship between vitamin E and lung health in CF is unclear. One study reported that vitamin E status is associated with an increased rate of pulmonary exacerbations in CF (Hakim 2007). However, a second study did not find any evidence to implicate vitamin E deficiency in the development of lung disease or airway inflammation (Bines 2005). None of the included studies reported lung function parameters for us to examine this relationship.

A Cochrane Review examined the effect of antioxidant supplementation (including vitamin E) on lung function in people with CF (Ciofu 2019). While this review concluded that it is difficult to assess the effect of antioxidants due to the very intensive antibiotic treatment and other concurrent treatments that people with CF take. There was limited evidence of some improvement in lung function with inhaled and oral glutathione and in nutritional status with oral glutathione, but no evidence of any positive treatment effect of antioxidants on quality of life, antibiotic days or adverse events.

As part of the Wisconsin CF Neonatal Screening Project, Kosciuk reported low cognitive scores in people with CF who had low serum vitamin E levels at diagnosis (Kosciuk 2005). None of the studies included in the review report cognitive scores as an outcome measure. We are thus unable to draw any firm conclusion about the effect of vitamin E on cognitive function in CF.

AUTHORS' CONCLUSIONS

Implications for practice

People with cystic fibrosis (CF) with pancreatic insufficiency have impaired absorption of fats which forms the clinical basis to supplement fat-soluble vitamins including vitamin E. Three of the four studies in our review demonstrate that supplementation of vitamin E in people with CF leads to an improvement in vitamin E levels (Harries 1969; Levin 1961; Wong 1988), but in none of these studies was the status of pancreatic sufficiency or insufficiency in participants clear. Although none of the studies reported any detrimental effects of low vitamin E, the consequences of low vitamin E are well-known and a deficient state is best avoided. None of the included studies reported other outcomes of interest (except a non-statistically significant change in weight in one study (Levin 1961), so it is difficult to draw any recommendations for treatment from vitamin E supplementation in people with CF. It may be prudent to extrapolate that clinical vitamin E deficiency would be detrimental to the health of people with CF and our review findings

do not challenge the established practice of supplementation to avoid deficiency.

Implications for research

It will be unethical to perform a study where vitamin E levels are not corrected (in the placebo group) to the point of clinical deficiency; however, studies looking at clinical or quality of life improvements with vitamin E supplementation are needed. Due to the heterogeneity of CF and the multiple concurrent therapies which people with CF are usually prescribed, it may be difficult to ascertain the extent of improvement related to vitamin E alone.

Despite these challenges, larger research studies are needed in people with CF who are pancreatic insufficient and who are being treated with enteric-coated pancreatic enzymes and supplemented with vitamin E (usually fat-soluble preparations, e.g. as in the UK). These studies should look at more specific outcome measures such as vitamin E status (as most participants will already be receiving supplements), lung function, nutritional status and perhaps the reduction in airway inflammation. It may be useful to consider

developing a core set of outcomes for research in this area. It is, however, beyond the mandate of this review to recommend clinical doses of vitamin E for CF therapy. However, future studies may decide to test or confirm the optimal dose of vitamin E required to achieve maximal clinical effectiveness.

ACKNOWLEDGEMENTS

We would like to thank Larissa Shamseer for her input into an early draft of the protocol and also Helen McCabe who was an author on the published protocol. Thanks also to Nikki Jahnke for all her help with editing the review and other administrative matters. Finally we would like to thank the authors of the included Keljo study for providing additional data.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Harries 1969

Study characteristics

Methods	<p>Randomised controlled study of parallel design with 3 arms.</p> <p>Single-centre study in UK.</p> <p>Duration 1 month.</p>
Participants	30 children with CF on pancreatic enzyme supplementation. Age range 6 months to 14.5 years.
Interventions	<p>Acute supplementation and long-term supplementation.</p> <p>Children received either:</p> <ul style="list-style-type: none"> • no supplementation; • water-miscible preparation of vitamin E at a dose of 10 mg/kg; • fat-soluble vitamin E at a dose of 10 mg/kg.
Outcomes	Serum vitamin E levels and serum RBC haemolysis.
Notes	<p>Acute supplementation (called oral load test in the paper) was only done in 2 participants without controls.</p> <p>The study does not clarify whether the participants were pancreatic sufficient or insufficient.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly specified in the the paper, states "chosen at random and arbitrarily assigned to one of three groups".
Allocation concealment (selection bias)	Unclear risk	Not clearly specified in the the paper.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not clearly specified in the the paper. Very likely not blinded, as 1 of arms was no treatment. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clearly specified in the the paper. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 1 month reported data for 9 out of 10 participants in fat-soluble group (i.e. 1 dropout) and for 8 out of 10 participants in water miscible group (i.e. 2 dropouts), no discussions of reasons for dropouts. However, these missing data are unlikely to have a significant impact on the results.
Selective reporting (reporting bias)	Unclear risk	Trial protocol not available, but outcomes stated in 'Methods' section reported in 'Results'.

Harries 1969 (Continued)

Other bias	Unclear risk	Limited information the basis of diagnosis of CF, pancreatic sufficiency/insufficiency etc.
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Keljo 2000

Study characteristics

Methods	<p>Randomised double-blind placebo-controlled study of parallel design.</p> <p>Single centre in the USA.</p> <p>Participants stratified according to FEV₁ (70% - 85% predicted and > 85% predicted) and use of DNase.</p> <p>Duration 3 months.</p>
Participants	40 participants with CF and mild lung disease (FEV ₁ % predicted > 70%). No details of age or gender split. Evenly distributed to treatment and placebo groups.
Interventions	<p>Participants randomised to take vegetable oil placebo or RRR alpha-tocopherol (participants < 20 kg = 600 IU/Day < 20 kg; participants > 20 kg = 1200 IU/day).</p> <p>All participants also took ADEKs[®] for the duration of the study.</p>
Outcomes	<p>Beginning and end of study: serum vitamin E levels; TNF-alpha measurements; and IL-6 measurements.</p> <p>End of study only: liver enzyme levels; PT measurements; and PTT measurements.</p> <p>Adverse effects reported.</p>
Notes	<p>Authors provided full manuscript later, but it did not have much more information.</p> <p>Vitamin E and placebo capsules donated by Henkel Corporation. ADEKs[®] vitamins and partial financial support provided by Axcan Scandipharm.</p> <p>The study does not clarify whether the participants were pancreatic sufficient or insufficient.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind, but not stated who was blinded. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.

Keljo 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Implies some dropouts as at end of study 20 participants stated as taking DNase and 15 as not taking DNase, but not clearly stated.
Selective reporting (reporting bias)	High risk	Protocol later provided by authors but did not provide much more information, no presentation of SD of the effect in the control group.
Other bias	Unclear risk	Limited information on the basis for diagnosis of CF. Not clear if pancreatic sufficient or insufficient.

Levin 1961
Study characteristics

Methods	<p>Randomised double-blind placebo-controlled study of parallel design.</p> <p>Single-centre trial in the USA.</p> <p>Duration 6 months, planned to see participants every 2 months when possible.</p> <p>No efforts made to counterbalance groups from which individuals were lost during study.</p>
Participants	<p>49 participants accepted with proven diagnosis of CF and stabilised; 45 children followed for at least 2 months; 37 completed 6 months (18 in treatment group; 19 in placebo group).</p> <p>Each participant rated independently by 2 observers as to condition at the beginning of study on an arbitrary scale (1 = good condition up to 5 = very severe illness).</p> <p>Tocopherol Group 20 participants, mean (SD) age 113.1 (65.12) months, 9 males and 11 females, mean (SD) illness severity score 2.22 (1.09), mean (SD) weight 24.3 (9.75) kg.</p> <p>Placebo Group 25 participants, mean (SD) age 113.5 (63.99) months, 17 males and 8 females, mean (SD) illness severity score 2.10 (0.913), mean (SD) weight 26.8 (12.0) kg.</p>
Interventions	10 mg/kg/day of vitamin E tocopherol (d-l alpha-tocopheryl acetate) in water-miscible solution in 2 or 3 divided doses (n = 20) versus placebo (n = 25).
Outcomes	Weight, muscle power, serum tocopherol, activity of S-GOT in serum and subjective improvement.
Notes	<p>Reported data at baseline, 2 and 6 months</p> <p>Tocopherol and placebo provided by U.S. Vitamin Corporation.</p> <p>Supported in part by grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Public Health, Public Health Service and the Muscular Dystrophy Associations of America.</p> <p>Limited information on the basis for diagnosis of CF.</p> <p>The study does not clarify whether the participants were pancreatic sufficient or insufficient.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed as follows: cards labelled 1 or 2 were individually placed in sealed envelopes in groups of 4 (2 for each mixture number). Envelopes were divided into 3 groups, according to age of participants: < 5 years,

Vitamin E supplementation in people with cystic fibrosis (Review)

Levin 1961 (Continued)

		5 - 10 years, and ≥ 10 years and over. Each child accepted into the study group was assigned an envelope from the appropriate age group, and the enclosed card indicated the mixture to be given.
Allocation concealment (selection bias)	Low risk	Sealed envelopes with designated randomisation, each child accepted into study was assigned an envelope from the appropriate age group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<i>From the paper in plan of study:</i> "Patients and testers did not know which preparation was taken" (double-blind method) also stated "Physicians blind to vitamin E results".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Out of the initial 49 participants accepted, 37 completed the study but intention-to-treat analysis was not carried out. 3 died within 6 months (all in placebo group), 2 declined to continue medication after 2 months, 1 participant removed due to diabetes mellitus and 7 participants studied for less than 6 months. However, we feel the attrition is balanced among the two groups; hence we judged this study to have a low risk of bias. Planned to measure data at baseline, end of study (6 months) and every 2 months where possible, reported data at baseline, 2 and 6 months.
Selective reporting (reporting bias)	Unclear risk	Protocol not available, but the paper reports data for each outcome measurement listed in the 'Methods' section of the paper.
Other bias	Unclear risk	None identified. Limited information on the basis for diagnosis of CF and whether pancreatic sufficient or insufficient.

Wong 1988
Study characteristics

Methods	Controlled clinical study. Single centre in Canada. Duration 10 - 14 days.
Participants	22 CF participants admitted for pulmonary infection.
Interventions	Group A: oral fat-soluble vitamin E 10 mg/kg/day (n = 8). Group B: oral water-miscible vitamin E (Aquasol E) 10 mg/kg/day (n = 5). Group C: no supplementation (n = 9).
Outcomes	Serum vitamin E levels, alpha-tocopherol/cholesterol ratio, 3-day faecal fat excretion.
Notes	All participants also received appropriate intravenous antibiotics, 10% Nutralipid 15 ml/kg/day and usual dosage of enteric-coated pancreatic enzymes. The study does not clarify whether the participants were pancreatic sufficient or insufficient.

Wong 1988 (Continued)

Abstract only available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not stated, abstract states participants divided into 3 groups.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not stated, blinding of no treatment compared to either of treatment arms not possible, but not clear if blinded between treatment arms. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of no treatment compared to either of treatment arms not possible, but not clear if blinded between treatment arms. Objective outcome is measured so absence of blinding unlikely to increase risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants recruited and randomized not stated, only numbers of participants for whom results available given.
Selective reporting (reporting bias)	Unclear risk	Protocol not available, abstract only so no 'Methods' section available to compare to 'Results' section.
Other bias	Unclear risk	None identified. Limited information on the basis for diagnosis of CF and if pancreatic sufficient or insufficient.

CF: cystic fibrosis
 DNase: dornase alfa
 IU: international units
 PI: pancreatic insufficient
 PS: pancreatic sufficient
 PT: prothrombin
 PTT: partial thromboplastin time
 RBC: red blood cell
 SD: standard deviation
 S-GOT: glutamic oxalacetic transaminase

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Homola 2017	A comparison of two types of vitamin E supplement and not a comparison of vitamin E to control.
Jacquemin 2009	Compares bioavailability of preparations, no placebo or control arm.
Kerem 2009	It is not a study of vitamin E supplementation compared to placebo or control.
Munck 2010	Lack of placebo or control group.

Study	Reason for exclusion
Nasr 1993	Compares two preparations of vitamin E, no control or placebo group.
Papas 2007	Compares bioavailability of preparations, no control group.
Sagel 2011	Not a randomised or quasi-randomised study.
Thomas 1995	Comparison of vitamin E given with placebo to vitamin E given with ursodeoxycholic acid in a single participant.
Winklhofer-Roob 1992	No placebo or control group. Compared 3 preparations of vitamin E to baseline status.
Winklhofer-Roob 1996	Compared levels of vitamin E after supplementation with 3 different preparations of vitamin E and compared to matched controls.
Wood 2003	Compared low-dose to high-dose supplements. No placebo or control group.

Characteristics of ongoing studies [ordered by study ID]

EUCTR2007-001007-38-FR

Study name	STUDY OF THE LONG TERM BIOLOGICAL EFFICACY AND TOLERABILITY OF VEDROP (VITAMIN E-TPGS FORMULATION) AFTER DAILY ORAL ADMINISTRATION IN 30 PAEDIATRIC PATIENTS WITH CYSTIC FIBROSIS - 1ORP2
Methods	Interventional clinical trial of medicinal product
Participants	Less than or equal to 15 years with Cystic fibrosis
Interventions	d-a-tocopheryl PEG 1000 succinate
Outcomes	The patient clinical and biological status; The patient tocopherolemia and lipidic status; The patient incidence of treatment-emergent adverse events (TEAEs); The patient incidence of serious adverse events (SAEs).
Starting date	25/04/2007
Contact information	
Notes	trial ongoing

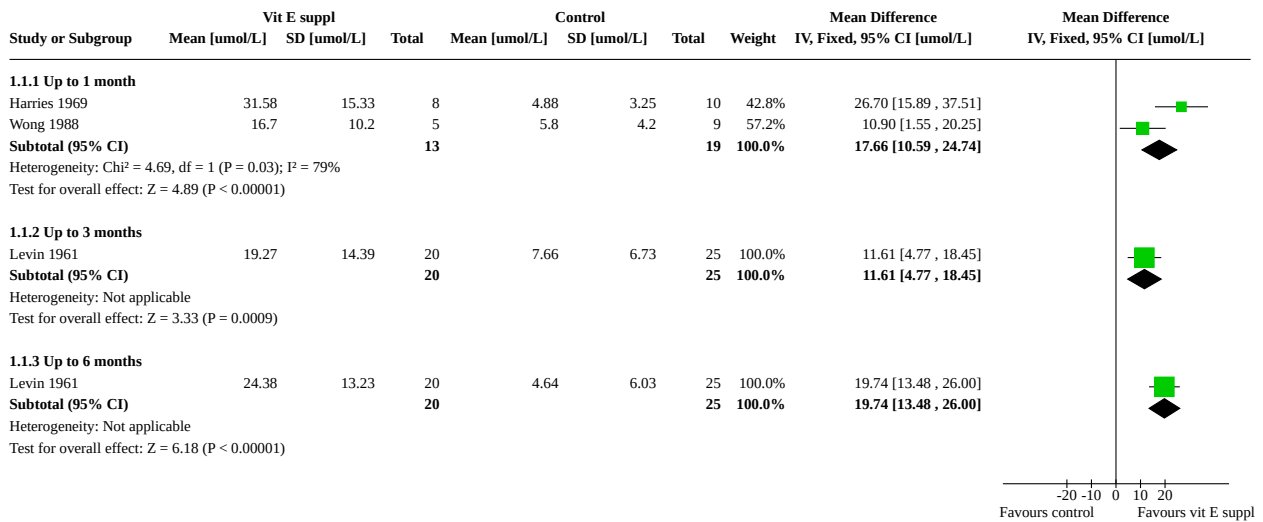
DATA AND ANALYSES

Comparison 1. Water-miscible vitamin E supplementation versus control

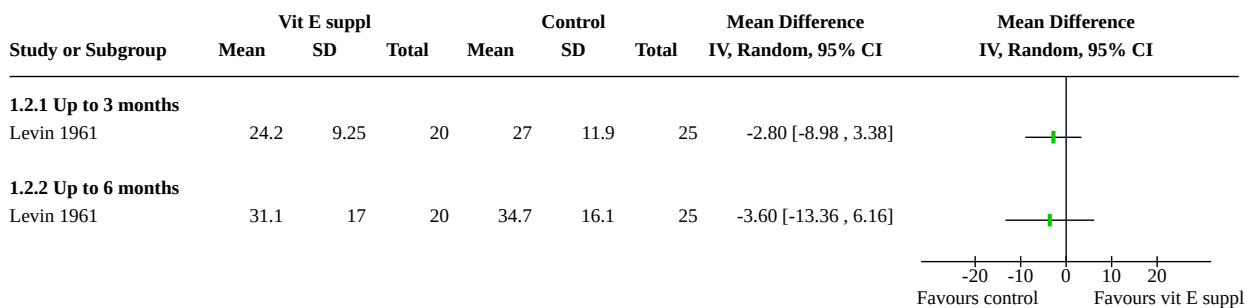
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Serum vitamin E levels	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Up to 1 month	2	32	Mean Difference (IV, Fixed, 95% CI)	17.66 [10.59, 24.74]
1.1.2 Up to 3 months	1	45	Mean Difference (IV, Fixed, 95% CI)	11.61 [4.77, 18.45]
1.1.3 Up to 6 months	1	45	Mean Difference (IV, Fixed, 95% CI)	19.74 [13.48, 26.00]
1.2 Weight	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.1 Up to 3 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.2 Up to 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Water-miscible vitamin E supplementation versus control, Outcome 1: Serum vitamin E levels



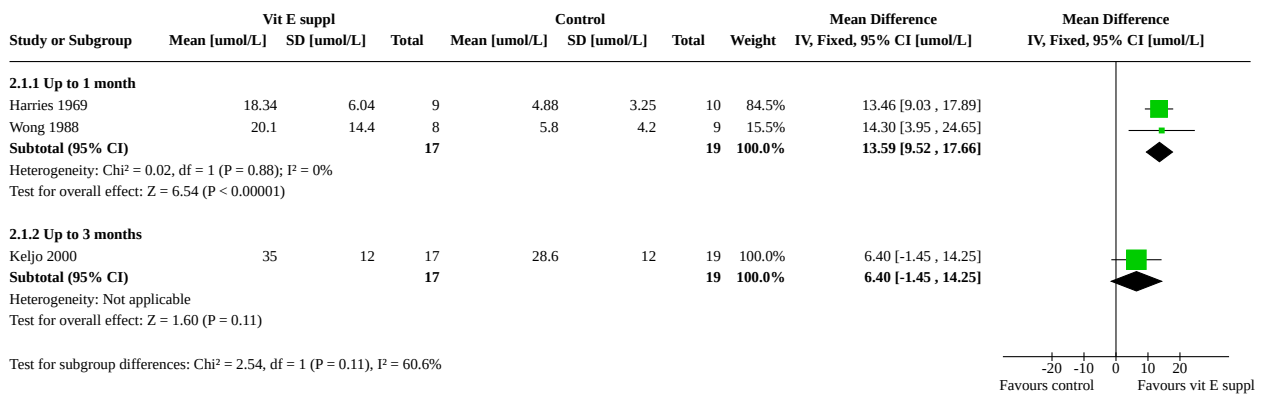
Analysis 1.2. Comparison 1: Water-miscible vitamin E supplementation versus control, Outcome 2: Weight



Comparison 2. Fat-soluble vitamin E supplementation versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Serum vitamin E levels	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1.1 Up to 1 month	2	36	Mean Difference (IV, Fixed, 95% CI)	13.59 [9.52, 17.66]
2.1.2 Up to 3 months	1	36	Mean Difference (IV, Fixed, 95% CI)	6.40 [-1.45, 14.25]

Analysis 2.1. Comparison 2: Fat-soluble vitamin E supplementation versus control, Outcome 1: Serum vitamin E levels



APPENDICES

Appendix 1. Search strategies of online trials registries

Database	Search terms	Date searched
ClinicalTrials.gov (www.clinicaltrials.gov)	cystic fibrosis cystic fibrosis AND vitamin E cystic fibrosis AND tocopherol cystic fibrosis AND toco* cystic fibrosis AND alpha tocopherol	20 July 2020
International Standard Randomised Controlled Trial Number Registry (isrctn.org/ctn.org/)	cystic fibrosis cystic fibrosis AND vitamin E cystic fibrosis AND tocopherol cystic fibrosis AND toco* cystic fibrosis AND alpha tocopherol	20 July 2020

(Continued)

WHO clinical trials platform (IC-TRP) (apps.who.int/trialsearch/)	cystic fibrosis	not searched as resource not available due to the Covid-19 pandemic
	cystic fibrosis AND vitamin E	
	cystic fibrosis AND tocopherol	
	cystic fibrosis AND toco*	
	cystic fibrosis AND alpha tocopherol	

Appendix 2. Glossary

Term	Explanation
cerebellar ataxia	failure of muscular coordination and irregularity of muscular action characterized by defects in rate, range, force and direction of movement of limbs
myopathy	a disease of muscle or muscle tissue, especially skeletal muscle
peripheral neuropathy	any damage to the peripheral nerves (which are the nerves outside the brain and the spinal cord)
pigmented retinopathy	a disorder of the retina characterized by deposits of pigment and increasing loss of vision
visual field conitriion	narrowing (or loss) of the visual fields - which is the area simultaneously visible to one eye without movement

WHAT'S NEW

Date	Event	Description
2 September 2020	New citation required but conclusions have not changed	No new data have been added to this review, therefore our conclusions remain the same.
2 September 2020	New search has been performed	<p>A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified two new references which were potentially eligible for inclusion in the review.</p> <p>One was an additional reference to an already included study (Harries 1969) and one new abstract was excluded (Homola 2017).</p> <p>Summary of findings tables have been added at this update.</p>

HISTORY

Protocol first published: Issue 11, 2011

Review first published: Issue 12, 2014

Date	Event	Description
27 February 2017	New citation required but conclusions have not changed	Since no additional references could be added to this review, our conclusions remain the same.
10 October 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register and searches of ongoing trials registries did not identify any new references potentially eligible for inclusion in this review.

CONTRIBUTIONS OF AUTHORS

Peter Okebukola conceived of and wrote the text of the protocol and review alongside Sonal Kansra with comments from Joanne Barratt.

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We originally planned to present all formulations of vitamin E supplements as a single intervention, but in the full review we have presented the comparisons of water-soluble vitamin E supplements versus control and fat-soluble vitamin E supplements versus control separately.

Following peer review comments, we updated our planned methods and for multi-arm studies, we now plan to include data from both arms of any such studies.

INDEX TERMS

Medical Subject Headings (MeSH)

alpha-Tocopherol [administration & dosage]; Bias; Cystic Fibrosis [*blood]; *Dietary Supplements; Exocrine Pancreatic Insufficiency [complications]; Placebos [administration & dosage]; Randomized Controlled Trials as Topic; Vitamin E [*administration & dosage] [blood] [chemistry]; Vitamin E Deficiency [prevention & control]; Vitamins [*administration & dosage] [chemistry]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Infant; Male