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**Vitamin D supplementation for 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 11, 2011.

Review content assessed as up-to-date: 30 August 2011.

Citation: Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007298. DOI: 10.1002/14651858.CD007298.pub2.

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**ABSTRACT**

**Background**

Cystic fibrosis (CF) is a genetic disorder with multiorgan effects. In a subgroup with pancreatic insufficiency malabsorption of the fat soluble vitamins (A, D, E, K) may occur. Vitamin D is involved in calcium homeostasis and bone mineralisation and may have extraskeletal effects. This review examines the evidence for vitamin D supplementation in CF.

**Objectives**

To assess the effects of vitamin D supplementation on the frequency of vitamin D deficiency, respiratory outcomes and vitamin D toxicity in the CF population.

**Search methods**

We searched the Cochrane CF and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 14 March 2011.

**Selection criteria**

Randomised and quasi-randomised controlled trials of vitamin D supplementation compared to placebo in the CF population regardless of exocrine pancreatic function.

**Data collection and analysis**

Both authors independently assessed the ‘risk of bias’ of each included trial and extracted outcome data (from published trial information) for assessment of bone mineralization, growth and nutritional status, frequency of vitamin D deficiency, respiratory status, quality of life and adverse events.

**Main results**

Three studies are included, although only data from two were available (41 adults and children with CF). One of these studies compared supplemental 800 international units (IU) vitamin D and placebo for 12 months in 30 osteopenic pancreatic insufficient adults; both groups continued 900 IU vitamin D daily. The other (abstract only) compared supplemental 1g calcium alone, 1600 IU vitamin D alone, 1600 IU vitamin D and 1g calcium and placebo in a double-blind randomised cross-over trial; only 11 children (vitamin
D and placebo groups) after six-months supplementation are included; inclusion criteria, pancreatic sufficiency or disease status of participants are not defined. There were no significant differences in primary or secondary outcomes in either study. The studies are not directly comparable due to differences in supplementation, outcome reporting and possibly participant characteristics (eg severity of lung disease, growth and nutrition, pancreatic sufficiency). There were no adverse events in either study. The third study (abstract only) compared daily calcitriol (0.25 or 0.5 micrograms) with placebo in pancreatic insufficient children and young adults, only pre-intervention data were available.

Authors’ conclusions

There is no evidence of benefit or harm in the limited number of small-sized published trials. Adherence to relevant CF guidelines on vitamin D should be considered until further evidence is available.

Plain Language Summary

The use of regular vitamin D preparations for children and adults with cystic fibrosis

Cystic fibrosis with pancreatic insufficiency can cause vitamins, such as vitamin D, to be inadequately absorbed leading to vitamin deficiencies. Lack of vitamin D (vitamin D deficiency) can cause specific problems such as bone deformity and bone fractures. It can also be associated with poorer general and respiratory health. Thus, people with cystic fibrosis are usually given regular vitamin D preparations from a very young age. However, excess vitamin D can also cause respiratory problems and problems with high calcium levels. The review contains three trials, but we could only extract data from two trials. We found no evidence to show whether giving vitamin D regularly to people with cystic fibrosis is beneficial or not. The authors are unable to draw any conclusions regarding the routine administration of Vitamin D supplements and recommend that until further evidence is available, local guidelines are followed regarding this practice.

Background

Please note: a glossary of medical terms used in this review is available in the appendices (Appendix 1).

Description of the condition

Cystic fibrosis (CF) is a genetic disorder that affects multiple organs. The dominant symptoms of CF are that of the respiratory and gastrointestinal (GI) systems (Wagener 2003). In a subgroup of people with CF, the GI system, liver dysfunction, intestinal obstruction and exocrine pancreatic insufficiency are the major issues. Pancreatic insufficiency affects up to 90% of people with CF, whereby fat malabsorption occurs and pancreatic enzyme replacement is required to prevent steatorrhoea and malnutrition (Dodge 2006). Fat soluble vitamins (A, D, E and K) are co-absorbed with fat and thus deficiency of these vitamins may occur. European and US guidelines recommend routine supplementation of these vitamins (Borowitz 2002; Sinaasappel 2002). Vitamin D with parathyroid hormone (PTH) regulates serum calcium and phosphate, maintaining adequate concentrations for bone mineralization (Dimitri 2007; Holick 2007). Vitamin D deficiency may present as symptomatic hypocalcaemia with tetany, seizures or myopathy during early childhood, particularly in exclusively breast-fed infants (Dimitri 2007; Wharton 2003) or as a range of bone deformities (rickets, kypho-scoliosis) or other effects such as delayed closure of anterior fontanelle, dentition problems (delayed eruption of teeth and enamel hypoplasia) (Dimitri 2007; Joiner 2000; Wharton 2003). Radiological changes of rickets include metaphyseal widening with cupping, splaying and fraying (Dimitri 2007; Joiner 2000; Wharton 2003). Generalised osteopenia may be an incidental X-ray finding of vitamin D deficiency in an asymptomatic child (Joiner 2000). Vitamin D deficiency after completion of skeletal growth or growth plate fusion causes osteomalacia without skeletal deformity due to unmineralised osteoid replacing mineralised bone as part of normal bony remodeling; X-rays demonstrate generalised osteopenia (Holick 2007). This bone is more likely to fracture with poor healing (Holick 2007). Diffuse bone pain accompanies osteomalacia in some adults (Holick 2007). Vitamin D may also have extra-skeletal effects. Epidemiological studies have also described a link between hypovitaminosis D and
lungs function (Black 2005); and plausible biological reasons include the effect of vitamin D on immunity and oxidative stress (Wright 2005). However, excessive high doses of vitamin D can also cause problems, albeit this rarely occurs. The effects of vitamin D toxicity are generally non-specific and include nausea, vomiting, poor appetite, constipation, weakness, and weight loss (Chesney 1989; NIH 2007). It can also cause hypercalcaemia leading to confusion, arrhythmia, and calcinosis (Chesney 1989; NIH 2007). As ultraviolet B radiation exposure results in the production of vitamin D3, vitamin D levels are likely seasonal.

**Description of the intervention**

Different vitamin D preparations are available; the D2 preparation has been the main form given and available as a pharmaceutical preparation. However, both vitamins D2 and D3 are available as supplementations and may vary in its efficacy for maintaining serum concentrations of 25 (OH) D. These are prepared by different methods and occur naturally in different foods.

**How the intervention might work**

Both forms of vitamin D, when ingested, undergo metabolism in the liver to form 25-hydroxyvitamin D (25 (OH) D) and in the kidneys to form 1,25-dihydroxyvitamin D (Holick 2008). Also vitamins D2 and D3 are equally efficacious in maintaining serum concentrations of 25 (OH) D (Holick 2008).

**Why it is important to do this review**

The UK CF Trust recommends dietary advice and vitamin D supplementation to maintain 25 (OH) vitamin D levels in the normal range of 30 to 60ng/ml for all individuals with pancreatic insufficiency (UK CF Trust 2007). Recommended starting doses vary with age (UK CF Trust 2007). The USA Cystic Fibrosis Foundation consensus panel recommends vitamin D supplementation to maintain 25 (OH) vitamin D levels in the normal range of 30 to 60ng/ml (Aris 2005). The vitamin D preparation used and dosing varies with age and treatment response (Aris 2005).

Deficiencies may occur from the disease process of CF and insufficient supplementation. Also vitamin D deficiency is increasingly reported even in people without medical risk factors of vitamin D deficiency. Nevertheless vitamin toxicity may also occur from excess supplements. Vitamin D deficiency may lead to specific symptoms and signs, as well as to other nutritional issues, and influence the general well-being and respiratory status (Dodge 2006; Sethuraman 2006). A Cochrane Systematic Review of vitamin A supplementation has already been published (O’Neil 2007). Vitamin E and K supplementation will be addressed in other Cochrane Reviews. This review will evaluate vitamin D supplementation.

**OBJECTIVES**

To determine if vitamin D supplementation in children and adults with CF:

1. reduces the frequency of vitamin D deficiency disorders;
2. improves general and respiratory outcomes;
3. increases the frequency of vitamin D toxicity.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
Randomised (RCTs) and quasi-randomised trials (controlled clinical trials).

**Types of participants**
Children or adults with CF (defined by sweat tests or genetic testing), with and without pancreatic insufficiency.

**Types of interventions**
All preparations of oral vitamin D used as a supplement compared to placebo or no supplementation at any dose and for any duration. Any preparation containing supplemental vitamin D was included.

**Types of outcome measures**

**Primary outcomes**
1. Bone mineral density or Vitamin D specific deficiency outcomes
   i) osteopenia (defined on dual energy X-ray absorptiometry (DXA) scans as T score between -1.0 and -2.5 standard deviations (SD) compared to a reference population (World Health Organization 1994)
   ii) osteoporosis (defined on DXA scans as T score less than or equal to - 2.5 SD compared to a reference population (World Health Organization 1994)
   iii) severe osteoporosis (defined on DXA scans as T score less than or equal to - 2.5 SD and with one or more fragility fractures compared to a reference population (World Health Organization 1994)
2. Growth and nutritional status (weight Z score)
Secondary outcomes

1. Other vitamin D related deficiency disorders
   i) fractures
   ii) tetany
   iii) rickets
   iv) other radiological abnormality
   v) measured levels of calcium and vitamin D (25-hydroxyvitamin D (25 (OH) D) or 1.25-dihydroxyvitamin D (1.25 (OH) D))

2. Respiratory outcomes
   i) bronchiectasis severity control (e.g. QoL, cough diary, Likert scale, visual analogue scale, level of interference of cough)
   ii) lung function indices (spirometry e.g. FEV₁, FVC)
   iii) proportions of participants who had respiratory exacerbations or hospitalisations or both
   iv) total number of hospitalised days
   v) other objective indices (e.g. airway markers of inflammation)

3. Quality of life

4. Adverse events including vitamin D toxicity (e.g. vomiting, loss of appetite, arrhythmia, confusion)

5. Parathyroid hormone levels

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, both authors independently reviewed results of the literature searches, identifying relevant studies according to the inclusion criteria for further assessment. From these studies, the same two authors independently examined the papers in further detail to select studies for inclusion using the stated criteria. There was no disagreement between authors. It was planned that any disagreement would have been settled by discussion and consensus would have been achieved.

Data extraction and management

The authors reviewed studies that satisfied the inclusion criteria for the review and recorded the following information, where available:

- study setting;
- year of study;
- source of funding;
- participant recruitment details (including number of eligible participants);
- season;
- latitude where study was conducted;
- parathyroid hormone;
- trial inclusion and exclusion criteria;
- randomisation and allocation concealment method;
- numbers of participants randomised;
- blinding (masking) of participants, care providers and outcome assessors;
- dose and type of intervention;
- duration of therapy;
- co-interventions;
- numbers of participants not followed up;
- reasons for withdrawals from study protocol (clinical, side effects, refusal and other);
- side effects of therapy;
- whether intention-to-treat analyses were possible.

The authors extracted data on the outcomes described above and were evaluated based on

1. short term (12 months or less), and
2. medium to long term (over one year)

We planned to extract data relevant for outcomes at one month, up to three months, up to six months, up to twelve months and annually thereafter. We planned to consider including outcome data of differing time periods. The duration of included studies ranged from nine to twelve months, thus this review reports only short term outcomes (up to twelve months).

Search methods for identification of studies

Electronic searches

Relevant trials from the Group’s Cystic Fibrosis Trials Register were identified using the term ‘vitamin D’.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of The Cochrane Library), quarterly 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 Cystic Fibrosis and Genetic Disorders Group Module.

Date of the latest search: 14 March 2011.

Searching other resources

We scanned the references in the papers of the included studies for further relevant papers.
Assessment of risk of bias in included studies
In order to assess the risk of bias for each of the included studies, the two review authors independently assessed the quality of included studies according to the Cochrane risk of bias tool (Higgins 2011).

Allocation concealment
Authors assessed allocation concealment in each study as follows:
1. Low risk of bias, if the allocation of participants involved 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;
2. Unclear risk of bias, if the method used to conceal the allocation was not described;
3. High risk of bias, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Generation of the allocation sequence
Authors graded each study for generation of allocation sequence as follows:
1. Low risk of bias, if methods of randomisation included use of a random number table, computer-generated lists or similar methods;
2. Unclear risk of bias, if the trial was described as randomised, but no description of the methods used to allocate participants to treatment group was described;
3. High risk of bias, if methods of randomisation included alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation.

Blinding (or masking)
Authors graded each study for blinding as follows:
1. blinding of clinician (person delivering treatment) to treatment allocation;
2. blinding of participant to treatment allocation;
3. blinding of outcome assessor to treatment allocation.
The more people blinded to an intervention, the lower the authors judged the risk of bias to be.

Follow up
Authors graded each study as to whether numbers of and reasons for dropouts and withdrawals in all intervention groups were described; or if it was specified that there were no dropouts or withdrawals.

We have reported on whether the investigators performed a sample-size calculation and if they used an intention-to-treat (ITT) analysis. The risk of bias is higher for lower follow-up rates.

Selective outcome reporting (or reporting bias)
Authors graded each study for selective outcome reporting based on all available results as follows:
1. Low risk of selective outcome reporting if all defined outcomes for each study participant were reported;
2. Unclear risk of selective outcome reporting if it study authors did not provide evidence of or report results for all defined outcomes in study participants;
3. High risk of selective outcome reporting if incomplete reporting or intention to report results of defined outcomes for all enrolled participants.

Measures of treatment effect
The authors included the results from studies meeting the inclusion criteria and which reported any of the outcomes of interest in the subsequent meta-analyses.
For dichotomous outcome variables of each individual study, we planned to calculate the odds ratio (OR) using a modified ITT analysis, i.e. if ITT analysis was not used by the original investigators, dropouts were considered treatment failures. We would have calculated the summary odds ratios and 95% confidence intervals (CIs) (fixed-effect model) using the Cochrane Collaboration’s statistical package (RevMan 5). Numbers needed to treat (NNT) and their 95% CIs were to be calculated from the pooled OR and its 95% CI for a specific baseline risk, which is the sum of all the events in the control groups (in all trials) divided by the total participant numbers in control groups in all trials using an online calculator (Cates 2003). For continuous outcomes, we recorded the mean change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. Post-intervention standard deviations were calculated, if not reported, from the reported mean difference between groups (intervention and control) and 95% confidence intervals using the formulae detailed in RevMan (RevMan 5). If standard errors had been reported, we planned to convert these to standard deviations. We then calculated a pooled estimate of treatment effect by the mean difference and 95% confidence interval (fixed-effect model) again using RevMan (RevMan 5).

Unit of analysis issues
The identified cross-over study published only baseline data, thus an analysis including the planned fixed-effect generic inverse variance (GIV) analysis in RevMan, summary weighted differences and 95% CIs (RevMan 5) was not possible.

Dealing with missing data
The authors requested further information from the primary investigators of two studies (Brown 2005; Haworth 2004). We re-
ceived a response from Haworth, but not from Brown; no additional information could be obtained.

Assessment of heterogeneity
Where possible we have combined study results with the same outcome measure, described heterogeneity between study results and used chi-squared test to determine any statistically significant difference. Heterogeneity was considered to be significant with a P value less than 0.10 (Deeks 2011). We also used the I² statistic, with heterogeneity categorised such that a value of under 25% was considered low, around 50% moderate and over 75% a high degree of heterogeneity (Higgins 2003).

Assessment of reporting biases
We had planned to assess publication bias using a funnel plot and analysed the included trials for selective reporting. We were unable to produce any funnel plots as there were insufficient studies i.e. less than 10. However, asymmetry in a funnel plot may be due to other reasons such as heterogeneity and reporting biases.

Data synthesis
We used a fixed-effect model in the analysis. A random-effects model was planned if there had been concerns regarding statistical heterogeneity (I² higher than 50%).

Subgroup analysis and investigation of heterogeneity
The planned subgroup analyses (children and adults, formulation of vitamin D, previous bowel resection, pancreatic insufficiency, method of CF diagnosis, gender and latitude bands) to investigate heterogeneity were not possible because there were too few trials included in the review.

Sensitivity analysis
Sensitivity analysis either by random-effects model or by “treatment received” was not possible because of the insufficient number of included studies in this review.

Results of the search
Ten published abstracts or full papers to eight studies were identified via the electronic search as detailed in the Electronic searches section. Two studies were excluded (Aris 2000; Gronowitz 2003); three studies are listed as ‘Studies awaiting classification’ (Hillman 2008; Judd 2008; Kumari 2009); thus this review consists of three studies (Brown 2005; Haworth 2004; Popescu 1998), of which only two had data that could be entered into the analysis (Haworth 2004; Popescu 1998).

Included studies
Three studies are included (Brown 2005; Haworth 2004; Popescu 1998); although only data from two were available (41 adults and children with CF) (Haworth 2004; Popescu 1998). One study was published as both an abstract and a full paper (Haworth 2004); two studies have, as yet, been published as abstracts only (Brown 2005; Popescu 1998). Both studies with available data were short term (one year or less) (Haworth 2004; Popescu 1998), the third study reported only baseline data prior to two years of calcitriol supplementation (Brown 2005). The Haworth study was a 12-month trial in osteopenic (z score <-1), pancreatic insufficient adults with CF (Haworth 2004). The trial compared the effects of additional vitamin D (800 IU) and calcium (1g) to placebo on BMD and biochemical markers of bone turnover; both groups continued standard vitamin D treatment (900IU daily). A second study had four arms comparing six months of supplemental vitamin D (1600 IU) alone, vitamin D (1600 IU) and calcium (1g), calcium (1g) alone and placebo in “mildly affected children with CF”; only the vitamin D and placebo arms were included (Popescu 1998). The data from the third study were not able to be included as only baseline BMD and markers of bone turnover in pancreatic insufficient children and young adults prior to two years of calcitriol supplementation (0.25 mcg if the participant weighed under 45 kg, 0.5 mcg if the participant weighed 45 kg and over) and some narrative adverse event information were reported (Brown 2005).

Excluded studies
Two studies were excluded due to interventions not forming part of this review - bisphosphate and ultraviolet (UV) B radiation (Aris 2000; Gronowitz 2003).

Risk of bias in included studies
Allocation
There were no details given on method of generation of allocation sequence or its concealment in any of the included studies,
although one study does state that participants were randomised by gender and age (8 to 10, 11 to 14, 15 to 18 years) to stratify for pubertal status (Brown 2005). We therefore judged there to be an unclear risk of bias for this for all included studies (Brown 2005; Haworth 2004; Popescu 1998).

**Blinding**

Two studies do not mention blinding at all (Brown 2005; Popescu 1998), the third study is described as double-blind, but does not give details of who was blinded (Haworth 2004). Therefore we judged there to be an unclear risk of bias from blinding for all studies (Brown 2005; Haworth 2004; Popescu 1998).

**Incomplete outcome data**

No data are available for any outcomes in one study (Brown 2005). Data from the other abstract were also limited (Popescu 1998). A further search did not yield any published papers subsequent to the abstracts. No additional outcome data could be obtained from the authors. In the final study, there was one withdrawal due to pregnancy in the intervention group (Haworth 2004). It is unclear if the data were removed from the baseline characteristics published since summary data alone are given. Therefore we judge there to be an unclear risk of bias for all three included studies due to incomplete outcome data (Brown 2005; Haworth 2004; Popescu 1998).

**Selective reporting**

In the Popescu study, data are reported after only 9 months of a 36-month study, we therefore judge this study to have a high risk of selective reporting (Popescu 1998). We did not identify any selective reporting in the other two included studies and judge there to be a low risk of bias from this for these studies (Brown 2005; Haworth 2004).

**Other potential sources of bias**

We did not identify any other potential sources of bias in any of the studies (Brown 2005; Haworth 2004; Popescu 1998).

**Effects of interventions**

No data could be combined as the studies presented results in different formats. Thus sensitivity analyses, subgroup analyses or assessment of heterogeneity could not be undertaken for this version of the review.

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**Primary outcomes**

1. **Bone mineral density or Vitamin D-specific deficiency outcomes**

There was no available data on the primary outcome from any study.

2. **Growth and nutritional status (weight z score)**

No study reports weight Z score (Brown 2005; Haworth 2004; Popescu 1998). Two studies reported baseline BMI but did not report either any follow up or end of intervention data or any change in BMI (Brown 2005; Haworth 2004). Popescu reports no growth or nutritional status measures (Popescu 1998).

**Secondary outcomes**

1. **Other vitamin D-related deficiency disorders**

   a. **fractures**

   This outcome was not reported in any of the included studies.

   b. **tetany**

   This outcome was not reported in any of the included studies.

   c. **rickets**

   This outcome was not reported in any of the included studies.

   d. **other radiological abnormality**

   This outcome was not reported in any of the included studies.

   e. **measured levels of calcium and vitamin D (25-hydroxyvitamin D (25 (OH) D) or 1.25-dihydroxyvitamin D (1.25 (OH) D))**

One study (Haworth 2004) reported data on serum calcium which showed no difference between groups (Analysis 1.1). Two studies reported data for vitamin D (25 (OH) D), one at nine months (Popescu 1998) and one at 12 months (Haworth 2004) and one study reported data for vitamin D (1,25 (OH) D) at nine months (Popescu 1998). We were able to combine the data for vitamin D (25 (OH) D) and have presented all data in the meta-analysis, but no significant differences between groups were reported. For 25 (OH) D, the mean difference between groups was -2.79 pg/ml (95% confidence interval (CI) -7.25 to 1.6) (Analysis 1.2); for 1,25 (OH) D the mean difference was -3.50 pg/ml (95% CI -22.51 to 15.510 (Analysis 1.3)).
2. Respiratory outcomes

a. Bronchiectasis severity control
This outcome was not reported in any of the included studies.

b. Lung function indices
All three included studies reported lung function indices at baseline only (Brown 2005; Haworth 2004; Popescu 1998).

c. Proportions of participants who had respiratory exacerbations or hospitalisations or both
This outcome was not reported in any of the included studies.

d. Total number of hospitalised days
This outcome was not reported in any of the included studies.

e. Other objective indices
This outcome was not reported in any of the included studies.

3. Quality of life
This outcome was not reported in any of the included studies.

4. Adverse events
Two studies did not report any adverse outcomes from either group of participants (Haworth 2004; Popescu 1998). One of the abstracts reported that two participants (one in each group) developed nephrolithiasis; furthermore one participant in the treatment group developed mild hypercalcaemia and two participants in the placebo group had hypercalciuria (Brown 2005). We could not present this data in the analysis as we could not ascertain from the abstract how many children were in each arm of the study.

5. Parathyroid hormone levels
Two studies reported on this outcome, but we were unable to combine the data since one reported an absolute value at the end of the study (Popescu 1998) and the other reported change in parathyroid hormone levels after 12 months of intervention (placebo or supplementation) (Haworth 2004). Neither study reported any significant difference between groups (Analysis 1.4; Analysis 1.5).

Post-hoc analysis
We include a post-hoc analysis of mean bone mineral density scores (z scores) which were reported in two studies (Haworth 2004; Popescu 1998). No data could be combined: Popescu reported per cent change in whole body mineral bone content, mean difference (MD) -3.00% (95% CI -13.63 to 7.63) (Analysis 2.1) and lumbar spine z score at nine months (six months of treatment and a three-month washout period), MD -0.24 (95% CI -1.27 to 0.79) (Analysis 2.2) (Popescu 1998); and Haworth reported per cent change in bone mineral density after 12 months of treatment measured in the lumbar spine, MD 1.90 (95% CI -0.90 to 4.70) (Analysis 2.3); the hip, MD 0.70 (95% CI -2.20 to 3.60) (Analysis 2.4); and the distal forearm, MD 1.70 (95% CI -2.20 to 5.60 (Analysis 2.5) (Haworth 2004). For all the available outcomes, there was no significant difference between the groups. Bone mineral density z score do not meet the primary bone mineral density outcome measures of this review, but are an objective and reproducible assessment of intervention effect (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5).

Discussion
Daily vitamin D supplementation is almost universally recommended for people with CF who are pancreatic insufficient (Borowitz 2002; Sinaasappel 2002; UK CF Trust 2007). In this review we attempted to evaluate the effect of vitamin D supplementation compared with placebo on the frequency of vitamin D deficiency, including BMD, growth and nutrition, respiratory status, biochemical markers of bone metabolism in children and adults with CF. However, it is unfortunate that there were only three small controlled studies that have examined this comparison and only two which have published any post-treatment data. Also the studies used different formulations of vitamin D.

Summary of main results
There was no clear benefit or harm identified with short-term vitamin D supplementation compared to placebo in the 41 people with CF completing the period of intervention in the two studies with available data (Haworth 2004; Popescu 1998). This number excludes one study which has only been published as an abstract and only contains baseline data and narrative information on adverse events (Brown 2005). This study reports adverse events in 6 out of 54 participants; nephrolithiasis occurred in two (placebo and calcitriol), mild asymptomatic hypercalcaemia in one receiving calcitriol, hypercalciuria in two receiving placebo, and hyperphosphataemia in one receiving placebo (Brown 2005). No adverse events occurred in the full publication included in this review (Haworth 2004).
Overall completeness and applicability of evidence

The three studies meeting inclusion criteria provided data for assessment of the efficacy of short-term (up to 12 months) vitamin D supplementation on BMD in a small number of children and adults with CF. There were no data on the effects of supplementation on growth and nutrition. No conclusions about the longer term effects of vitamin D supplementation, either beneficial or harmful, can be drawn due to the short-term nature of supplementation and follow up. All participants in the Haworth study continued the centre’s routine vitamin D supplement of 900 IU daily (Haworth 2004). This was in keeping with the UK guidelines (UK CF Trust 2007) and may not be standard practice in all centres. Many of the secondary outcomes (effect of vitamin D supplementation on the frequency of clinical markers of vitamin D deficiency, respiratory outcomes and quality of life) were not assessable from data in any study which limits the external validity of the outcomes. No study provided information to address potential confounders during the study period, including measures of pancreatic sufficiency or adequacy of pancreatic enzyme replacement in pancreatic-insufficient participants; the season, latitude and ethnicity of participants (which will directly impact on 25-OHD levels and thus BMD); the amount of weight-bearing activity; respiratory status; or frequency of illness. These factors limit the generalisability of these results to other CF populations.

Quality of the evidence

This review includes only three small studies of short term vitamin D supplementation with BMD (either as percent change or z score) the only consistently reported primary outcome measure. The lack of information regarding methods used to diagnose CF; respiratory and disease status, growth and nutrition during the study; and the adequacy of exocrine pancreatic function or enzyme replacement restrict the generalisation of each study’s findings to the general CF population. All relevant studies are likely to have been identified by our search methods. Two papers were abstracts and thus assessment was limited (Brown 2005; Popescu 1998).

Potential biases in the review process

The two authors’ independent review of included studies and data extraction minimised the potential for additional bias beyond that detailed in the risk of bias tables. Neither of the authors have any conflict of interest.

Authors’ conclusions

Implications for practice

There is a lack of published data on the effect of vitamin D supplementation, including benefits and adverse effects, in people with CF. The data, which are limited by very small numbers, showed no benefit or harm in the supplemented group. Until further studies are available, adherence to relevant guidelines on supplementation with vitamin D and calcium, such as the UK guidelines (UK CF Trust 2007), should be considered. Toxicity is an uncommon occurrence in the small number of published randomised, controlled studies of vitamin D supplementation. Further randomised controlled trials are clearly required.

Also it is biologically plausible that currently, with improved pancreatic replacement therapies and attention to macro nutrition and caloric supplements, the majority of people with CF are vitamin D sufficient and may not require daily vitamin D supplementation. Daily supplementation in these situations at best causes no harm, but adds a further burden to the daily medical regimen of people with CF.

Implications for research

The available data suggest the CF population have lower vitamin D levels and bone mineral density than age and gender-matched unaffected individuals, but this is likely to be multifactorial (e.g. malabsorption, chronic illness, pubertal delay, reduced activity particularly weight bearing activity and medications impairing physiological bone remodeling) which may not necessarily be overcome by supplementation. Parallel randomised controlled trials of vitamin D supplementation in CF are required and should take into account the effects of pubertal stage, latitude and season, ethnicity, severity of lung disease and adequacy of enzyme replacement in pancreatic-insufficient patients. Future studies may also need to take broad genetic mutations groups (such as Δ508 or not) into account although this likely increases the complexity of the study.

Acknowledgements

We thank Natalie Yates for performing the searches and obtaining the articles and Nikki Jahnke for the review of the manuscript and advice on analysis. We also thank Kerry Dwan for help with the statistics and the Cochrane CFGD Group for their support during the development of the protocol and review. We also thank Professor Howarth for responding to our correspondence.
References to studies included in this review

Brown 2005 [published data only (unpublished sought but not used)]

Haworth 2004 [published data only]


Popescu 1998 [published data only]

References to studies excluded from this review

Aris 2000 [published data only]


Gronowitz 2003 [published data only]

References to studies awaiting assessment

Hillman 2008 [published data only]

Judd 2008 [published data only]

Kumari 2009 [published data only (unpublished sought but not used)]

Additional references

Aris 2005

Black 2005

Borowitz 2002

Brenckmann 2001

Cates 2003

Chesney 1989

Deeks 2011

Dimitri 2007

Dodge 2006
**Higgins 2003**

**Higgins 2011**

**Holick 2007**

**Holick 2008**
Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *Journal of Clinical Endocrinology and Metabolism* 2007;Dec 18:[Epub ahead of print]. [DOI: 10.1210/jc.2007-2308]

**Joiner 2000**

**NIH 2007**

**O’Neil 2007**

**RevMan 5**

**Sethuraman 2006**

**Sinaasappel 2002**

**UK CF Trust 2007**

**Wagener 2003**

**Wharton 2003**

**World Health Organization 1994**

**Wright 2005**

* Indicates the major publication for the study
### CHARACTERISTICS OF STUDIES

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

**Brown 2005**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, parallel, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>54 (31 male, 23 female) pancreatic insufficient children and young adults with CF. Age range 8 -18 years (mean age 12.1 (SD 3.1) years), mean (SD) BMI 18.1 (2.9) kg/m(^2), mean (SD) FEV(_1) 80 (20) % predicted, range 36 - 129%. Numbers in intervention and control groups not stated. 31 (18 male, 13 female) healthy sibling or community controls mean age 11.7 (2.9) years were recruited to assess BMD normative data</td>
</tr>
<tr>
<td>Interventions</td>
<td>Participants randomised to 2 years supplementation with oral calcitriol (1,25 (OH)(_2)D (0.25 \text{ mcg daily if under } 45 \text{ kg, } 0.5 \text{ mcg daily if weight was } 45 \text{ kg or above} )) or placebo  All participants continued their usual calcium (500 mg daily) and vitamin D (dose and preparation not specified)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Data only published for baseline/pre-intervention characteristics and some adverse events  BMD (whole body, lumbar spine, hip and radius; method not specified) measured at baseline, 6, 12 and 24 months  Serum and urine chemistry (including calcium and phosphate), vitamin D and bone markers (not otherwise specified) measured at baseline, 3, 6, 12-18 and 24 months  Frequency of supplementation related complications  Bone age at baseline, pubertal status and dietary intake recorded</td>
</tr>
<tr>
<td>Notes</td>
<td>Abstract of poster presented at 19th Annual North American CF Conference 2005  No reply to email requesting further data. No reference to season, latitude or compliance.</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not reported but states that participants were randomised by gender and age (8-10, 11-14,15-18 yrs) to stratify for pubertal status  Healthy siblings and community subjects recruited to assess normative BMD data</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No method reported.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No method reported.</td>
</tr>
</tbody>
</table>
### Brown 2005 (Continued)

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
<th>Unclear risk</th>
<th>Baseline/pre-intervention data only. Numbers in each group not reported. 32/54 reported to complete study; only 4 withdrawals accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes are recorded.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Follow up data not published. No description of CF diagnosis method. No reports of compliance with enzyme replacement or study medications No season or latitude specified.</td>
</tr>
</tbody>
</table>

### Haworth 2004

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel, randomised, double-blind, placebo-controlled study over 12 months Single centre (Manchester adult CF unit).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>31 pancreatic-insufficient and osteopenic adults (over 18 years) with CF (confirmation of CF diagnosis by genetic testing). No definition of pancreatic insufficiency. BMD z score less than -1 (lumbar spine, proximal femur or distal forearm) 16 in intervention group (9 female, 7 males). Mean age 29.4 years; mean FEV(_1) 66.1% predicted; mean BMI 23.0kg/m(^2)). 15 in control group (7 females, 8 males) Mean age 25.9 years; mean FEV(_1) 60.9%; mean BMI 21.1kg/m(^2).</td>
</tr>
<tr>
<td>Interventions</td>
<td>Supplementation with 1g calcium and 800 IU vitamin D daily (Calichew D3 forte 1 tablet twice daily) or placebo for 12 months All participants continued standard daily vitamin D supplements (900 IU)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Outcomes measured at baseline and after 12 months. BMD (DXA lumbar spine and total hip, peripheral CT distal forearm) Biochemical markers of bone turnover (25-OHD, PTH, osteocalcin, bone specific alkaline phosphatase, urinary crosslinks)</td>
</tr>
<tr>
<td>Notes</td>
<td>8 participants in each intervention had corticosteroids during study period, but dose not reported. Compliance - treatment group 3.1 days/week, controls 3.7 days/week Prof Howarth was contacted and replied but was unable to provide any unpublished data</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No details of randomisation.</td>
</tr>
</tbody>
</table>
### Haworth 2004

<table>
<thead>
<tr>
<th>Allocation concealment (selection bias)</th>
<th>Unclear risk</th>
<th>No description of allocation concealment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Method notes double blinding although no details of blinding or method used</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>1 study withdrawal due to pregnancy in intervention group, although this wasn’t a specified exclusion criteria. Thus good follow-up rate (97%) All others enrolled completed study period.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All defined outcomes are reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>All subjects were participants of a longitudinal BMD study preceding this study Only 31/55 eligible participants enrolled, no specifics given for those who declined to participate</td>
</tr>
</tbody>
</table>

### Popescu 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind, randomised, cross-over study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>22 children with CF (mean 9.3 years, range 6.1 - 12.2 years). No disease status indicators reported - authors comment that all were “mildly affected”</td>
</tr>
<tr>
<td>Interventions</td>
<td>Supplementation with 1g calcium, 1600 IU vitamin D, 1g calcium and 1600 IU vitamin D and placebo each for 6 months with a 3-month washout period between interventions</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Outcomes reported at baseline and at 9 months (after 6 months of intervention and 3 month washout period): BMD (lumbar spine, femoral neck, distal radius and whole body; method not described) Outcomes reported at baseline and at 6 months of supplementation: serum and urine chemistry, 25-OHD, 1,25-(OH)₂D, PTH, bone turnover markers (osteocalcin, bone specific alkaline phosphatase)</td>
</tr>
<tr>
<td>Notes</td>
<td>Abstract of poster presented at 12th annual North American CF conference No inclusion criteria, no numbers of eligible participants stated No reporting of method of CF diagnosis, rates of pancreatic insufficiency, nutrition or growth parameters Abstract was more than 10 years ago and a search using authors’ name did not reveal full publication. We could not find authors and hence not contacted</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aris 2000</td>
<td>Intervention (pamidronate, a bisphosphonate) does not meet review inclusion criteria</td>
</tr>
<tr>
<td>Gronowicz 2003</td>
<td>Intervention (Ultraviolet B radiation) does not meet review inclusion criteria</td>
</tr>
</tbody>
</table>
## Characteristics of studies awaiting assessment  [ordered by study ID]

### Hillman 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blinded randomized cross-over trial with 4 arms. Single centre in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>15 children aged 7 to 13, remained on standard medication (including pancreatic enzymes and ADEK vitamins). Children on oral or glucocorticoids were excluded</td>
</tr>
</tbody>
</table>
| Interventions | 4x 6 month treatments (including placebo) with 3-month washout period between each  
Placebo vs calcium (1g) vs vitamin D (1,600 IU) vs calcium (1g) plus vitamin D (1,600 IU) |
| Outcomes | Blood and urine collected at beginning and end of each treatment  
DXA performed at baseline, the beginning of each period and at 36 months (9 months between DXA - 6 month treatment plus washout)  
Calcium absorption at end of each period.  
Also, serum calcium, phosphorus, magnesium, parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, osteocalcin, bone alkaline phosphatase, tartrate resistant acid phosphatase, urine calcium/creatinine ratio |

### Judd 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized (in blocks of 6) cross-over trial with 3 arms. Single centre in USA</th>
</tr>
</thead>
</table>
| Participants | 30 adults (16 - 70 years old) with CF and with screening 25-hydroxyvitamin D levels between 10 and 40 ng/ml randomized; 18 completed trial  
Exclusion criteria: renal or hepatic disease, history of skin cancer, treatment with more than 2000 IU of vitamin D or prednisone or a history of more than 6 hospitalizations in past year |
| Interventions | Treatment 1: cholecalciferol 50,000 IU once a week for 12 weeks  
Treatment 2: ergocalciferol 50,000 IU once a week for 12 weeks  
Treatment 3: UV light therapy given for 3 - 10 mins 5 times per week for 12 weeks |

### Kumari 2009

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised (in blocks of 6) to intervention or placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>30 adults (age over 18 years old) with CF and hospitalised with acute respiratory exacerbation</td>
</tr>
</tbody>
</table>
| Interventions | 250,000 IU vitamin D3 or placebo as single dose within 48 hours of hospital admission  
Exclusion criteria: current therapy with high dose vitamin D (over 2000 IU daily) or admission for serious terminal illness |
| Outcomes | Blood collected for 25-hydroxyvitamin D level at randomization and hospital discharge, results reported for the first 12 of 30 enrolled participants |
Kumari 2009  (Continued)

<table>
<thead>
<tr>
<th>Notes</th>
<th>Abstract only. Trial completed, paper submitted for editorial review and consideration of publication</th>
</tr>
</thead>
</table>

CF: cystic fibrosis  
IU: international units  
UV: ultra-violet  
vs: versus