Vitamin D supplementation for cystic fibrosis

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[Intervention Review]

Vitamin D supplementation for cystic fibrosis

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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 cystic fibrosis.

Objectives

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

Search methods

We searched the Cochrane Cystic Fibrosis 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.

Date of the most recent search: 08 July 2013.

Selection criteria

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

Data collection and analysis

Both authors independently assessed the risk of bias of each included study and extracted outcome data (from published study 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

Six studies (239 participants) are included, although only three studies provided data from 69 adults and children with cystic fibrosis for analysis. One study compared a single high dose of vitamin D (250,000 IU) to placebo at the time of hospital admission with a respiratory exacerbation in 30 pancreatic insufficient adults with cystic fibrosis. The second study 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 third study compared supplemental 1 g calcium alone, 1600 IU vitamin D alone, 1600 IU vitamin D and

1 g calcium and placebo in a double-blind randomised cross-over study; only nine children who completed both vitamin D and placebo groups after six-months supplementation and a three-month washout period are included; pancreatic sufficiency or disease status of participants are not defined. The studies are not directly comparable due to differences in supplementation, outcome reporting and possibly participant characteristics (e.g. severity of lung disease, growth and nutrition, pancreatic sufficiency).

The only outcome for which we could combine data from more than two studies was 25-hydroxyvitamin D levels; patients receiving vitamin D supplementation had significantly higher levels, mean difference 7.24 ng/ml (95% confidence interval 5.01 to 9.46). However, ironically one study reported $1,25(OH)_2D$ with levels significantly favouring the placebo group, mean difference -30.30 pmol/ml (95% confidence interval -59.89 to -0.71). Bone mineral density was measured in two studies; both described no significant change between groups. There were no adverse events in any study.

The remaining three studies are published as abstracts only and did not provide data for analysis. These abstracts include: a report of pre-intervention data in a study comparing daily calcitriol (0.25 or 0.5 micrograms) with placebo in pancreatic insufficient children and young adults; an interim report of a double-blind randomised control study comparing 5000 IU vitamin D daily for 12 weeks during winter in 67 adult cystic fibrosis patients; and a comparison of the effect of three months of vitamin D supplementation (dose not specified) with placebo on bone mineral density in 42 children with cystic fibrosis and low bone mineral density.

Risk of bias was highly variable between all studies. Only one study had a low risk of bias for the five main criteria (random sequence generation, allocation, blinding, attrition and reporting). The rest of the studies had unclear or high risks of bias. Two studies had a low risk of bias for blinding and another two studies for attrition bias. In the studies published as abstracts, assessment of the risks of bias was uncertain in many aspects.

Authors' conclusions

In patients receiving vitamin D supplementation, 25-hydroxyvitamin D levels are significantly higher. However, there is no evidence of clinical benefit or harm in the limited number of small-sized published studies. Adherence to relevant cystic fibrosis guidelines on vitamin D supplementation 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 mean that fat-soluble vitamins, such as vitamin D, are poorly absorbed. This can lead to vitamin deficiencies. Lack of vitamin D (vitamin D deficiency) can cause specific problems such as bone deformity and bone fractures. It may also be associated with poorer general and respiratory health. Therefore, 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 six studies, however we could only analyse data from three of these studies. Three studies were only published as conference abstracts.

The included studies varied greatly in quality, the amount of vitamin D administered, the duration of treatment and the outcomes that were measured. Three studies were in children and adolescents and three in adults. Few outcome data could be combined. The sole outcome that included data from two or more studies was vitamin D levels. Our analysis showed increased vitamin D levels in people who were given vitamin D supplements. For other outcomes, we found no evidence to show whether giving vitamin D regularly to people with cystic fibrosis is beneficial or not. We are unable to draw any conclusions about giving routine vitamin D supplements and recommend that, until more 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 lung 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. There may be variance in efficacy between D2 and D3 in maintaining serum concentrations of 25-hydroxyvitamin D (25(OH)D). Although available information suggests D2 and D3 are equally efficacious. (Holick 2008) 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(OH)D and in the kidneys to form 1.25-dihydroxyvitamin 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)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)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 and there is a large disparity in the non-skeletal benefits of vitamin D between observational studies and randomised controlled trials (Theodoratou 2014). 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 (Bonifant 2012), as has a review of vitamin K supplementation (Jagannath 2013). A review of vitamin E supplementation is in progress (Okebukola 2011). This version of the review to evaluate vitamin D supplementation is an update of previous versions (Ferguson 2010; Ferguson 2012).

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 studies (controlled clinical studies).

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 (either 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. FEV_1, 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

Search methods for identification of studies

Electronic searches

Relevant studies 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 (CENTRAL) (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: 08 July 2013.

Searching other resources

We scanned the references in the papers of the included studies for further relevant papers.

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. The authors planned to settle any disagreement by discussion to achieve consensus.

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;
- study 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 evaluated these based on

1. short-term data (12 months or less); and
2. medium- to long-term data (over 12 months).

The authors 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. We planned to consider including outcome data of differing time periods. The duration of included studies ranged from nine to 12 months, thus this review reports only short-term outcomes (up to 12 months).

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 study 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 2012). 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 studies) divided by the total participant numbers in control groups in all studies 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 (SD). We combined change scores with final scores where appropriate using the mean difference (MD). We calculated the post-intervention SDs, if not reported, from the reported MD between groups (intervention and control) and 95% confidence intervals using the formulae detailed in Revman (RevMan 2012). If standard errors had been reported, we planned to convert these to SDs. We then calculated a pooled estimate of treatment effect by the MD and 95% CI (fixed-effect model) again using RevMan (RevMan 2012).

Unit of analysis issues

In the 2012 version of this review, the identified cross-over study described in an abstract (Popescu 1998) published only baseline data. It was not possible to undertake the planned analysis, including the fixed-effect generic inverse variance (GIV) analysis, in RevMan, summary weighted differences and 95% CIs (RevMan 2012). In this current version, data from the full paper (Hillman 2008) could be included in some of the analyses.

Dealing with missing data

The authors requested further information from the primary investigators of two studies (Brown 2005; Haworth 2004). We did not receive a response from Brown, but did receive a response from Haworth, who provided information ahead of the publication of the full paper.

Assessment of heterogeneity

Where possible we have combined study results with the same outcome measure, described heterogeneity between study results and used chi^2 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 I^2 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 analyse the included studies 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. If we had had any concerns regarding statistical heterogeneity (I^2 higher than 50%), we planned to use a random-effects model.

Subgroup analysis and investigation of heterogeneity

We were not able to investigate any heterogeneity using the planned subgroup analyses (children and adults, formulation of vitamin D, previous bowel resection, pancreatic insufficiency, method of CF diagnosis, gender and latitude bands) because there were too few studies included in the review.

Sensitivity analysis

It was not possible to undertake a sensitivity analysis either by random-effects model or by 'treatment received' because of the insufficient number of included studies in this review.

RESULTS

Description of studies

Results of the search

An additional four published abstracts or full papers describing two studies were identified since the last citation version of this review via the electronic search as detailed in the Electronic searches section. This review now includes eighteen published abstracts or full papers describing 10 studies. Four studies have been excluded (Aris 2000; Gronowitz 2003; Homola 2010; Khazai 2009). The full paper to one previously included study (Popescu 1998) has been published and has added data and information (Hillman 2008). Three studies listed as 'Studies awaiting classification' in

the previous citation version of the review have been reclassified; two as included studies (Grossmann 2012; Sciuca 2011) and one as excluded (Homola 2010). One newly identified study has also been included at the 2013 update (Deghan Manshadi 2012). Thus this review currently consists of six studies (Brown 2005; Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008; Sciuca 2011). We were able to enter data from four of these studies into the analysis (Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008).

Included studies

Study characteristics

Five studies were described as randomised controlled studies, but the abstract for the remaining study just describes participants being split into two groups (Deghan Manshadi 2012). One study was of cross-over design (Hillman 2008). This was a four-arm study and described a three-month washout period between each of the treatment arms (Hillman 2008). Study duration ranged from a single treatment (Grossmann 2012) with 12 months follow up to two years (Brown 2005). Three studies took place in the USA (Brown 2005; Grossmann 2012; Hillman 2008) one in Canada (Deghan Manshadi 2012), one in the UK (Haworth 2004) and one in Moldova (Sciuca 2011). Four of these specified the patients were from a single centre (Deghan Manshadi 2012;Grossmann 2012; Haworth 2004; Hillman 2008). The size of the studies varied, with the number of participants in each ranging from 15 (Hillman 2008) to 67 (Deghan Manshadi 2012).

Participants

A total of 239 participants were included within the review, but with data available for only 69. Three studies were in children and adolescents (Brown 2005; Hillman 2008; Sciuca 2011) and three in adults (Deghan Manshadi 2012; Haworth 2004; Grossmann 2012). In the paediatric studies the mean age ranged from three to 15 years (Hillman 2008); one study did not give details, but did stratify groups according to age (up to 12 years and 12 years and over) (Sciuca 2011). The gender split was reported in three studies and was approximately equal in each study (Brown 2005; Grossmann 2012; Haworth 2004). Three studies described pancreatic insufficiency in participants (Brown 2005; Grossmann 2012; Haworth 2004); participants were pancreatic insufficient in two of these studies (Brown 2005; Haworth 2004;) and a mix of pancreatic sufficient and insufficient in one study (Grossmann 2012). Only four studies included BMD status (Brown 2005; Deghan Manshadi 2012; Haworth 2004; Sciuca 2011).

Interventions

Five studies compared treatment to placebo (Brown 2005; Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008) and one study employed a no-supplement control arm (Sciuca 2011). Five studies state that participants continued with their usual routine vitamin D supplements (Brown 2005; Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008). Supplements and dosages varied as follows:

Study	Treatment	Control	Concommitant treatment
Brown 2005	Calcitriol (0.25mcg or 0.5mcg based on weight)	Placebo	Usual calcium (500 mg daily) and vitamin D supplements (dose not stated)
Deghan Manshadi 2012	Cholecalciferol (5000 IU/day)	Placebo	Routine vitamin D supplements
Grossmann 2012	Cholecalciferol single high dose (250,000IU)	Placebo	Usual 400 IU daily vitamin D supplementation
Haworth 2004	Vitamin D (800 IU) and calcium (1g)	Placebo	Standard vitamin D treatment (900 IU daily)
Hillman 2008	(1) Vitamin D (1600 IU daily) (2) Calcium (1g daily) (3) Vitamin D (1600 IU daily) and calcium (1g daily)	Placebo	Routine 400 IU daily vitamin D as part of routine fat soluble vitamin supplementation

(*Continued*)

Sciuca 2011	Vitamin D and calcium supplements (dose not stated)	No supplement	

Outcomes measured

Four studies reported results for BMD (Brown 2005; Haworth 2004; Hillman 2008; Sciuca 2011) and three of these additionally reported markers of bone turnover (Brown 2005; Haworth 2004; Hillman 2008). Only Sciuca did not report the site of the BMD measurement which precluded the inclusion of the data in the analysis (Sciuca 2011). Hillman additionally reported on percent calcium absorption (Hillman 2008). Two studies reported on levels of 25(OH)D (Deghan Manshadi 2012; Grossmann 2012). Grossmann additionally reported on calcium and PTH levels, hospital and antibiotic free days, lung function and mortality rates (Grossmann 2012). Only one study specifically reported adverse events or supplementation-related complications (Brown 2005).

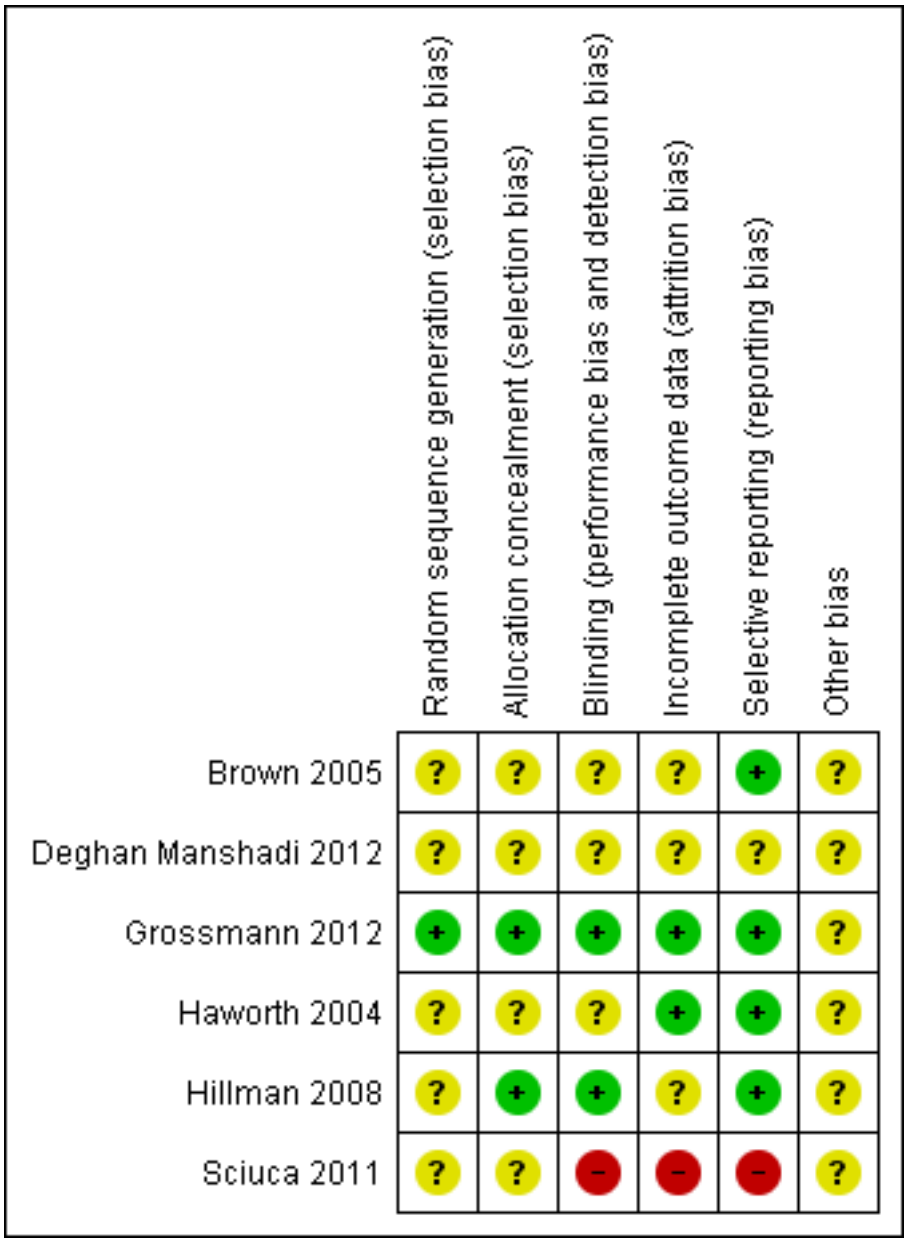
Excluded studies

Two studies were excluded due to interventions not forming part of this review - bisphosphate and ultraviolet (UV) B radiation (Aris 2000; Gronowitz 2003). Two studies were excluded as a placebo or no supplement arm was not included in the study design (Homola 2010; Khazai 2009).

Risk of bias in included studies

The summary is presented in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation

Only one study provides details of how allocation sequence was determined (computer-generated sequence) and is judged to have a low risk of bias (Grossmann 2012). The remaining five studies have an unclear risk of bias (Brown 2005; Deghan Manshadi 2012; Haworth 2004; Hillman 2008; Sciuca 2011). Four of these are described as randomised, but do not define how allocation sequence was generated (Brown 2005; Deghan Manshadi 2012; Haworth 2004; Hillman 2008). However, one study does state participants were randomised by gender and age bands (8 to 10 years, 11 to 14 years, 15 to 18 years) to stratify for pubertal status (Brown 2005). The remaining study simply describes patients being split into two groups (Sciuca 2011).

Allocation concealment

Only one study provides details of how the concealment of the allocation sequence was maintained - all medications were prepared and administered by hospital investigational drug service - and is judged to have a low risk of bias (Grossmann 2012). The remaining included studies did not describe how allocation sequence was concealed and are judged to have an unclear risk of bias (Brown 2005; Deghan Manshadi 2012; Haworth 2004; Hillman 2008; Sciuca 2011).

Blinding

Two studies report that participants, clinicians and assessors were blinded by using matching placebo drugs (Grossmann 2012; Hillman 2008). We judged these two studies to have a low risk of bias. Of the remaining studies, two describe the study as double-blinded but do not define how this occurred or was maintained (Deghan Manshadi 2012; Haworth 2004); the remaining two studies do not mention blinding at all (Brown 2005; Sciuca 2011). Of these four studies blinding is possible in three studies as they used a placebo and we judge these to have an unclear risk of bias from blinding (Brown 2005; Deghan Manshadi 2012; Haworth 2004). However, in one study the comparator arm was no supplementation and we therefore judge this to have a high risk of bias (Sciuca 2011).

Incomplete outcome data

Outcome data are complete in two studies which are at a low risk of bias (Grossmann 2012; Haworth 2004).

The Hillman study details outcome data for each separate arm of the cross-over study, reasons for participant attrition are not stated (Hillman 2008). Hence we judge this study to have an unclear risk of outcome bias (Hillman 2008). The remaining three studies are also assessed as being at unclear risk of incomplete outcome data bias (Brown 2005; Deghan Manshadi 2012; Sciuca 2011). The two studies in abstract form provide either only baseline data (Brown 2005) or interim data for 60% of enrolled participants (40 out of 67 participants) (Deghan Manshadi 2012). A further search did not yield any published papers subsequent to the abstracts and no additional outcome data was obtained from the authors. The remaining study reported in abstract form is at unclear risk of bias based on available data (Sciuca 2011).

Selective reporting

As already stated three studies have, as yet, only been published as abstracts and it is therefore difficult to identify any selective reporting (Brown 2005; Deghan Manshadi 2012; Sciuca 2011). Two of these abstracts detail only short-term or interim data (one year or less) (Deghan Manshadi 2012; Sciuca 2011); the third abstract reports only baseline data prior to two years of calcitriol supplementation (Brown 2005). We therefore judge these three studies to have an unclear risk of bias from selective reporting. We did not identify any selective reporting in the other three included studies and judge there to be a low risk of bias from this for these studies (Grossmann 2012; Haworth 2004; Hillman 2008).

Other potential sources of bias

Although each of the included studies had a range of potential risks of bias, we judged each to have an unclear risk of bias for this criteria as we are uncertain how these would potentially affect the study results.

Brown did not state the season or latitude where the study took place or publish any follow-up data; nor did the report include details of the method of CF diagnosis or compliance with enzyme replacement or study medications (Brown 2005). Deghan Manshadi stated that potential confounders, such as genotype, pancreatic status, age, gender, microbiology, BMI, CF-related diabetes and lung function, were recorded but these were not reported in the paper (Deghan Manshadi 2012). Grossmann stated that there were differences between the baseline characteristics of the intervention and placebo groups (e.g. age, BMI, pancreatic sufficiency, CF-related diabetes, lung function, numbers of participants with a greater than 10% reduction in FEV_1 at time of admission and rates of routine vitamin D supplementation) (Grossmann 2012). Haworth reported that all the participants in his study were part of a longitudinal BMD study preceding this one; only 31 out of 55 eligible participants enrolled, no specifics were given for those who declined to participate (Haworth 2004). Hillman was a cross-over

study with only a small number of participants and the washout period was only for three months (Hillman 2008). Sciuca provided too little information in the publication for us to determine any other bias (Sciuca 2011).

Effects of interventions

A limited amount of data from a small number of studies were available for the analysis, therefore sensitivity analyses, subgroup analyses or assessment of heterogeneity could not be undertaken for this version of the review. All available data are reported within the analysis section (Data and analyses). Within the text below, we have elaborated (i.e. described summary statistics) only on the statistically significant results.

Primary outcomes

1. BMD or vitamin D-specific deficiency outcomes

Only one study reported BMD as a primary outcome measure (Sciuca 2011). However the body site at which BMD was measured was not specified, neither was the vitamin D supplementation regimen. Two other papers provided data relating to BMD indices and these are presented as *post hoc* analyses (see further details below) (Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6).

2. Growth and nutritional status (weight z score)

Weight z score was not reported in any of the included studies either at baseline or follow up. Baseline BMI was reported in five included studies, but no study reported BMI or change in BMI at end of the intervention or follow up (Brown 2005; Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008).

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.

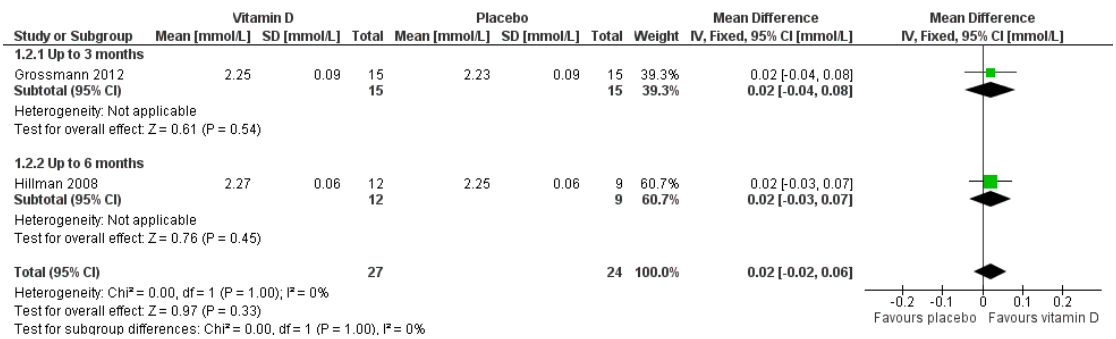
d. Other radiological abnormality

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))

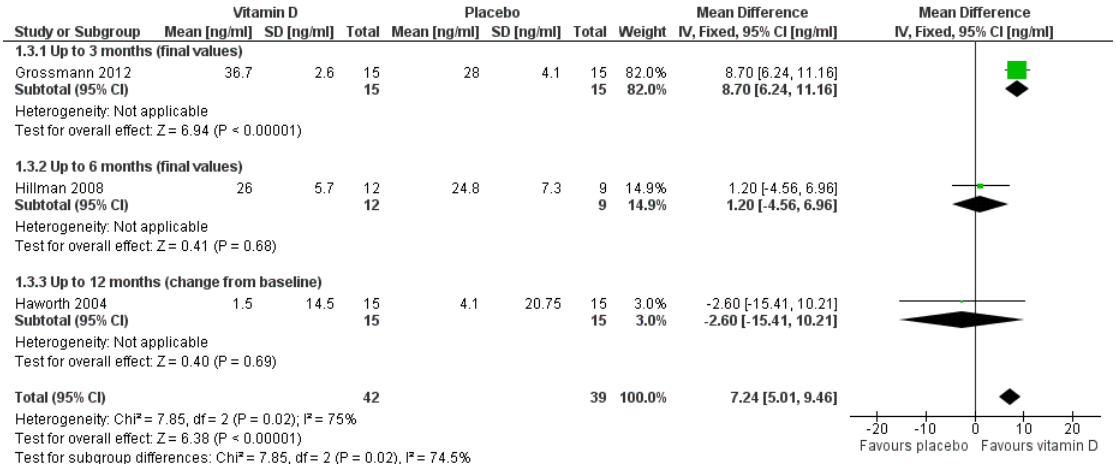
Three studies reported serum calcium at baseline and end of intervention (Grossmann 2012; Haworth 2004; Hillman 2008), but data from only two studies could be combined (Grossmann 2012; Hillman 2008). The analysis showed no difference between groups (Figure 2; Analysis 1.1; Analysis 1.2).

Figure 2. Forest plot of comparison: 1 Vitamin D versus placebo, outcome: 1.2 Serum calcium (absolute final) [mmol/L].



Four studies reported data for vitamin D (25(OH)D), each study used a different dosing regimen and preparation of vitamin D (Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008). One study reported the mean 25(OH)D level at baseline and end of intervention for participants receiving D3 but not those treated with D2; thus these data were not able to be included in the meta-analysis (Deghan Manshadi 2012). This study reported a statistically significant ($p < 0.01$) increase in mean (SD) 25(OH)D serum level from 48.2 (18.9) nmol/l to 73.5 (27.4) nmol/l in cholecalciferol group compared to no change in placebo group (values not reported) (Deghan Manshadi 2012). One study reported 25(OH)D levels at baseline, one week and 12 weeks (Grossmann 2012); one study reported 25(OH)D levels at baseline and mean change after 12 months of intervention (Haworth 2004); and the cross-over study reports 25(OH)D levels and $1,25(OH)_2D$ levels at the end of each six-month intervention in each of the four intervention arms (Hillman 2008). We were able to combine the 25(OH)D data from three studies and have presented the data in the meta-analysis (Grossmann 2012; Haworth 2004; Hillman 2008). The mean difference between groups for 25(OH)D significantly favoured vitamin D supplementation, MD 7.24 ng/ml (95% CI 5.01 to 9.46) (Figure 3; Analysis 1.3).

Figure 3. Forest plot of comparison: 1 Vitamin D versus placebo, outcome: 1.3 25(OH)D [ng/ml].



Only one study reported $1,25(OH)_2D$ showing a significant difference between groups favouring the placebo group, MD -30.30 pmol/L (95% CI -59.89 to -0.71) (Hillman 2008) (Analysis 1.4).

2. Respiratory outcomes

a. Bronchiectasis severity control

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

b. Lung function indices

Three included studies reported lung function indices at baseline only (Brown 2005; Deghan Manshadi 2012; Haworth 2004). One study reported lung function (FEV_1) at baseline and also the proportion of participants whose lung function returned to baseline (best FEV_1 in one to six months prior to randomisation) over the 12 months after randomisation, where there had been a 10% or larger decline in lung function at the time of study randomisation (Grossmann 2012). The authors reported that nine out of 10 of the group receiving vitamin D, who had a 10% or larger decline in lung function (FEV_1) at the time of study randomisation, had improvement in lung function (FEV_1) to 95% or more of baseline lung function compared to four out of eight in the control group ($P = 0.12$) (Grossmann 2012).

c. Proportions of participants who had respiratory exacerbations or hospitalisations or both

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

e. Total number of hospitalised days

Only one study reported number of hospital free days; the trend was toward fewer hospital days and days of intravenous antibiotics in the intervention group (Grossmann 2012).

f. Other objective indices

One study reported serum cytokine and antimicrobial peptide concentrations at baseline and 12 weeks after intervention (Grossmann 2012); this was reported in a separate publication. The authors reported a "50.4% reduction in tumor necrosis factor-α (TNF-α) at 12 weeks (P < 0.01)", but no significant changes in interleukins-1β, -8, -10, -18BP and neutrophil gelatinase-associated lipocalin. The mean change in interleukin-6 (IL-6) concentration in the vitamin D intervention group was a decrease of 12.39 pg/ml (P = 0.004) at week 1 and of 5.19 pg/ml (P = 0.35) at week 12 compared to baseline, whilst there was no change in IL-6 concentration from baseline in the placebo group (Grossmann 2012). The clinical benefit from these changes are unknown.

3. Quality of life

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

4. Adverse events

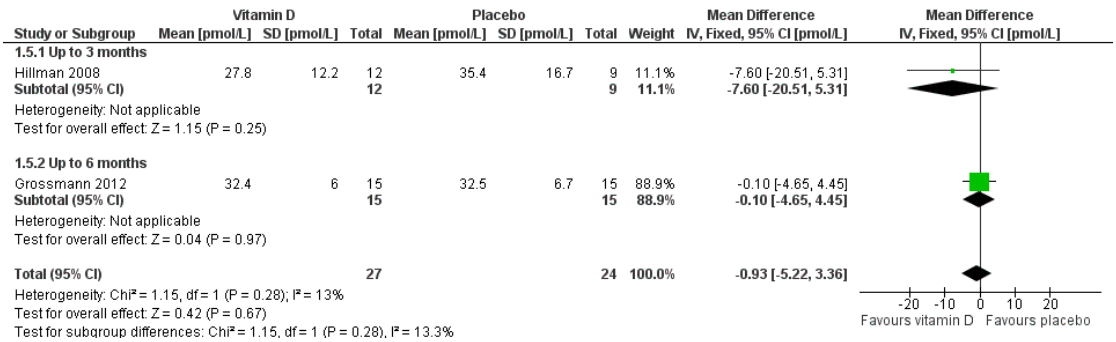
Four studies did not report any adverse outcomes in either participant group (Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Sciuca 2011).

Two participants (one in each group) developed nephrolithiasis in one study which was reported as abstract; furthermore one participant in the treatment group developed mild hypercalcaemia and two in the placebo group had hypercalciuria (Brown 2005). We could not present these 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

Three studies reported on this outcome; two studies presented absolute data for parathyroid hormone levels at the end of treatment (Grossmann 2012; Hillman 2008) and one study reported the change from baseline (Haworth 2004). When combined, there was no significant difference between groups at the end of intervention (Figure 4; Analysis 1.5). This was also true for the analysis of the single study reporting the change in PTH levels (Analysis 1.6).

Figure 4. Forest plot of comparison: 1 Vitamin D versus placebo, outcome: 1.5 PTH levels (absolute final) [pmol/L].



Post-hoc analyses

Four studies planned to measure BMD indices following vitamin D supplementation (Brown 2005, Haworth 2004, Hillman 2008; Sciuca 2011); this was a primary outcome in only one study (Sciuca 2011). However, BMD or bone mineral content measurement and method of reporting (z score versus per cent change from baseline) differed between studies such that data could not be combined when results were reported (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6). In this review BMD z score was not a primary outcome measure; however, BMD z scores are an objective and reproducible assessment of the effect of vitamin D supplementation on bone mineralisation. For all the available outcomes, there was no significant difference between the groups except for the change in hip BMD, MD -0.05 g/cm^2 (95% CI -0.06 to -0.03) (Analysis 2.6).

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 and health and well-being consequences of this by using clinically measurable markers of BMD, growth and nutrition, respiratory status, and biochemical markers of bone metabolism in children and adults with CF. There were only six small, short-term studies included; five have examined vitamin D supplementation compared with placebo and one compared the intervention with no treatment. Only five of these studies have published any post-treatment data, the follow-up intervals in these studies were short (longest follow-up interval being 24 months). The studies have used different durations of intervention and doses of vitamin D for supplementation.

Summary of main results

There was a significant increase in vitamin D levels in those in the supplemented group. There was no clear benefit or harm identified with short-term vitamin D supplementation compared to placebo in the 185 people with CF completing the period of intervention in the five studies with available data (Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Hillman 2008; Sciuca 2011). 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 six 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 publications in this review (Grossmann 2012; Haworth 2004; Hillman 2008). There were no reported adverse events in two remaining studies in abstract form only (Deghan Manshadi 2012; Sciuca 2011).

Overall completeness and applicability of evidence

The six studies meeting inclusion criteria provided data assessing 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 predominately short-term nature of supplementation, follow up and small sample size.

Participants in the Haworth and Hillman studies continued the centre's routine vitamin D supplement of 900 IU daily (Haworth 2004) and 400IU daily respectively (Hillman 2008). This was in keeping with UK CF guidelines (UK CF Trust 2007), but may not be standard practice in all centres.

Many of the secondary outcomes (effect of vitamin D supplementation on clinical markers of vitamin D deficiency, respiratory outcomes and quality of life) were not assessable from data in any study. This 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(OH)D 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 six small studies of short-term vitamin D supplementation; BMD (either as percent change or z score) was the only consistently reported primary outcome measure across studies. Relevant outcome measures could not be combined due to variation in dose, preparation, duration and timing (as part of routine care versus time of hospital admission with respiratory exacerbation) of vitamin D supplementation and between studies. Five of the six included studies are limited by the lack of details with regard to methods of randomisation and blinding, incomplete outcome reporting (only baseline or interim data reported) and selective outcome reporting bias (Brown 2005; Deghan Manshadi 2012; Haworth 2004; Hillman 2008; Sciuca 2011). Five of the included studies were of a parallel design format (Brown 2005; Deghan Manshadi 2012; Grossmann 2012; Haworth 2004; Sciuca 2011), whilst the remaining study was of a cross-over design with a washout period between each intervention arm (Hillman 2008). Randomisation in a cross-over study is of the treatment order rather than a direct comparison of intervention with placebo. Cross-over study design is better suited to interventions that have a short-term effect, whereas the role of vitamin D supplementation in CF is to optimise bone health in the longer term. 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.

Potential biases in the review process

All relevant studies are likely to have been identified by our search methods. Three papers were available as abstracts only and thus assessment was limited (Brown 2005; Deghan Manshadi 2012; Sciuca 2011). 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 are 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 should be considered (UK CF Trust 2007). Toxicity is an uncommon occurrence in the small number of published randomised, controlled studies of vitamin D supplementation. Further randomised controlled studies are clearly required.

It is biologically plausible that currently, with improved pancreatic replacement therapies and attention to macro-nutrition and caloric supplements, the frequency of clinically significant vitamin D insufficiency is less than historically reported. Daily supplementation in these situations causes no harm, but adds a further burden to the daily medical regimen of people with CF. As previously stated, adherence to relevant existing guidelines on supplementation with vitamin D and calcium should be considered until more comprehensive parallel, long-term randomised controlled studies of vitamin D supplementation in CF, with long-term follow up, are published.

Implications for research

The available data suggest the CF population have lower vitamin D levels and BMD than age- and gender-matched unaffected individuals, but this is likely to be multifactorial (e.g. malabsorption, liver dysfunction, 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, long term intervention and follow up, randomised controlled studies 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 mutation groups (such as Δ508 or not) into account although this would likely increase the complexity of a study. Outcome measures should include skeletal and non-skeletal effects of vitamin D.

Data obtained from RCTs comparing the outcome of vitamin D supplementation with placebo may be supplemented with information from non-randomised, longitudinal CF registry databases, which include details of genetic mutation, pancreatic sufficiency, adequacy of pancreatic enzyme supplementation, disease and nutritional status, disease complications (CF-related diabetes, CF-related liver disease) and clinical markers of bone health and vitamin D status.

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REFERENCES

References to studies included in this review

Brown 2005 *{published data only (unpublished sought but not used)}*
Brown SA, Aris RM, Leigh MW, Retsch-Bogart GZ, Caminiti MJ, Jennings-Grant T, et al. Baseline BMD status in children and young adults with CF: calcitriol intervention study [abstract]. *Pediatric Pulmonology* 2005; **40 Suppl 28**:354. [CFGD Register: CO20]

Deghan Manshadi 2012 *{published data only}*
Deghan Manshadi S, Robert R, Brotherwood M, Tullis E, Stephenson A. A randomized placebo-controlled trial of cholecalciferol for vitamin D deficiency in adults with cystic fibrosis [abstract]. *Pediatric Pulmonology* 2012;**47 Suppl 35**:412, Abstract no:515. [CFGD Register: GN228]

Grossmann 2012 *{published data only}*
Grossmann RE, Zughaier S, Kumari M, Seydafkan S, Liu S, Lyles R, et al. Clinical responses to a novel vitamin D supplementation strategy in adult CF patients hospitalized for pulmonary exacerbations [abstract]. *Pediatric Pulmonology* 2011;**46 Suppl 34**:404, Abstract 526. [CFGD Register: GN217b]
* Grossmann RE, Zughaier SM, Kumari M, Seydafkan S, Lyles RH, Liu S, et al. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial. *Dermato-endocrinology* 2012;**4**(2):191–7. [CFGD Register: GN217d;]
Grossmann RE, Zughaier SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of

inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. *European Journal of Clinical Nutrition* 2012;**66**(9):1072–4. [CFGD Register: GN217c]
Kumara M, Colman L, Grossmann R, Wolfenden LL, Tangpricha V. High dose vitamin D supplementation in cystic fibrosis patients hospitalised for respiratory exacerbation [abstract]. *Pediatric Pulmonology* 2009;**44 Suppl 32**:Abstract 549. [CFGD Register: GN217a]

Haworth 2004 *{published data only}*
Haworth CS, Jones A, Selby PL, Adams JE, Mawer EB, Webb AK. Randomised, double blind, placebo controlled trial investigating the effect of calcium and vitamin D supplementation on bone mineral density and bone metabolism in adults with cystic fibrosis [abstract]. *Pediatric Pulmonology* 2001;**32 Suppl 22**:330–1. [CFGD Register: CO18a]
* Haworth CS, Jones AM, Adams JE, Selby PL, Webb AK. Randomised double blind placebo controlled trial investigating the effect of calcium and vitamin D supplementation on bone mineral density and bone metabolism in adult patients with cystic fibrosis. *Journal of Cystic Fibrosis* 2004;**3**(4):233–6. [CFGD Register: CO18b]

Hillman 2008 *{published data only}*
* Hillman LS, Cassidy JT, Popescu MF, Hewett JE, Kyger J, Robertson JD. Percent true calcium absorption, mineral metabolism, and bone mineralization in children with cystic fibrosis: effect of supplementation with vitamin D and calcium. *Pediatric Pulmonology* 2008;**43**(8):772–80. [CFGD Register: CO21]
Popescu M, Morris J, Hillman L. Calcium and vitamin D supplementation in CF children [abstract]. *Pediatric Pulmonology* 1998;**26 Suppl 17**:359, Abstract no: 539.

Sciuca 2011 *{published data only}*
Sciuca S, Turcu O. Correction of low bone mass density in patients with cystic fibrosis [abstract]. *Journal of Cystic Fibrosis* 2011;**10 Suppl 1**:S78, Abstract no: 308. MEDLINE: 97400975; CO46

References to studies excluded from this review

Aris 2000 *{published data only}*
Aris RM, Lester GE, Neuringer IP, Winders AW, Gott KK, Rea J, et al. Efficacy of pamidronate for osteoporosis in cystic fibrosis patients following lung transplantation [abstract]. *Pediatric Pulmonology* 1998;**26**(Suppl 17):365.
* Aris RM, Lester GE, Renner JB, Winders A, Denene Blackwood A, Lark RK, et al. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. *American Journal of Respiratory and Critical Care Medicine* 2000;**162**(3 part 1):941–6.
Aris RM, Ontjes DA, Winders AW, Blackwood D, Lester GE. Effect of pamidronate on bone biomarkers in post-transplant osteoporotic cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 1998;**26**(Suppl 17):364–5.

Gronowitz 2003 *{published data only}*
Gronowitz E, Gilljam M, Hollsing A, Lindblad A, Larko O, Strandvik B. Ultraviolet B radiation improves serum levels of vitamin D in patients with cystic fibrosis (abstract). *Pediatric Pulmonology* 2003;**36**(Suppl 25):345.

Homola 2010 *{published data only}*
Homola L, Holcikova A, Mikolasek P, Pavelka J. Vitamin D supplementation in children with cystic fibrosis:sunshine, cholecalciferol and ergocalciferol [abstract]. *Journal of Cystic Fibrosis* 2011;**10 Suppl 1**:S76, Abstract no: 302. CFGD Register: GN220; MEDLINE: 97400975

Khazai 2009 *{published data only}*
Judd SE, Khazai N, Jeng L, Stecenko A, Wolfenden L, Tangpricha V. Evaluation of ergocalciferol, cholecalciferol or UVB light therapy to improve vitamin D status in cystic fibrosis: a prospective randomized study [abstract]. *Pediatric Pulmonology* 2008;**43**(Suppl 31):420.
Khazai NB, Judd SE, Jeng L, Wolfenden LL, Stecenko A, Ziegler TR, Tangpricha V. Treatment and prevention of vitamin D insufficiency in cystic fibrosis patients: comparative efficacy of ergocalciferol, cholecalciferol, and UV light. *Journal of Clinical Endocrinology and Metabolism* 2009;**94**(6):2037–43. MEDLINE: 97400975

Additional references

Aris 2005
Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Consensus statement: Guide to bone health and disease in cystic fibrosis. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(3):1888–96.

Black 2005
Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005;**128**(6):3792–8.

Bonifant 2012
Bonifant CM, Shevill E, Chang AB. Vitamin A supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD006751.pub3]

Borowitz 2002
Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition* 2002;**35**:246–59.

Brenckmann 2001
Brenckmann C, Papaioannou A. Bisphosphonates for osteoporosis in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD002010]

Cates 2003 [Computer program]
Cates C. Visual Rx. Online NNT Calculator. http://www.nntonline.net/: Cates C, 2003.

Chesney 1989
Chesney RW. Vitamin D: Can an Upper Limit be Defined?. *Journal of Nutrition* 1989;**119**(12 Suppl):1825–8.

Deeks 2011
Deeks J, Higgins J, Altman D. Chapter 9 Analysing data and undertaking meta-analysis. In: Higgins JPT, Green

S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Dimitri 2007
Dimitri P, Bishop N. Rickets. *Paediatrics and Child Health* 2007;**17**(7):279–87.

Dodge 2006
Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. *Best Practice & Research. Clinical Gastroenterology* 2006;**20**(3):531–46.

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

Higgins 2011
Julian PT Higgins, Douglas G Altman and Jonathan AC Sterne on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

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

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]

Jagannath 2013
Jagannath VA, Fedorowicz Z, Thaker V, Chang AB. Vitamin K supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD008482.pub3]

Joiner 2000
Joiner TA, Foster C, Shape T. The many faces of vitamin D deficient rickets. *Pediatrics in review* 2000;**21**(9):296–302.

NIH 2007
NIH. Office of Dietary Supplements. Dietary Supplement Fact Sheet: Vitamin D. http://ods.od.nih.gov/factsheets/vitamind.asp (accessed 31st October 2007).

Okebukola 2011
Okebukola PO, Kansra S, McCabe H. Vitamin E supplementation in people with cystic fibrosis (Protocol). *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD009422]

Popescu 1998
Popescu M, Morris J, Hillman L. Calcium and vitamin D supplementation in CF children [abstract]. *Pediatric Pulmonology* 1998;**26 Suppl 17**:359.

RevMan 2012 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Sethuraman 2006
Sethuraman U. Vitamins. *Pediatric Review* 2006;**27**(2): 44–55.

Sinaasappel 2002
Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. *Journal of Cystic Fibrosis* 2002;**1**:51–75.

Theodoratou 2014
T heodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014;**348**:g2035.

UK CF Trust 2007
The UK Cystic Fibrosis Trust Bone Mineralisation Working Group. *Bone mineralisation in cystic fibrosis. Report of the UK Cystic Fibrosis Trust Bone Mineralisation Working Group*. Cystic Fibrosis Trust, February 2007.

Wagener 2003
Wagener JS, Headley AA. Cystic fibrosis: current trends in respiratory care. *Respiratory Care* 2003;**48**(3):234–45.

Wharton 2003
Wharton B, Bishop N. Rickets. *Lancet* 2003;**362**(9393): 1389–400.

World Health Organization 1994
World Health Organization. Definition of osteoporosis. Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis 1994:1–129.

Wright 2005
Wright RJ. Make no bones about it: increasing epidemiologic evidence links vitamin D to pulmonary function and COPD. *Chest* 2005;**128**(6):3781–3.

References to other published versions of this review

Ferguson 2010
Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD007298.pub2]

Ferguson 2012
Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD007298.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brown 2005

Methods	Randomised double-blind, placebo-controlled study. Parallel design. Based in USA. Duration: 2 years.
Participants	54 (31 male, 23 female) pancreatic insufficient children and young adults with CF. Numbers in intervention and control groups not stated Age: mean (SD) 12.1 (3.1) years; range 8 - 18 years. Baseline characteristics: BMI mean (SD) 18.1 (2.9) kg/m^2; FEV_1 mean (SD) 80 (20) % predicted, range 36 - 129%. 31 (18 male, 13 female) healthy sibling or community controls were recruited to assess BMD normative data (mean (SD) age 11.7 (2.9) years)
Interventions	**Treatment**: supplementation with oral calcitriol (1,25 $(OH)_2D$, dose based on weight (0.25 mcg daily if < 45 kg, 0.5 mcg daily if 45 kg or heavier) **Control**: placebo. Usual calcium (500mg daily) and vitamin D supplements (dose not specified) continued in all participants
Outcomes	Baseline/pre-intervention characteristics and data only published Adverse events of study medications (calcitriol and placebo) reported 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
Funding source	National Institutes for Health, University of North Carolina General Clinical Research Centre, Cystic Fibrosis Foundation
Exclusions	Corticosteroid use over 5 mg/day for 3 months, organ transplantation, nephrolithiasis or severe liver dysfunction
Study withdrawals and adverse events	32/54 participants completed the 2 years of the study period 2 withdrawals due to persistent hypercalciuria, one each from placebo and intervention group. Nephrolithiasis in 2 (1 on calcitriol, 1 on placebo) presumed to be withdrawn as this is a specific exclusion in study protocol In calcitriol group: 1 asymptomatic mild hypercalcaemia. In placebo group: 1 asymptomatic hyperphosphataemia.
Notes	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 with study medications

Brown 2005 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported. States that participants were randomised by gender and age (8 - 10, 11 - 14,15 - 18 years) to stratify for pubertal status Healthy siblings and community participants recruited to assess normative BMD data
Allocation concealment (selection bias)	Unclear risk	No method reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No method reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Baseline/pre-intervention data only. Numbers in each group not reported 32/54 participants reported to complete study; but only 4 withdrawals accounted for
Selective reporting (reporting bias)	Low risk	All outcomes are recorded.
Other bias	Unclear risk	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.

Deghan Manshadi 2012

Methods	Double-blind, randomised, placebo-controlled study of additional cholecalciferol supplementation in vitamin D deficient adults with CF Parallel design. Based in Toronto, Canada. Duration: 12 weeks during winter months (September-March 2009-2012)
Participants	67 (33 treatment arm, 34 placebo arm) adults in the Toronto Adult CF program Age: over 18 years. Baseline characteristics: vitamin D deficient (25(OH)D level <75nmol/l) Potential confounders of genotype, pancreatic status, age, gender, microbiology, BMI, CF-related diabetes and lung function were recorded though not reported

Deghan Manshadi 2012 (*Continued*)

Interventions	**Treatment**: 5000IU daily of cholecalciferol. **Control**: placebo. All patients continued with routine vitamin D supplements.
Outcomes	Interim results on 40/67 randomised participants (18 treatment, 22 placebo) Outcome measure: change in mean serum 25(OH)D levels.
Funding source	Not reported.
Exclusions	History of, or known condition associated with, hypercalcaemia, renal stones, psychiatric illness; sunbed use or travel to a sunny location during the study period; pregnancy or lactation; organ transplantation
Study withdrawals and adverse events	No mention of study withdrawals. No adverse events were identified
Notes	Interim results. Abstract only - poster presented at 26th Annual North American CF Concerfence 2012. Unable to add any data in review at this stage as insufficient data provided in abstract

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Participants and study investigators were blinded to the treatment groups." No further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Interim results only.
Selective reporting (reporting bias)	Unclear risk	Interim results only.
Other bias	Unclear risk	Potential confounders (genotype, pancreatic status, age, gender, microbiology, BMI, CF related diabetes and lung function) recorded but not reported

Grossmann 2012

Methods	Randomised, double-blind, placebo-controlled study. Parallel design. Single centre in Atlanta USA. Duration: single intervention with 12 months follow up.
Participants	30 adults with CF. 15 (9 males) in treatment group and 15 (8 males) in placebo group Age: over 18 years. Diagnosis based on genotype. Baseline characteristics: both pancreatic sufficient and insufficient, hospitalised with acute respiratory exacerbation of CF (increased cough, sputum production, weight loss and/or decline in FEV_1).
Interventions	**Treatment**: 250,000 IU vitamin D3 as single dose within 48 hours of hospital admission for respiratory exacerbation **Control**: placebo. All participants continued with usual vitamin D supplement of up to 2,000 IU/day
Outcomes	Primary outcomes: change in 25(OH)D, calcium, PTH levels between baseline, 1 week and 12 weeks post intervention Secondary outcomes (based on review at routine quarterly CF clinic visits) at 6 and 12 months post intervention: FEV_1 % compared with baseline, number of hospital-free days, number of IV antibiotic-free days (home IV therapy) and mortality In the second paper published in the European Journal of Clinical Nutrition, as secondary analyses, the outcomes were: an antimicrobial peptide (LL-37) and markers of inflammation (IL-1β, IL-10, IL-18-binding protein (IL-18BP), IL-6, IL-8 and TNF-α) measured in the blood
Funding source	Study supported by grants from CF Foundation, Center for Cystic Fibrosis Research, Children's Healthcare of Atlanta, PHS Grant from the Clinical and Translantional Science Award Programme, National Institutes of Health, National Center for Research Resources and JoAnne and James Grote
Exclusions	Exclusion criteria: current therapy with high dose vitamin D (over 2000 IU daily), history of disorder affecting vitamin D, calcium or phosphorus metabolism, organ transplant, pregnancy or planning pregnancy or admission for serious terminal illness
Study withdrawals and adverse events	No withdrawals from study; 5 deaths in placebo group (3 prior to week 12) during period of follow up (12 months); 1 death in intervention group
Notes	Same study (i.e. 30 adult patients randomised to single dose of 250,000 IU cholecalciferol or placebo during hospital admission with pulmonary exacerbation) in each of these 3 reports (2 published articles, 1 abstract). Outcome measures (as noted above) differed between the 2 published articles. Abstract details both sets of outcome measures

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

Grossmann 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation within 48 hours of hospital admission by computer-generated balanced randomisation scheme in blocks of 6
Allocation concealment (selection bias)	Low risk	All medications (intervention and placebo) prepared and administered by hospital investigational drug service
Blinding (performance bias and detection bias) All outcomes	Low risk	Study personnel, caregivers, subjects and outcome assessors blinded to allocation of study drug. Patients received either active treatment or a matched, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals from treatment intervention, no loss to follow up; 6 deaths during follow-up period of study
Selective reporting (reporting bias)	Low risk	Outcomes reported for all study participants.
Other bias	Unclear risk	Differences between intervention and placebo group at baseline in age, BMI, pancreatic sufficiency, CF related diabetes, baseline lung function, numbers with >10% reduction in FEV_1 at time of admission and rates of routine vitamin D supplementation

Haworth 2004

Methods	Randomised, double-blind, placebo-controlled study. Parallel design. Single centre (Manchester adult CF unit). Duration: 12 months.
Participants	31 adults with CF. 16 in intervention group (9 female, 7 males), 15 in control group (7 females, 8 males) Age: over 18 years; intervention group mean age 29.4 years, control group mean age 25.9 years Diagnosis: confirmation of CF diagnosis by genetic testing. Baseline characteristics: pancreatic-insufficient (but no definition of pancreatic insufficiency) and osteopenic (BMD z score less than -1 measured at lumbar spine, proximal femur or distal forearm). Intervention group: mean FEV_1 66.1% predicted; mean BMI 23.0kg/$m^{2.}$ Control group: mean FEV_1 60.9%; mean BMI 21.1kg/m^2.

Haworth 2004 (*Continued*)

Interventions	**Treatment**: Supplementation with 1g calcium and 800 IU vitamin D daily (Calichew D3 forte 1 tablet twice daily) **Control**: placebo. All participants continued standard daily vitamin D supplements (900 IU)
Outcomes	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(OH)D, PTH, osteocalcin, bone specific alkaline phosphatase, urinary crosslinks)
Funding source	UK Cystic Fibrosis Trust.
Exclusions	No exclusion criteria reported.
Study withdrawals and adverse events	1 withdrawal (female) from vitamin D supplementation group due to pregnancy No adverse events reported.
Notes	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 Professor Howarth was contacted and replied but was unable to provide any unpublished data

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method notes double blinding, although no details of blinding or method used
Incomplete outcome data (attrition bias) All outcomes	Low risk	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.
Selective reporting (reporting bias)	Low risk	All defined outcomes are reported.
Other bias	Unclear risk	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

Hillman 2008

Methods	Randomised, double-blind controlled study with 4 arms. Cross-over design (comparison of 4 treatments within a single study group) SIngle centre (University of Missouri CF Clinic) in USA. Duration: 6 months supplementation in each arm with 3-month washout period between each arm
Participants	15 children and adolescents with CF. While total number recruited was 15, different numbers of children completed different arms (n = 9 to n = 12) Age: mean (SD) 9.1 (2.3) years; range 3 - 15 years. Baseline characteristics: Tanner stage I-III on self report; mean (SD) FVC 86.5 (12.3)% predicted, mean (SD) FEV_1 77.2 (16.7)% predicted.
Interventions	**Treatment**: vitamin D supplement 1600IU/day. **Control**: placebo. All participants continued routine daily vitamin D (400IU) as part of fat soluble multi-vitamin supplement (ADEK) There were a total of 4 arms in the study (placebo versus vitamin D alone (1600IU/day) versus calcium alone (1g/day) versus vitamin D (1600IU/day) with calcium (1g/day)), but only data for the placebo and vitamin D supplementation alone arms presented in the review
Outcomes	Primary outcome: change in BMC/BMD (whole body, distal radius, hip and lumbar spine). Measurement at baseline and 9-month intervals Secondary outcomes: calcium, phosphate, magnesium, PTH, 25(OH)D, $1,25(OH)_2D$, measurement of calcium absorption. Measurements at baseline and Blood and urine collected at beginning and end of each arm (6 months). DXA performed at baseline, beginning of each arm and at 36 months
Funding source	Cystic Fibrosis Foundation. Supplements provided by Mead Johnson and Smith, Kline, Beecham
Exclusions	Oral or IV corticosteroids, post-pubertal status (Tanner stage IV)
Study withdrawals and adverse events	No adverse events noted. No reasons given for withdrawals from study. 9 completed placebo arm, 12 vitamin D arm, 10 calcium arm, 11 vitamin D and calcium arm
Notes	This study was previously identified as an abstract published in 1998 as Popescu et al Only comparison of calcium arm and placebo arm eligible for inclusion in review

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Hillman 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified .
Allocation concealment (selection bias)	Low risk	Study medications prepared and dispensed by investigational pharmacy according to a blinded code
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebos for vitamin D and calcium were used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Complete data given for study withdrawals. Analysis of each group suggests no treatment order effect. Reasons for drop out were unclear. Complete data provided for those who completed the different arms. CONSORT diagram not provided
Selective reporting (reporting bias)	Low risk	No selective reporting identified.
Other bias	Unclear risk	Very small study with washout for only 3 months.

Sciuca 2011

Methods	Controlled study, randomisation process not clear, abstract states that children with CF divided into 2 groups stratified by age. Parallel design. Duration: 3 months. Based in Moldova.
Participants	Total number of participants not clear. Abstract states 42 patients with CF examined but then states that children with CF divided into 2 groups of 26 children <12 years and 21 children >12 years and supplements given (treatment group). Further states that control group consisted of 21 children with CF (8 children <12 years and 13 children > 12 years)
Interventions	**Treatment**: calcium supplements with vitamin D (dose not stated). **Control**: no calcium supplements.
Outcomes	Quantitative ultrasound was performed (Omnisense 7000P) and z score of BMD, effects of therapy
Funding source	Not stated.
Exclusions	Not stated.
Study withdrawals and adverse events	Not stated.

Sciuca 2011 (*Continued*)

Notes	Abstract only. Unable to add any data in review at this stage as insufficient data provided in abstract

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Comparator was 'no supplementation'. Hence, high risk of bias as blinding not possible
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear reporting of numbers enrolled in intervention group.
Selective reporting (reporting bias)	High risk	Numbers studied and description of numbers in intervention and control groups don't add up
Other bias	Unclear risk	Little data provided in paper. Unable to determine other bias

25(OH)D: 25-hydroxyvitamin D
$1,25(OH)_2D$: 1,25-dihydroxyvitamin D
BMC: bone mineral content
BMD: bone mineral density
BMI: body mass index
CF: cystic fibrosis
CT: computerised tomography
DXA: dual energy X-ray absorptiometry
FEV_1: forced expiratory volume at one second
g: gram
IU: international units
PTH: parathyroid hormone
SD: standard deviation

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

Study	Reason for exclusion
Aris 2000	Intervention (pamidronate, a bisphosphonate) does not meet review inclusion criteria
Gronowitz 2003	Intervention (ultraviolet B radiation) does not meet review inclusion criteria
Homola 2010	No appropriate control group. Randomised part of study compared ergocalciferol (D2) to cholecalciferol (D3); no supplement data were averages of previous years
Khazai 2009	No placebo - 30 adults with CF and vitamin D insufficiency were randomized into 1 of 3 treatment arms: D3, D2, or ultraviolet light

CF: cystic fibrosis
D2: ergocalciferol
D3: cholecalciferol

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum calcium change (mmol/L)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
1.1 Up to 12 months	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serum calcium (absolute final)	2	51	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.02, 0.06]
2.1 Up to 3 months	1	30	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.04, 0.08]
2.2 Up to 6 months	1	21	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.03, 0.07]
3 25(OH)D	3	81	Mean Difference (IV, Fixed, 95% CI)	7.24 [5.01, 9.46]
3.1 Up to 3 months (final values)	1	30	Mean Difference (IV, Fixed, 95% CI)	8.70 [6.24, 11.16]
3.2 Up to 6 months (final values)	1	21	Mean Difference (IV, Fixed, 95% CI)	1.20 [-4.56, 6.96]
3.3 Up to 12 months (change from baseline)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-15.41, 10.21]
4 $1,25(OH)_2D$ (absolute final)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Up to 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 PTH levels (absolute final)	2	51	Mean Difference (IV, Fixed, 95% CI)	-0.93 [-5.22, 3.36]
5.1 Up to 3 months	1	21	Mean Difference (IV, Fixed, 95% CI)	-7.60 [-20.51, 5.31]
5.2 Up to 6 months	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-4.65, 4.45]
6 PTH levels (change from baseline)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
6.1 Up to 12 months	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Post-hoc analysis: Vitamin D versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Whole body bone mineral content change (g)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Up to 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Lumbar spine z score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Up to 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Lumbar spine bone mineral density (% change)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3.1 Up to 12 months	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Hip bone mineral density (% change)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
4.1 Up to 12 months	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Distal forearm bone mineral density (% change)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5.1 Up to 12 months	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

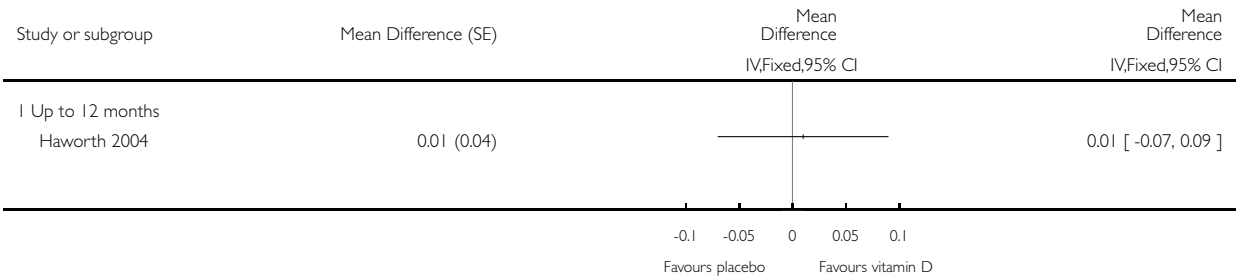
6 Hip bone mineral density (change)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Up to 12 months	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Vitamin D versus placebo, Outcome 1 Serum calcium change (mmol/L).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

Outcome: 1 Serum calcium change (mmol/L)



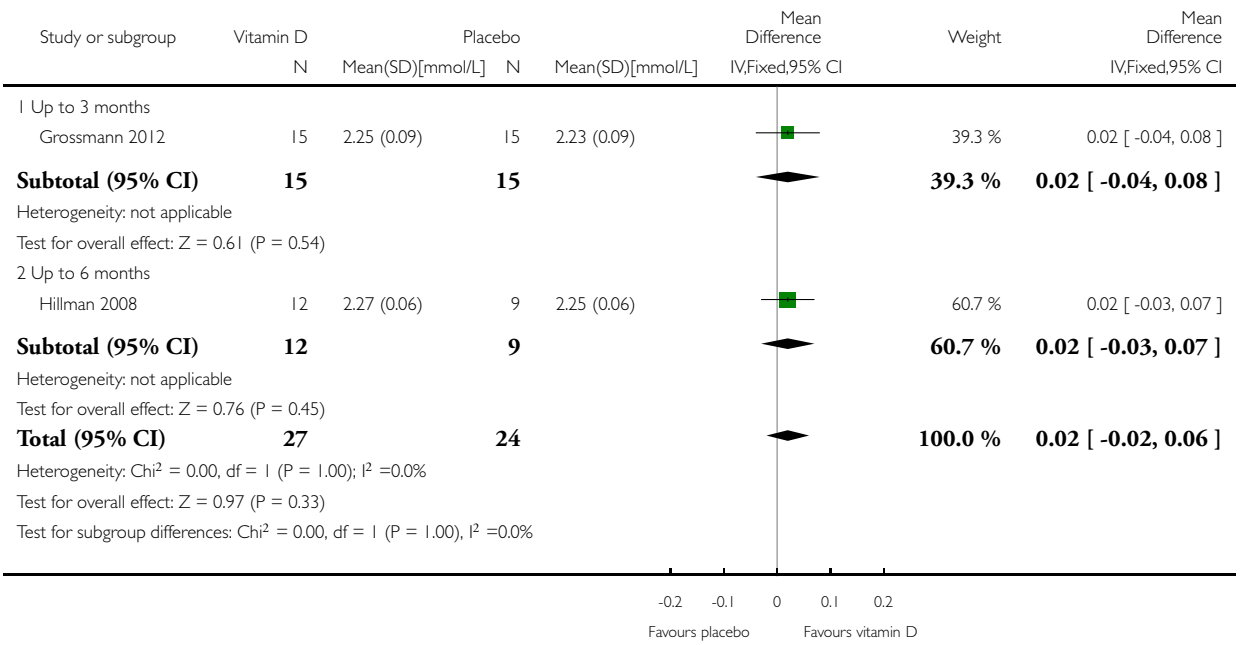
Analysis 1.2. Comparison 1 Vitamin D versus placebo, Outcome 2 Serum calcium (absolute final).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

Outcome: 2 Serum calcium (absolute final)

Study or subgroup	Vitamin D N	Mean(SD)[mmol/L]	Placebo N	Mean(SD)[mmol/L]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Up to 3 months							
Grossmann 2012	15	2.25 (0.09)	15	2.23 (0.09)		39.3 %	0.02 [-0.04, 0.08]
Subtotal (95% CI)	**15**		**15**			**39.3 %**	**0.02 [-0.04, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 Up to 6 months							
Hillman 2008	12	2.27 (0.06)	9	2.25 (0.06)		60.7 %	0.02 [-0.03, 0.07]
Subtotal (95% CI)	**12**		**9**			**60.7 %**	**0.02 [-0.03, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
Total (95% CI)	**27**		**24**			**100.0 %**	**0.02 [-0.02, 0.06]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 0.97 (P = 0.33)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 =0.0%							

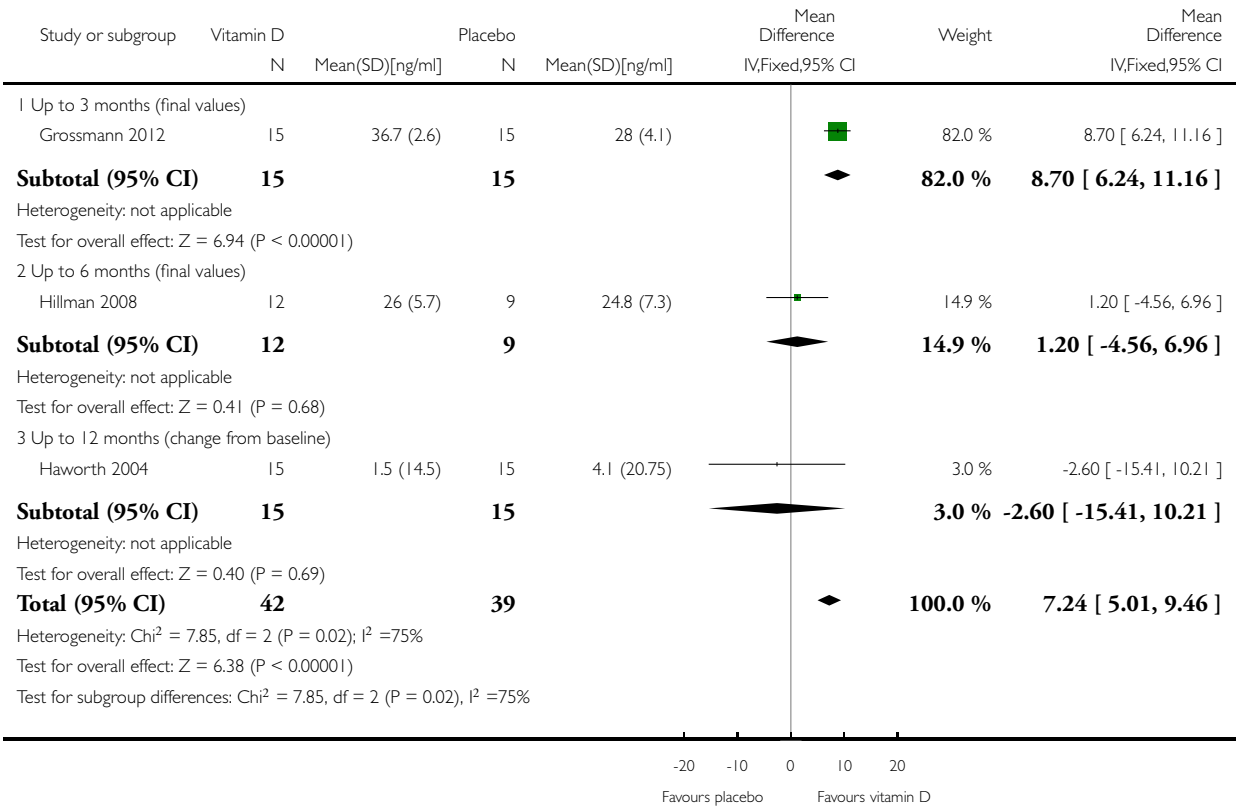


Analysis 1.3. Comparison 1 Vitamin D versus placebo, Outcome 3 25(OH)D.

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

Outcome: 3 25(OH)D

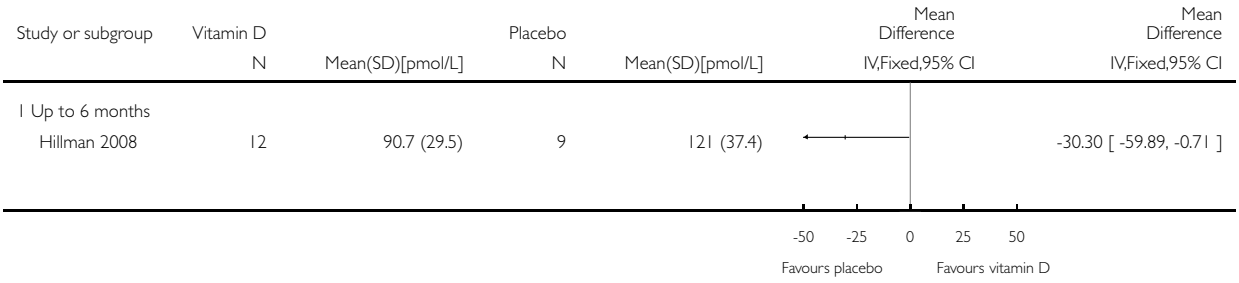


Analysis 1.4. Comparison 1 Vitamin D versus placebo, Outcome 4 1,25(OH)2D (absolute final).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

Outcome: 4 1,25(OH)$_2$D (absolute final)

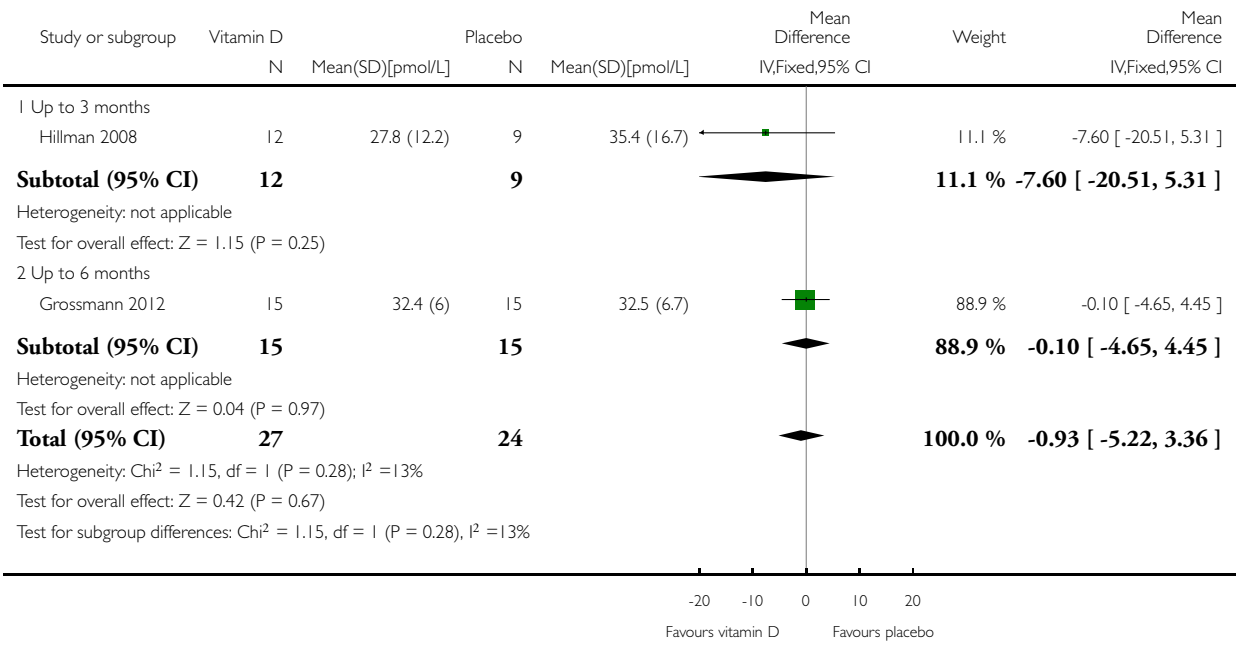


Analysis 1.5. Comparison 1 Vitamin D versus placebo, Outcome 5 PTH levels (absolute final).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

Outcome: 5 PTH levels (absolute final)



Analysis 1.6. Comparison 1 Vitamin D versus placebo, Outcome 6 PTH levels (change from baseline).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 1 Vitamin D versus placebo

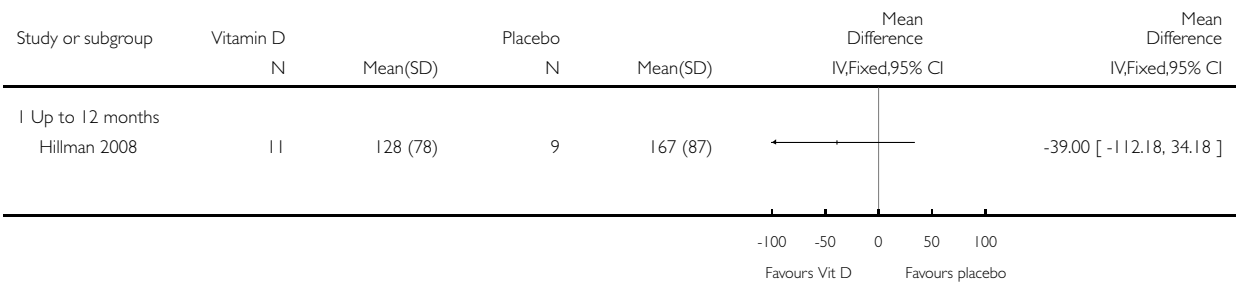
Outcome: 6 PTH levels (change from baseline)

Analysis 2.1. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 1 Whole body bone mineral content change (g).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 1 Whole body bone mineral content change (g)

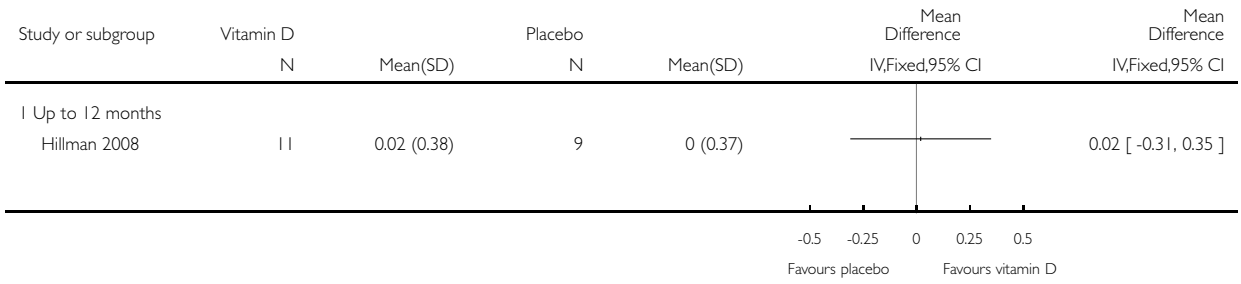


Analysis 2.2. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 2 Lumbar spine z score.

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 2 Lumbar spine z score

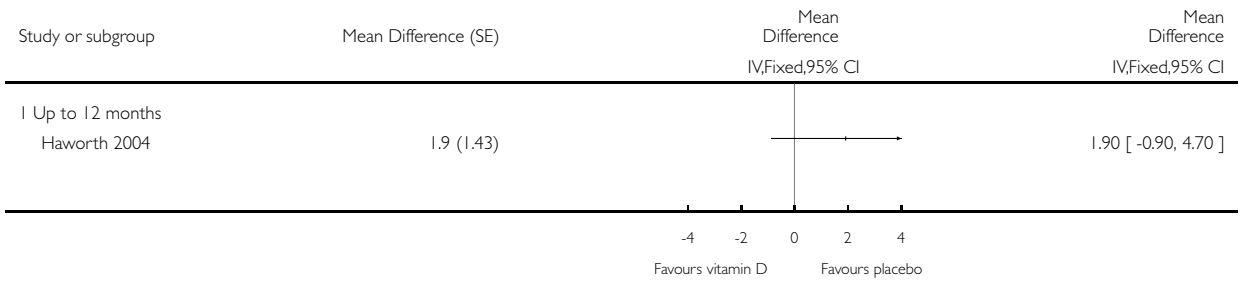


Analysis 2.3. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 3 Lumbar spine bone mineral density (% change).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 3 Lumbar spine bone mineral density (% change)

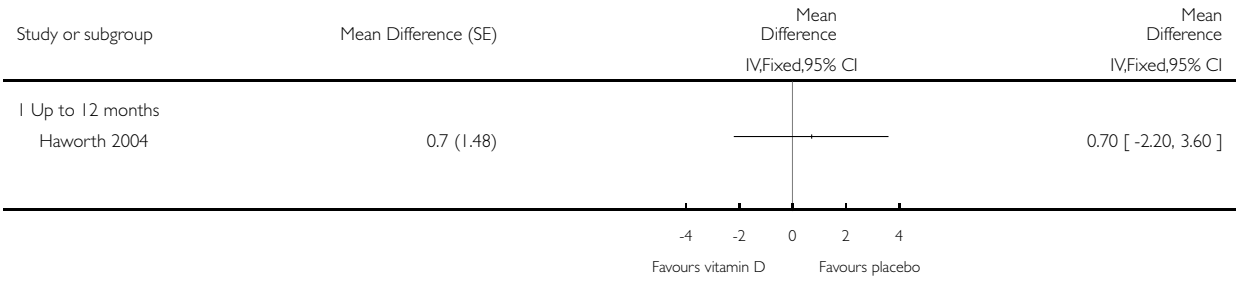


Analysis 2.4. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 4 Hip bone mineral density (% change).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 4 Hip bone mineral density (% change)

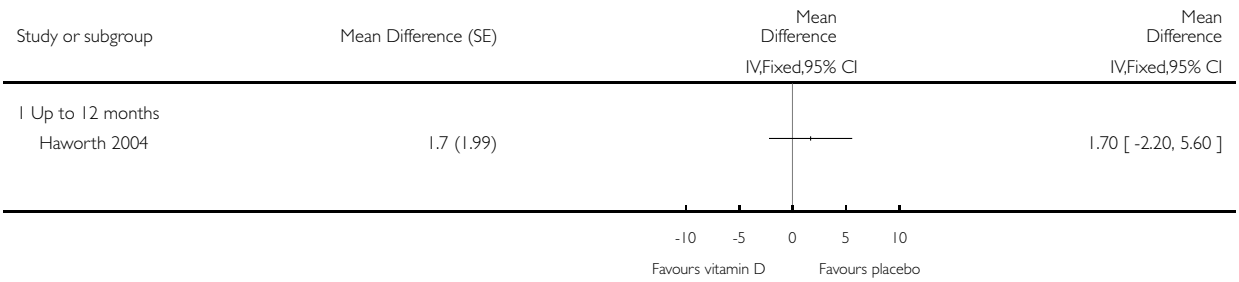


Analysis 2.5. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 5 Distal forearm bone mineral density (% change).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 5 Distal forearm bone mineral density (% change)

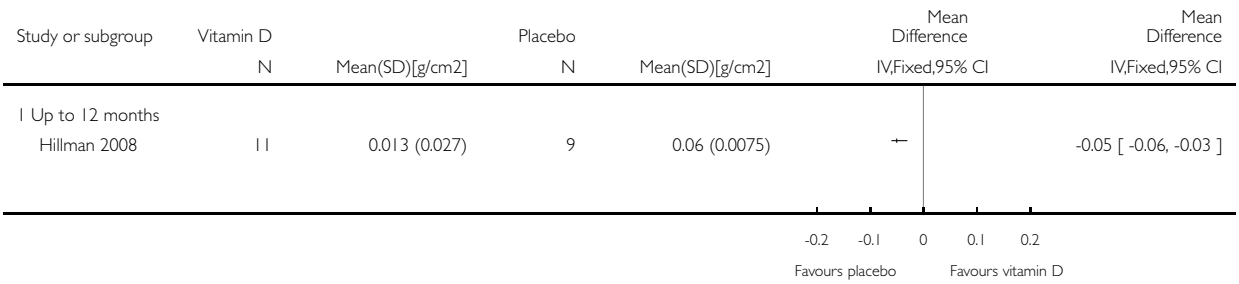


Analysis 2.6. Comparison 2 Post-hoc analysis: Vitamin D versus placebo, Outcome 6 Hip bone mineral density (change).

Review: Vitamin D supplementation for cystic fibrosis

Comparison: 2 Post-hoc analysis: Vitamin D versus placebo

Outcome: 6 Hip bone mineral density (change)



APPENDICES

Appendix 1. Glossary of medical terms

Term	Explanation
anterior fontanelle	the fontanelle occurring at the meeting point of the coronal and sagittal sutures (fibrous joints)
arrhythmia	an alteration in rhythm of the heartbeat either in time or force
bone matrix	the major constituent of bone
calcinosis	deposition of calcium and phosphate in tissues such as the kidney
enamel hypoplasia	arrested development, normal size or an immature state of part of the teeth structure

(*Continued*)

exocrine pancreatic insufficiency	a condition in which the pancreas stops producing and secreting enough digestive enzymes to digest food in the small intestine
hypercalcaemia	increased calcium level measured in the blood
hypocalcaemia	low calcium level measured in the blood
hypovitaminosis	any of several diseases caused by deficiency of one or more vitamins
kyphoscoliosis	backward and lateral curvature of the spine
metaphysis	the metaphysis is the growing portion of a long bone which lies between the diaphysis (shaft) and epiphysis (end)
myopathy	weak muscles
nephrolithiasis	stones in the kidney
non-ossified	not yet converted into bone
osteoid	the organic portion of the matrix of bone tissue, when the osteoid becomes mineralised, it and the adjacent bone cells have developed into new bone tissue
osteomalacia	a disease of adults that is characterized by softening of the bones and is similar to rickets in the young
osteopenia	reduction in bone volume to below normal levels especially due to inadequate replacement of bone lost to normal lysis (cell death)
rickets	a disease caused by vitamin D deficiency, characterized by softening and distortion of the bones typically resulting in bow legs
steatorrhoea	fatty stools
tetany	a muscular twitching disorder associated with low calcium in the blood

WHAT'S NEW

Last assessed as up-to-date: 7 May 2014.

Date	Event	Description
7 May 2014	New citation required but conclusions have not changed	Despite the inclusion of new studies and some new data, the conclusions of this review have not changed
7 May 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register identified four new references. Three of these were additional references to a study listed as 'Awaiting classification' (Grossmann 2012) and the fourth is an abstract of a new study (Deghan Manshadi 2012). Both of these studies have been included in this review, as have two further studies which were listed as 'Awaiting classification' (Hillman 2008; Sciuca 2011) . A further study which was listed as 'Awaiting classification' has been excluded as there was no appropriate control group (Homola 2010).

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 4, 2009

Date	Event	Description
16 February 2012	New citation required but conclusions have not changed	One study has now been excluded (Khazai 2009) and two others listed as 'Studies awaiting classification' (Homola 2011; Sciuca 2011)
16 February 2012	New search has been performed	A search of the Group's trials registers identified a full paper to an abstract previously listed as 'Awaiting classification' (Khazai 2009). Two further references were identified and added to the list of 'Studies awaiting classification'
31 August 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified one new reference which has been listed as 'Studies awaiting classification' until the full paper is published (Grossmann 2012a)
14 September 2010	Amended	Minor grammar correction in Results section.
26 April 2010	Amended	Contact details updated.
12 September 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both JF and AC extracted the data and wrote the protocol and review.

JF acts as guarantor of the review.

DECLARATIONS OF INTEREST

JF has attended paediatric diabetes and endocrinology conferences and workshops sponsored by Novo Nordisk and Medica Pacifica, for continuing medical education purposes. Neither herself nor Canterbury District Health Board have received payment for her attendance of these conferences.

AC declares receipt of a grant provided by GSK is unrelated to this topic.

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Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We include a post-hoc analysis of BMD outcomes (z scores: deviation from population mean matched for age and gender) which is different from the planned primary BMD outcome measures of the protocol. Values for BMD can be expressed as T-scores or z scores, with different advantages and disadvantages, but equal validity in studies. As we could not use both as the primary outcome in the protocol, we elected to choose T-score in the protocol. However the studies included provided only z scores and hence this was included as a post-hoc analysis; we did request additional data but none were available. This is also now consistent with the primary outcomes in the Cochrane review on 'Bisphosphonates for adults and children with cystic fibrosis' (Brenckmann 2001).

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Bone Density Conservation Agents [*administration & dosage; adverse effects]; Bone Diseases, Metabolic [*drug therapy; etiology]; Calcifediol [blood]; Calcitriol [administration & dosage; adverse effects]; Calcium, Dietary [administration & dosage]; Cystic Fibrosis [*complications; metabolism]; Exocrine Pancreatic Insufficiency [complications]; Randomized Controlled Trials as Topic; Vitamin D [*administration & dosage; adverse effects]; Vitamin D Deficiency [complications; drug therapy]

MeSH check words

Adult; Child; Humans