



## Important New Evidence Service In Partnership with The Centre for Medicines Optimisation at Keele University

Rapid Update October 10th

### Asthma: Cochrane review finds vitamin D supplements may lower risk of severe asthma exacerbations

A [Cochrane systematic review](#) of randomised placebo-controlled trials found that vitamin D supplementation in addition to standard asthma treatment reduced the rate of asthma exacerbations requiring systemic corticosteroids (by 37%) and decreased the risk of having at least one exacerbation requiring hospitalisation or an emergency department visit. **Although these results are promising**, further research is required to confirm the study findings and to clarify whether vitamin D supplements reduce asthma exacerbations in all patient groups.

**Reference:** Martineau AR, Cates CJ, Urashima M *et al.* [Vitamin D for the management of asthma.](#) Cochrane database for systematic reviews. First published: 5 September 2016, DOI: 10.1002/14651858.CD011511.pub2

#### What do we know already?

- Inadequate vitamin D status has been reported to be common among adults and children with asthma and has been associated with an increased risk of asthma exacerbations.<sup>1,2,3</sup>
- Several clinical trials have investigated whether vitamin D supplements reduce asthma exacerbations and improve lung function but studies have differed widely in design and duration. Definitions of exacerbations have also varied significantly between trials.<sup>4</sup>
- The level of 25-hydroxyvitamin D (25[OH]D) in the blood is the most reliable indicator of vitamin D status. There is consensus that levels below 50 nmol/L indicate deficiency; concentrations less than 25 nmol/L represent profound deficiency. Concentrations of 50 to 74 nmol/L may represent a milder state of inadequate vitamin D status, often described as “vitamin D insufficiency”.<sup>4</sup>
- [Public Health England](#) recommend that all people in the UK should consider taking a daily 10 microgram vitamin D supplement during autumn and winter months. People who have a higher risk of vitamin D deficiency are advised to take a supplement year-round. At risk groups include people who have no or limited exposure to the sun, people over 65 years, children less than 5 years and individuals with darker skin.

#### What does this evidence add?

- This Cochrane systematic review and meta-analysis adds to the growing evidence that vitamin D supplementation may be beneficial for people with asthma. The rate of severe asthma exacerbations requiring systemic corticosteroids was 37% lower in relative terms among people who received vitamin D supplements compared with those who received placebo (0.28 vs. 0.44 events per person per year respectively, [rate ratio](#) [RR] 0.63, high-quality evidence).
- People taking vitamin D were also significantly less likely to experience an asthma exacerbation that required hospitalisation or an emergency department visit ([odds ratio](#) [OR] 0.39). However, vitamin D had little or no effect on lung function or day-to-day asthma symptoms.
- Although the finding that vitamin D supplementation reduced asthma exacerbations is promising, the study has some important limitations and the results should be treated with caution. As noted by the study authors, the data come from relatively few trials, none of which individually reported a statistically significant effect of vitamin D on risk of exacerbations requiring systemic corticosteroids as a prespecified outcome. Adults with severe asthma and children were under represented in the trials and analysis of the effect of baseline vitamin D status was not possible. Further research is needed to clarify whether vitamin D supplements can reduce the risk of severe attacks in all people with asthma or only those with lower baseline vitamin D status.

- The [Royal College of General Practitioners \(RCGP\)](#) has commented on the review, describing it as “encouraging” but cautioning that “it is still too early to make general recommendations on prescribing vitamin D to patients with asthma.”

## Study details

### Participants:

- This systematic review and meta-analysis of double-blind randomised placebo-controlled trials involved a total of 435 children (seven studies) and 658 adults (two studies) with a clinical diagnosis of asthma. The trials were conducted in a broad range of countries including Canada, India, Japan, Poland, the UK, and USA. The majority of study participants had mild or moderate asthma.
- Where measured, mean/median baseline serum 25 (OH)D concentrations ranged from 48 to 89 nmol/L. A small number of participants were considered to be profoundly vitamin D deficient with 25 (OH)D levels below 25 nmol/L.

### Intervention and comparison:

- The review assessed whether vitamin D supplementation reduced the risk of severe asthma exacerbations (primary outcome) and improved asthma symptom control compared with placebo. Severe exacerbations were defined as those requiring treatment with systemic corticosteroids.
- In all included trials, participants in the intervention arm received oral vitamin D<sub>3</sub> (cholecalciferol). Dose regimens varied from 500 to 1200 IU/day, to weekly, monthly, or twice-monthly dosing, sometimes with a bolus dose at the start of the study. Most people also continued to take their usual asthma medication. Study duration ranged from four to 12 months.

### Outcomes and results:

- For the primary outcome, the rate of asthma attacks requiring systemic corticosteroids was significantly lower among participants who received vitamin D supplements compared with those who received placebo (0.28 vs. 0.44 events per person per year respectively; RR 0.63, 95% [confidence interval \[CI\]](#) 0.45 to 0.88; 680 participants; 3 studies; high-quality evidence). Results of this analysis were primarily driven by the findings of two trials conducted in adults. Only two of the trials that involved children reported severe exacerbations and the total number of events in these trials was small.
- Subgroup analysis to determine whether the effect of vitamin D on the risk of severe exacerbation was modified by baseline vitamin D status was not performed, due to the unavailability of suitably disaggregated data
- Vitamin D supplements were associated with reduction in the risk of having at least one asthma exacerbation requiring an emergency department visit or hospital admission or both (from 6% to around 3%, OR 0.39, 95% CI 0.19 to 0.78, 963 participants; 7 studies; high-quality evidence).
- Vitamin D supplementation did not effect:
  - % predicted forced expiratory volume in one second (mean difference 0.48, 95% CI -0.93 to 1.89; 387 participants; 4 studies; high quality evidence).
  - end-study peak expiratory flow rate (mean difference 3.16, 95% CI -13.40 to 19.72; 302 participants; 2 studies, high-quality evidence).
  - asthma control test scores (mean difference -0.08, 95% CI -0.70 to 0.54; 713 participants; 3 studies; high quality evidence).
  - eosinophilia count in the lower airway (mean difference -0.38, 95% CI -1.92 to 1.15; 525 participants, 3 studies, high quality evidence).
  - fractional exhaled nitric oxide concentration (1 study)
  - work absence events (adjusted rate ratio 0.86, 95% CI 0.50 to 1.46; 1 study in adults). No trials assessed school absence in children.
- Vitamin D was not found to influence the risk of serious adverse events although the confidence interval for this outcome was wide (OR 1.01 95% CI 0.54 to 1.89; 879 participants, 5 studies; moderate-quality evidence).
- No fatal asthma exacerbations were reported in the trials.

### Level of evidence:

Level 1 (good quality patient-oriented evidence) according to the [SORT criteria](#)

### Study funding

Systematic review was conducted by Cochrane authors and supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure, Cochrane Programme Grant, or Cochrane Incentive funding to Cochrane Airways. The majority of included trials reported funding from non-commercial organisations.