


ONLINE EXCLUSIVE

Jaspreet Jaura, MD;
Gary Kelsberg, MD
Valley Family Medicine Residency, University of Washington at Valley Medical Center, Renton

Sarah Safranek, MLIS
University of Washington Health Sciences Library, Seattle

DEPUTY EDITOR

Jon Neher, MD
Valley Family Medicine Residency, University of Washington at Valley Medical Center, Renton

Q/Does vitamin D supplementation reduce asthma exacerbations?

EVIDENCE-BASED ANSWER

A YES, to some extent it does, and primarily in patients with low vitamin D levels. Supplementation reduces asthma exacerbations requiring systemic steroids by 30% overall in adults and children with mild-to-moderate asthma (number needed to treat [NNT] = 7.7). The outcome is driven by the effect in patients with vitamin D levels < 25 nmol/L (NNT = 4.3), however; supplementation doesn't decrease exacerbations in patients with higher levels. Supplementation also reduces, by a smaller amount (NNT = 26.3), the odds of exacerbations requiring emer-

gency department care or hospitalization (strength of recommendation [SOR]: A, meta-analysis of randomized controlled trials [RCTs]).

In children, vitamin D supplementation may also reduce exacerbations and improve symptom scores (SOR: C, low-quality RCTs).

Vitamin D doesn't improve forced expiratory volume in 1 second (FEV₁) or standardized asthma control test scores. Also, it isn't associated with serious adverse effects (SOR: A, meta-analysis of RCTs).

Evidence summary

A Cochrane systematic review of vitamin D for managing asthma performed meta-analyses on RCTs that evaluated several outcomes.¹ The review found improvement in the primary outcome of asthma exacerbations requiring systemic steroids, mainly in adult patients, and in the secondary outcomes of emergency department visits or hospitalization, in a mix of adults and children (TABLE¹⁻⁶).

Most participants had mild-to-moderate asthma; trials lasted 4 to 12 months. Vitamin D dosage regimens varied, with a median daily dose of 900 IU/d (range, 400-4000 IU/d). Six RCTs were rated high-quality, and 1 had unclear risk of bias.

Supplementation reduced exacerbations in patients with low vitamin D levels

A subsequent (2017) systematic review and meta-analysis evaluating the primary out-

come of exacerbations requiring steroids⁷ included another study⁸ (in addition to the 6 RCTs in the Cochrane review).

When researchers reanalyzed individual participant data from the trials in the Cochrane review, plus the additional RCT, to include baseline vitamin D levels, they found that vitamin D supplementation reduced exacerbations overall (NNT = 7.7) and in patients with low baseline vitamin D levels (25[OH] vitamin D < 25 nmol/L; 92 participants in 3 RCTs; NNT = 4.3) but not in patients with higher baseline levels (764 participants in 6 RCTs). Vitamin D supplementation reduced the asthma exacerbation rate in patients with low baseline vitamin D levels (0.19 vs 0.42 events per participant-year; *P* = .046).

Smaller benefit found on ED visits and hospitalizations

The Cochrane review, with 2 RCTs with

TABLE

Effect of Vitamin D supplementation on frequency and severity of asthma exacerbations in patients with mild-to-moderate persistent asthma

Outcome measured	Studies	Population (mean ages)	Intervention vitamin D dose vs placebo ^a	Result (significant results in bold)	Comment
Asthma exacerbations requiring systemic steroids	658 Adults (2 RCTs ¹) 22 Children (1 RCT ¹)	Adults (40-48 y) Children (1-15 y)	Adults: 2000-4000 IU/d Children: 400-2000 IU/d	Overall: 0.28 vs 0.44 events/person-year	Low vitamin D = < 25 nmol/L
Asthma exacerbations requiring emergency department visit ± hospitalization	658 Adults (2 RCTs ¹) 305 Children (5 RCTs ²⁻⁶)	Adults (40-48 y) Children (1-18 y)	Adults: 2000-4000 IU/d Children: 400-1200 IU/d	25/1000 vs 63/1000 events in adults; NNT = 26.3	

NNT, number needed to treat.

^aAdditional Vitamin D dosing details: 400 IU/d,² 1000 IU/wk,³ 500 IU/d,⁴ 800 IU/d,⁵ 1200 IU/d.⁶

adults ($n = 658$)¹ and 5 RCTs with children ($n = 305$),²⁻⁶ evaluated whether Vitamin D reduced the need for emergency department visits and hospitalization with asthma exacerbations; they found a smaller benefit (NNT = 26.3).

Effects on FEV₁, daily asthma symptoms, and serious adverse effects

Several RCTs included in the 2017 meta-analysis found no effect of vitamin D supplementation on FEV₁, daily asthma symptoms (evaluated with the standardized Asthma Control Test Score), or reported serious adverse events.^{2-6,9,10} No deaths occurred in any trial.

Additional findings in children from lower-quality studies

A 2015 systematic review and meta-analysis of RCTs evaluating vitamin D supplementation for children with asthma found¹¹:

- moderate-quality evidence for decreased emergency department visits (1 RCT from India, 100 children ages 3 to 14 years, decrease not specified; $P = .015$);
- low-quality evidence for reduced exacerbations (6 RCTs [3 RCTs also in Cochrane review], 507 children ages 3 to 17 years; risk ratio = 0.41; 95% confidence interval, 0.27-0.63); and
- low-quality evidence for reduced standardized asthma symptom scores

(6 RCTs [2 RCTs also in Cochrane review], 231 children ages 3 to 17 years; amount of reduction not listed; $P = .01$).

Recommendations

No published guidelines discuss using vitamin D in managing asthma. An American Academy of Family Physicians (AAFP) summary of the Cochrane systematic review recommends that family physicians await further studies and updated guidelines before recommending vitamin D for patients with asthma.¹² The AAFP also points out that the Endocrine Society has recommended vitamin D supplementation for adults (1500-2000 IU/d) and children (at least 1000 IU/d) at risk for deficiency.

Editor's takeaway

In the meta-analyses highlighted here, researchers evaluated asthma patients with a wide range of ages, baseline vitamin D levels, and vitamin D supplementation protocols. Although vitamin D reduced asthma exacerbations requiring steroids overall, the effect was driven by 3 studies of patients with low baseline vitamin D levels. As a result, disentangling who might benefit the most remains a challenge. The conservative course for now is to manage asthma according to cur-

rent guidelines and supplement vitamin D in patients at risk for, or with known, deficiency.

JFP

References

1. Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for the management of asthma. *Cochrane Database Syst Rev*. 2016;9:CD011511.
2. Jensen M, Mailhot G, Alos N, et al. Vitamin D intervention in preschoolers with viral-induced asthma (DIVA): a pilot randomised controlled trial. *Trials*. 2016;26:17:353.
3. Majak P, Jerzyńska J, Smejda K, et al. Correlation of vitamin D with Foxp3 induction and steroid-sparing effect of immunotherapy in asthmatic children. *Ann Allergy Asthma Immunol*. 2012;109: 329-335.
4. Majak P, Olszowiec-Chlebna M, Smejda K, et al. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol*. 2011;127:1294-1296.
5. Tachimoto H, Mezawa H, Segawa T, et al. Improved control of childhood asthma with low-dose, short-term vitamin D supple-mentation: a randomized, double-blind, placebo-controlled trial. *Allergy*. 2016;71:1001-1009.
6. Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in school children. *Am J Clin Nutr*. 2010;91:1255-1260.
7. Joliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet* 2017;381:890.
8. Kerley CP, Hutchinson K, Cormican L, et al. Vitamin D3 for uncontrolled childhood asthma: a pilot study. *Pediatr Allergy Immunol*. 2016;27:404-412.
9. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *JAMA*. 2014;311:2083-2091.
10. Martineau AR, MacLaughlin BD, Hooper RL, et al. Double-blind multi-centre randomised controlled trial of vitamin D3 supplementation in adults with inhaled corticosteroid-treated asthma (ViDiAs). *Thorax*. 2015;70:451-457.
11. Riverin B, Maguire J, Li P. Vitamin D supplementation for childhood asthma: a systematic review and meta-analysis. *PLOS One*. 2015;10:e0136841.
12. Qiu J. Vitamin D for the management of asthma. *Am Fam Phys*. 2017;96:290-293.