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Vitamin D and Childhood Asthma - causation and contribution to disease activity

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Abstract

Purpose of Review: To review the literature of the past 18 months (April, 2017 through September, 2018) relating to vitamin D and childhood asthma.

Recent Findings: A combined analysis of two clinical trials of maternal vitamin D supplementation trials showed a significant protective effect of vitamin D supplementation trials in the primary prevention of asthma and recurrent wheeze up to age 3 years. Secondary analyses from these trials have also suggested that initial maternal vitamin D status could affect the response to supplementation during pregnancy, with the biggest protective effect in children born to mothers with initial 25hydroxyvitamin D (25OHD) levels of at least 30 ng/ml. A post-natal, six-month vitamin D supplementation trial in black, premature babies showed a 34% decreased risk of recurrent wheezing at 1 year among the infants who received supplementation. An individual patient data meta-analysis of published clinical trials concluded that vitamin D supplementation decreased the risk of asthma exacerbations in those with 25OHD levels < 10 ng/ml. Results of observational analyses on primary prevention of asthma and in prevention of exacerbations remain mixed, with the bulk of the evidence suggesting that there is a protective effect of higher vitamin D levels.

Summary: Evidence continues to accumulate that vitamin D supplementation helps to prevent the development of asthma and recurrent wheeze in early life, and may also help in the management of asthma. The level(s) of circulating vitamin D that maximizes these effects remains to be identified.

Keywords

childhood asthma; vitamin D; asthma incidence; asthma management

Introduction

The role of vitamin D in the development and management of asthma remains an active area of research. The purpose of this review is to synthesize the literature over the past 18 months. Articles relating to vitamin D and childhood asthma published roughly between

Conflicts of Interest

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April 2017 and September 2018 were included. Although outside of the time period, two vitamin D prenatal supplementation trials were published in early 2016 and were included in this review.

Most of the studies that have been published continue to come from observational cohorts. The availability of a stable biomarker of vitamin D status – 25 hydroxyvitamin D (25OHD) – has facilitated research in this field. However, many measurement methods are available and these have provided variable results whose reliability have been brought into question, prompting efforts for standardization and for assessment of quality.(1, 2) In addition to the issue of vitamin D status measurement, readers should be cognizant of other issues relating to studying vitamin D in observational cohorts. These include widespread vitamin D deficiency and insufficiency (thus, making it harder to find signals related to higher levels), the seasonal variation in the Northern hemisphere of vitamin D status (unless sufficient supplementation is obtained), and measuring vitamin D status at one point and relating this to outcomes months or years later.(**3) While clinical trials are the gold standard for evidence, readers should also be aware that nutrient supplementation trials have additional considerations compared with pharmacologic trials in that all participants have a baseline intake and circulating level of the nutrient which should be addressed in the trial design.(4) Throughout this review, these issues will be raised when appropriate, to help with the interpretation of the findings.

Asthma Development

Vitamin D deficiency has been hypothesized to contribute to the increase in incidence of asthma. Mechanistic studies in animal models and human in vitro studies have shown that vitamin D is involved in fetal lung development and lung maturation, and in immune cell function.(*5, *6)

Observational studies.

Because asthma begins early in life, it is hypothesized that maternal exposures during pregnancy, in this case vitamin D status of the mother, might play a role in the development of asthma and allergies. Three observational studies of either maternal vitamin D status in pregnancy(7, 8) or estimates of maternal intakes in pregnancy(9), and 2 meta-analyses(10, 11) of observational data were published during this time period. Boyle et al(7) analyzed data for 922 mother-child pairs from the Auckland, New Zealand center of the international Screening for Pregnancy Endpoints (SCOPE) cohort study. Mothers were originally recruited at 15 weeks gestation and blood was obtained for later processing of 25OHD levels. They re-contacted the women for follow-up of their children between 5 and 6.25 years. While maternal levels of 25OHD tended to be lower for children with asthma and eczema, these were not statistically significant. Vereen et al(8) studied 853 women from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE), a prospective cohort in Memphis, TN. Women were enrolled at 16–28 weeks gestation and the children were followed through 3 years of age, and 25OHD levels were measured at enrollment and at delivery. They only reported a protective effect of second trimester 25OHD levels on current wheeze at 3 years in white children (aOR=0.44,

95%CI=0.19.0.99 for 25OHD in the highest tertile compared with levels in the lower tertile). They did not find any statistically significant associations in 25OHD levels at delivery among the white children nor in 25OHD levels at either time point among the black children. The limitations of both these studies is that associations were reported with only one measure of vitamin D status. The investigators of the CANDLE study did look at the joint effect on current wheezing in children born to mothers with levels in the highest tertiles at both time points (enrollment and delivery) vs children born to mothers in the lowest tertiles at both time points and found a stronger effect only among white children (aOR=0.33, 95%CI=0.11, 0.96) (Carroll, KN, personal communication).

In the third observational study, Parr and colleagues(9) reported on results from the Norwegian Mother and Child Cohort. They reported on 61,676 school-age children who had estimated nutrient intakes for vitamin A and vitamin D from food frequency questionnaires administered at around 20 weeks gestation. Children born to mothers with the highest quintile of vitamin D intake (≥13.6 μg/d, equivalent to ≥544 IU/d) compared with mothers with the lowest quintile (≤3.5 μg/d, equivalent to ≤140 IU/d) had decreased risk for asthma at 7 years (aRR=0.81, 95%CI=0.67, 0.97). This effect of maternal intake was independent of infant supplementation assessed at 6 months of age. Of note, these estimates of daily intake are quite low compared with intakes among US women. Additionally, dietary assessment by food frequency questionnaire generally reflect chronic intakes of a nutrient, which is different from a one-time measurement of 25OHD. However, dietary assessment does not account for non-dietary acquisition of vitamin D (i.e. by sun exposure) as opposed to measurement of 25OHD.

Two meta-analyses of previously published studies, not including the three studies cited above, were published during the review period. In the study by Feng et al,(10) they report non-significant protective associations between higher maternal 25OHD concentrations and offspring asthma and wheeze. The results were stronger when they analyzed studies that measured cord blood 25OHD and offspring wheeze. The meta-analysis by Shen et al(11) also found non-significant associations between maternal 25OHD concentrations and offspring asthma, but also found a significant inverse association between vitamin D intake and childhood asthma.

While prenatal vitamin D status may affect the risk for asthma in the offspring, vitamin D deficiency early in life may also increase the risk for asthma as the child grows. One study investigated the effect of dietary vitamin D intakes in the first 4 years of life and asthma development by the fifth year.(12) In this case-control study nested in the Finnish Type 1 Diabetes Prediction and Prevention study, the investigators found that higher vitamin D intake particularly in the first 2 years increased the risk for asthma by age 5 years. The mean estimated intakes for the first 2 years for either case or control ranged from 3.05 μg/day (equivalent to 121.6 IU/day) to 5.84 μg/day (equivalent to 233.6 IU/day). These are very low amounts of intake. Aside from the low amounts of intake, one must be wary of these results as the study did not account for prenatal vitamin D status of the mothers, nor the initial vitamin D status of the children.

Clinical Trials.

Vitamin D deficiency in pregnant mothers has been hypothesized to contribute to the development of asthma. To address this, 2 clinical trials of prenatal vitamin D supplementation were published in 2016. The Vitamin D Antenatal Asthma Reduction Trial (VDAART) randomized 881 women to 4,400 IU vitamin D/day vs 400 IU vitamin D/day, beginning at about the 14th week of gestation.(13) The trial showed a 20% reduction in the incidence of the composite outcome of asthma or recurrent wheeze by age 3 yrs and was of borderline statistical significance (p=0.051). A second trial from the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC$_{2010}$) randomized 623 women at 24 weeks of pregnancy, also showed a non-significant protective effect of supplementation with 2800 IU/day of vitamin D vs 400 IU/day vitamin D beginning in the 26th week of gestation on persistent wheeze (HR=0.76, 95%CI-0.52, 1.12) and asthma at 3 years (OR=0.82, 95%CI=0.50, 1.36). Several issues in the design of the studies have come to light. First, neither trial made initial vitamin D level a criterion for entry into the trial (e.g. only taking those who were deficient on entry). It has become clear that nutrient trials are not the same as pharmacologic trials as all participants have some baseline circulating level of the nutrient.(4) Thus, all participants are exposed to vitamin D to different degrees, and this baseline exposure may confound the results. Secondly, neither trial supplemented the infants post-natally. Thus, the results can only speak to prenatal supplementation and not post-natal supplementation. Hollams et al(14) showed that the number of 25OHD measures below 20 ng/ml over the first 10 years of life was positively associated with the risk for asthma/ wheeze and allergic outcomes at 10 years of age in a birth cohort of Australian children. These issues motivated additional analyses of the trial data.

In secondary analysis of data from the VDAART study, Wolsk et al(**15) investigated the effect of the initial maternal 25OHD level on entry into the trial. They showed that children born to the mothers with the higher 25OHD levels on entry, and who were randomized to the high vitamin D arm, had the lowest risks for asthma or recurrent wheeze by the age of 3 years (Figure 1). Additional findings from that analysis showed that the effects of vitamin D supplementation with 4,400 IU/day had the same effects in blacks and non-blacks (Caucasians and Hispanics) in the study. In a second series of analyses, Wolsk et al(**16) performed a meta-analysis of the data from both the VDAART and the COPSAC trials. In the meta-analysis, they showed that supplementation with vitamin D in pregnancy conferred a protective effect against offspring asthma and recurrent wheeze by age 3 years. This combined analysis also confirmed that higher initial maternal levels (at least 30 ng/ml) on entry into the studies and being randomized to the supplement arm, conferred greater protection against asthma and recurrent wheeze by age 3. These results suggest that a higher maternal 25OHD level early in pregnancy and supplementation to maintain these levels are needed to maximally prevent the development of asthma and recurrent wheeze in the offspring.

Both VDAART and COPSAC did not undertake vitamin D supplementation in the infants and children. A recent trial suggests that post-natal supplementation may be important. Hibbs and colleagues recently published the results of the D-Wheeze trial(**17). They recruited 300 black infants who were born prematurely (born at 28 to 36 weeks gestation),

and randomized them to either a sustained supplementation group vs a diet-limited supplementation group. All infants from both groups received a daily open-label multivitamin containing 400 IU of vitamin D, until they were ingesting 200 IU/day of vitamin D from formula or human milk fortifiers. At this point, they received the blinded study drug containing 400 IU/d of vitamin D (sustained supplementation group) or placebo (diet-limited group). Study drugs were given until the children reached 6 months adjusted gestational age. Additionally, all infants who were exclusively fed with maternal milk received the multivitamin until they reached 12 months of age. In this population, rates of recurrent wheezing were high – 31.1% in the sustained vitamin D supplementation arm vs 41.8% in the diet-limited arm – and the results showed a 34% decreased risk for recurrent wheezing by 12 months among infants in the sustained vitamin D supplementation arm compared with infants who were randomized to the diet-limited supplementation arm (Relative Risk = 0.66, 95%CI=0.47, 0.94). While this report looked at recurrent wheezing as the primary outcome, infants with recurrent wheezing are at greater risk for developing asthma later in life. Additional trials including non-black and non-premature infants are needed to determine the generalizability of the D-Wheeze study findings. Overall, further studies are needed to determine whether both pre-natal and postnatal supplementation can further decrease the risk of wheezing illnesses and asthma in children, and whether more prolonged supplementation will be needed.

Asthma exacerbations, asthma control, and related phenotypes

Insufficient and deficient vitamin D status has been related to increased risks for worse asthma outcomes.(18, 19) Vitamin D has been hypothesized to play a role with asthma management, given its effects on immune cell function(6), on corticosteroid responsiveness through various pathways including those that involve IL-10,(20) IL-17,(21) on oxidative stress,(22) and on airway remodeling.(23) Observational studies have measured 25OHD levels in participants, investigating associations between those levels and asthma control. Majority of the published clinical trials were performed in adults.

Observational Studies.

Many observational studies have related vitamin D status with risks for asthma exacerbations or indices of more severe asthma. Most of the published studies have performed cross-sectional associations with single measurements of 25OHD and asthma severity, and as expected, results have been mixed, with some showing more symptoms,(24) increased risks for exacerbations,(25) poorer asthma control,(26) and lower lung function with low 25OHD levels;(24) others show no association with levels;(27, 28) while others report an inverse association between asthma and 25OHD levels.(29) The cross-sectional nature of these studies are a limitation, in addition to the single measurement of 25OHD levels.

Vitamin D has been shown in cellular studies to enhance antioxidant responses to exposures. (*30) Using data from 6–17 year old participants from several National Health and Nutrition Examination Surveys (2007 – 2012), Han et al(31) showed that among children with asthma, 25OHD levels modified the effect of exposure to polycyclic aromatic hydrocarbons (PAH,

measured by levels of urinary metabolites), such that those with low 25OHD levels (<30 ng/ml) had lower lung function with higher exposure to PAH. Additional studies are needed to investigate the modifying effects of vitamin D status on exposures related to oxidative stress.

Clinical Trials.

A clinical trial among 2–14 year old children was conducted in Qatar,(32) to test whether an intervention to rapidly supplement vitamin D vs maintenance supplementation in vitamin D deficient children could prevent asthma exacerbations. Alansari and colleagues randomized 256 children to either IM ergocalciferol + oral cholecalciferol (“rapid”) or to maintenance oral cholecalciferol, and showed that the rapid supplementation prevented exacerbations but only in the first 3 months of beginning supplementation, and only in the children with the lowest levels of 25OHD. It is unclear whether there were any differences in the 25OHD levels of the children in each arm after supplementation was begun.

A prior Cochrane review and meta-analysis of clinical trials found that vitamin D supplementation decreased asthma exacerbations.(33) However, because aggregate data from clinical trials was used, it was unclear whether initial levels modified the effect of vitamin D supplementation. Jolliffe et al.(**34) conducted a meta-analysis of individual participant data on 955 participants from 7 studies and showed that vitamin D supplementation decreased the rate of asthma exacerbations in those with baseline 25OHD levels < 10 ng/ml (25 nmol/L): adjusted incidence rate ratio (aIRR) 0.33, 95%CI = 0.11, 0.98). While a protective effect was also seen for participants with higher baseline levels of 25OHD, the effect was not statistically significant: aIRR 0.77, 95%CI = 0.58, 1.03). Most of the data in this IPD analysis came from subjects older than 16 years of age, and only 30.4% came from participants < 16 years of age. In my opinion, further studies need to be done in children. A vitamin D supplementation trial in children 6–16 years of age is currently ongoing (Vit-D-Kids Asthma, ClinicalTrials.gov Identifier: NCT02687815).

Conclusion

Evidence continues to accumulate from clinical trials regarding the protective effects of vitamin D supplementation on the development of asthma and its beneficial effects in the management of asthma. However, the 25OHD level at which beneficial effects in either disease prevention or disease management can be definitively seen remains unclear, and more studies are needed. Results from observational studies continue to be mixed, with more studies showing a beneficial effect. Aside from the cross-sectional nature of many of these studies, issues relating to vitamin D levels limit conclusions from these observational studies. Despite these issues, because it is a relatively low-cost and safe intervention, supplementation with vitamin D to reverse deficiency and insufficiency in childhood asthmatics should be considered in the management of the disorder.

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Key Points

- Vitamin D insufficiency and deficiency have been related to asthma development and asthma exacerbations
- Results of new clinical trials and secondary analyses of these trials suggest that prenatal supplementation and post-natal supplementation with vitamin D have the potential to prevent the development of asthma and recurrent wheeze
- Individual participant data meta-analysis has shown that vitamin D supplementation may prevent asthma exacerbations, particularly in those subjects with very low initial circulating vitamin D levels (25OHD < 10 ng/ml or 25 nmol/L)

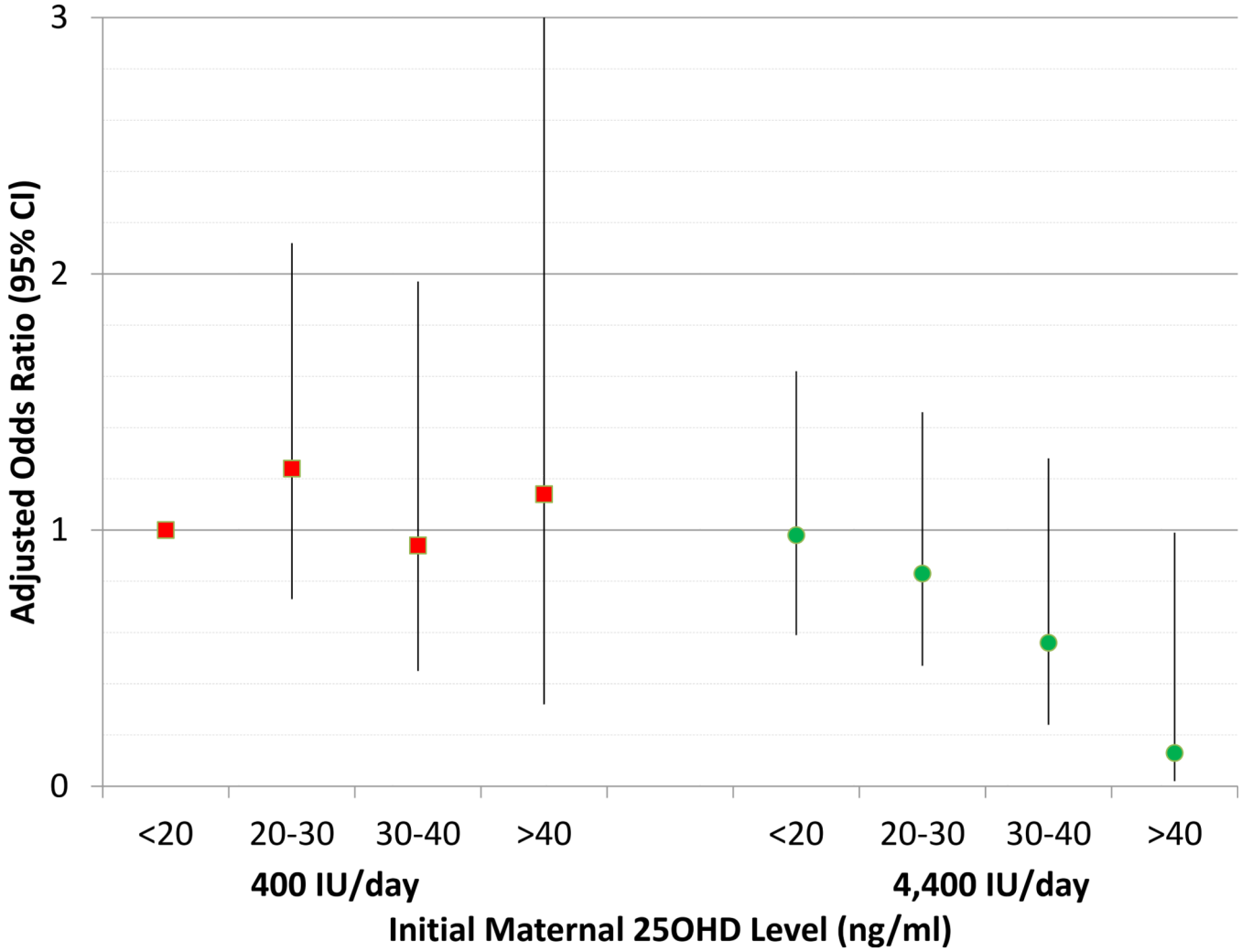

Figure 1. Prenatal vitamin D supplementation and asthma or recurrent wheeze in offspring at age 3 years, stratified by initial maternal 25OHD.

The effect on prevention of childhood asthma and recurrent wheeze was greatest in children born to mothers who had initial 25OHD levels of at least 40 ng/ml and who were randomized to 4,400 IU/day of cholecalciferol (odds ratio=0.13, 95%CI=0.02,0.99). There was a significant trend over the effects of categories of 25OHD in the 4,400 IU/day arm (p=0.03). Figure is redrawn from data presented in Table E5 in the online repository of Wolsk, et al.(**15)