Vitamin D supplementation in pregnancy, prenatal 25(OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: Secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial

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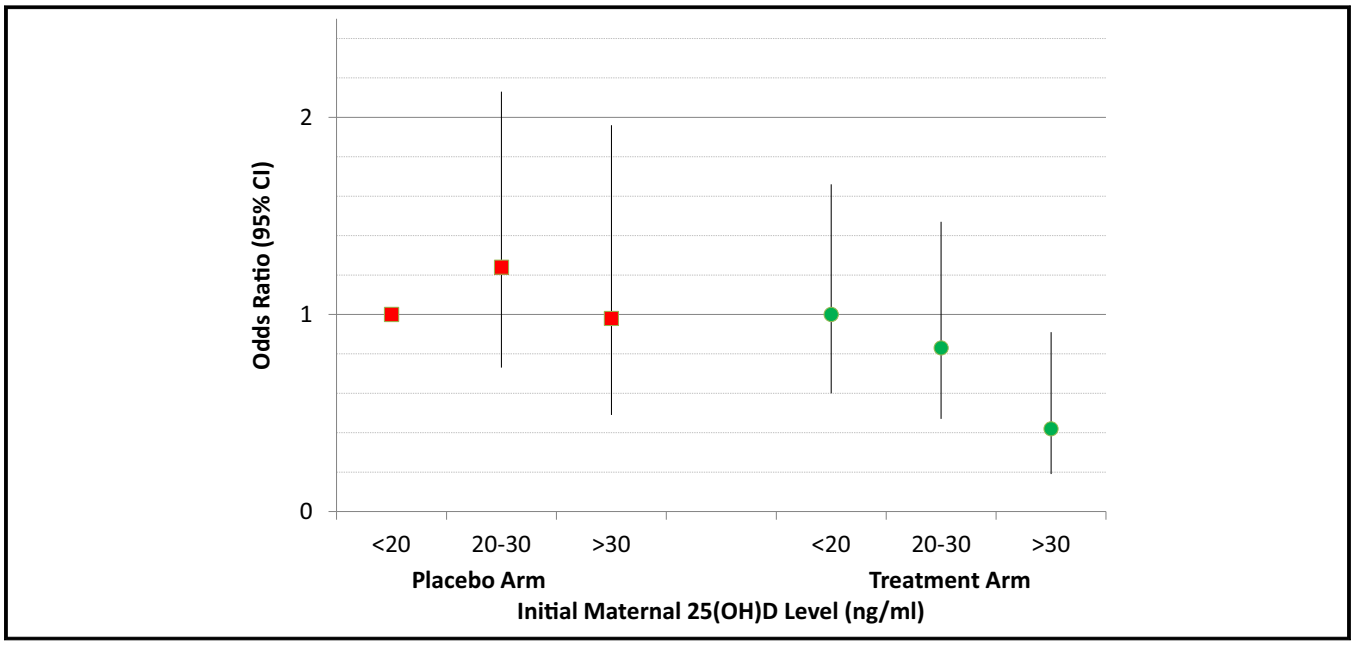
GRAPHICAL ABSTRACT



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Background: Nutrient trials differ from drug trials because participants have varying circulating levels at entry into the trial.
Objective: We sought to study the effect of a vitamin D intervention in pregnancy between subjects of different races and the association between 25-hydroxyvitamin D_3 (25[OH]D) levels in pregnancy and the risk of asthma/recurrent wheeze in offspring.
Methods: The Vitamin D Antenatal Asthma Reduction Trial is a randomized trial of pregnant women at risk of having children with asthma randomized to 4400 international units/d vitamin D or placebo plus 400 international units/d vitamin D. Asthma and recurrent wheezing until age 3 years were recorded.
Results: African American (AA) women (n = 312) had lower initial levels of 25(OH)D (mean [SD], 17.6 ng/mL [8.3 ng/mL]) compared with non-AA women (n = 400; 27.1 ng/mL [9.7 ng/mL], $P < .001$). No racial difference was found from vitamin D supplementation in pregnancy on asthma/recurrent wheezing in offspring (P for interaction = .77). Having an initial level of greater than 30 ng/mL and being randomized to the intervention group was associated with the lowest risk for asthma/recurrent wheeze by age 3 years compared with having an initial level of less than 20 ng/mL and receiving placebo (adjusted odds ratio, 0.42; 95% CI, 0.19-0.91).
Conclusions: We did not find differences between AA and non-AA mothers in the effect of maternal vitamin D supplementation and asthma/recurrent wheeze in offspring at 3 years. Maternal supplementation of vitamin D, particularly in mothers with initial 25(OH)D levels of greater than 30 ng/mL, reduced asthma/recurrent wheeze in the offspring through age 3 years, suggesting that higher vitamin D status beginning in early pregnancy is necessary for asthma/recurrent wheeze prevention in early life. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Vitamin D, asthma, allergy, randomized controlled trial, prenatal*

Asthma, wheeze, or both are common childhood conditions and impose a great cost on society.[1] Many potential risk factors have been identified for asthma development,[2-4] and several preventive trials have been undertaken,[5-7] but no single intervention has been proved effective. The Vitamin D Antenatal Asthma Reduction Trial (VDAART) is a randomized, double-blind, placebo-controlled trial of 881 pregnant women at risk of having children with asthma randomized to 4000 international units (IU)/d vitamin D plus a prenatal vitamin containing 400 IU of vitamin D or placebo plus 400 IU/d vitamin D. Recently, we reported that maternal vitamin D supplementation with 4400 IU/d in this trial led to an estimated 20% reduction in the incidence of asthma/recurrent wheeze in offspring through age 3 years compared with the control group (hazard ratio, 0.8; 95% CI, 0.6-1.0).[8] The effect did not reach statistical significance ($P = .051$), and several issues might have affected the results. It has been argued that nutrient trials are inherently different from drug trials for several reasons, including that (1) the participants have varying baseline nutrient status before entry into the trial, (2) the intervention needs to be sufficient to produce a change in nutrient status, (3) and the response to the change in nutrient status will depend on initial status on entry into the trial.[9]

Abbreviations used
25(OH)D: 25-hydroxyvitamin D_3
AA: African American
IU: International units
OR: Odds ratio
VDAART: Vitamin D Antenatal Asthma Reduction Trial

VDAART did not select participants based on initial 25-hydroxyvitamin D_3 (25[OH]D) levels, and results might have been affected by variation in these levels.[9] African American (AA) subjects have lower 25(OH)D levels than non-AA subjects.[10,11] Furthermore, AA subjects have a higher incidence of asthma in children compared with subjects of other races,[12] but whether this is explained by the 25(OH)D level is unknown.

We undertook secondary analyses of VDAART data to investigate whether treatment had differential effects by race either on maternal levels of 25(OH)D or on asthma/recurrent wheeze in the offspring and whether the initial and achieved prenatal levels of 25(OH)D were associated with the outcome of asthma/recurrent wheeze in the offspring. We first hypothesized that vitamin D supplementation would elicit a significant increase in 25(OH)D levels in all women, regardless of race/ethnicity. We next hypothesized that the initial and achieved 25(OH)D levels in pregnancy in this vitamin D supplementation trial are associated with a reduction in asthma or recurrent wheeze in offspring.

METHODS

Participants

Pregnant women were recruited from 3 clinical sites across the United States: Boston Medical Center, Boston, Massachusetts; Washington University at St Louis, St Louis, Missouri; and Kaiser Permanente Southern California Region, San Diego, California, as previously described.[13] The Data Coordinating Center was based in the Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts. Eligible participants were pregnant nonsmoking women between the ages of 18 and 39 years, who presented between the estimated gestational ages of 10 and 18 weeks and who had or who conceived the child with a man who had a history of asthma, eczema, or allergic rhinitis. The VDAART protocol was approved by the institutional review boards at each participating institution and at the Brigham and Women's Hospital. All women provided written informed consent.

For this study, we included women with full information about 25(OH)D levels at entry into the trial and at the third trimester. Furthermore, offspring with missing data on asthma/recurrent wheeze through age 3 years were excluded from the analysis, leaving us with a total of 712 participants (Fig 1).

Study design

Details of the study design and the protocol have previously been published.[8,13] We conducted a randomized, double-blind, placebo-controlled study of vitamin D_3 (4000 IU/d vitamin D_3 plus a multivitamin with 400 IU of vitamin D_3) versus placebo (daily placebo pill plus a multivitamin with 400 IU of vitamin D_3). Content of prenatal interval visits and postnatal visits have previously been detailed.[13]

The primary outcome was parental report of a physician's diagnosis of asthma or occurrence of recurrent wheeze in the child's first 3 years of life. Recurrent wheeze was defined by the occurrence of at least 1 of the following 5 conditions: (1) parental report of wheeze after the child's second birthday preceded by at least 1 report of wheeze before the second birthday; (2) report