RESEARCH LETTER

High-Dose Vitamin D Supplementation During Pregnancy and Asthma in Offspring at the Age of 6 Years

Evidence suggests that low in utero vitamin D levels may be associated with risk of asthma in offspring.[1] The Copenhagen Prospective Studies on Asthma in Childhood 2010 vitamin D randomized clinical trial (RCT) found that at the age of 3 years, children of women randomized to high-dose vs standard-dose vitamin D did not have a statistically significant reduced risk of persistent wheeze; however, a clinically important protective effect could not be excluded (hazard ratio, 0.76 [95% CI, 0.52-1.12]).[2] Because diagnosing asthma early in life is difficult, we followed up the children at the age of 6 years to assess the risk of current asthma.

Supplemental content

Methods | During week 24 of pregnancy, women were randomized to receive 2400 IU/d of vitamin D or placebo in addition to the recommended intake of 400 IU/d of vitamin D at 1 center in Copenhagen between March 2009 and November 2010. Their offspring attended 12 scheduled clinic visits until the age of 6 years, with additional acute care visits for any respiratory symptom; follow-up was through March 2017. Because of the delay in receiving ethical approval, 623 women of the 738 eligible were enrolled; 581 children were analyzed at the age of 3 years, at which time the study was unblinded.

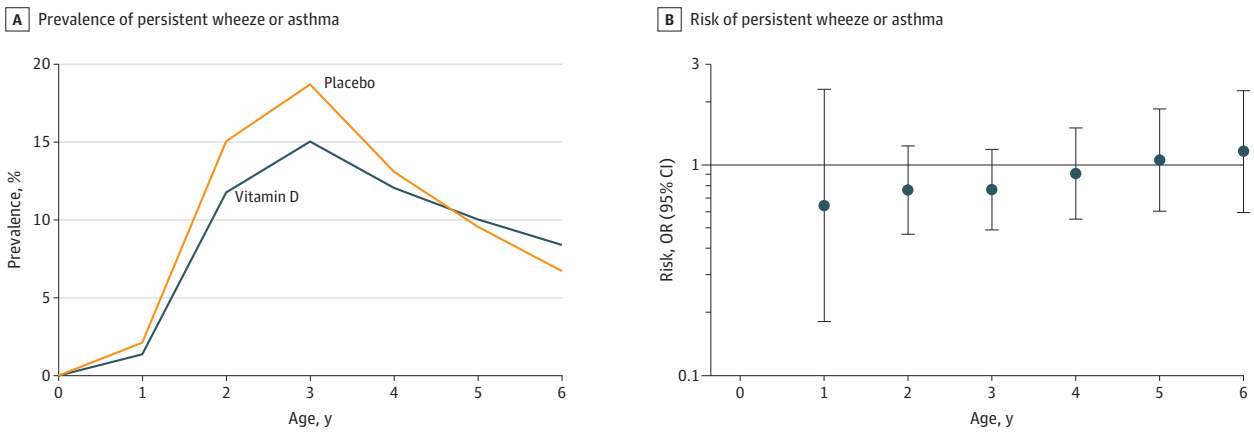
Details of the study have been published.[2] Extension of the trial was planned in mid-2013 before any data were examined. The National Committee on Health Research Ethics approved the follow-up by October 2013. Oral and written informed consent for the follow-up was obtained from the parents. The protocol for the trial extension appears in Supplement 1.

The primary outcome of the RCT[2] was persistent wheeze through the age of 3 years that was diagnosed by study pediatricians following a predefined, validated diagnostic algorithm.[3] The diagnosis was termed *persistent wheeze* during the first 3 years of life and *asthma* thereafter. Asthma at the age of 6 years was the primary outcome of the follow-up and was defined as fulfilling the diagnostic criteria at any point during childhood and needing inhaled corticosteroids at the age of 6 years. Prespecified secondary outcomes at the age of 6 years were lung function measurements, bronchial reactivity to methacholine, fractional exhaled nitric oxide concentration, allergic sensitization, and rhinitis.

The primary outcome was analyzed using logistic regression and was adjusted for sex, season of birth, the mother's vitamin D level at randomization, and randomization group of a concomitant RCT on n-3 long-chain polyunsaturated fatty acids.[4] The yearly prevalence of persistent wheeze or asthma at the ages of 1 through 6 years was analyzed post hoc with a repeated-measures generalized estimating equation model. Secondary outcomes were analyzed using logistic and linear regression models. Analyses were performed using SAS version 9.4 (SAS Institute Inc) and a 2-sided statistical significance threshold of .05. No imputation was performed for missing data.

Results | At the age of 6 years, 545 of the 581 children (94%) were available for the analysis. Mothers of children lost to

Figure. Effect of Vitamin D Supplementation on Yearly Prevalence of Persistent Wheeze or Asthma



A, Yearly prevalence of persistent wheeze or asthma during 6 years of clinical follow-up of children born to mothers receiving high-dose vitamin D or placebo in addition to the recommended intake of 400 IU/d during the third trimester of pregnancy. B, Corresponding yearly odds ratios (ORs) for the risk of persistent wheeze or asthma at the ages of 1 through 6 years. Error bars indicate 95% confidence intervals.

Table. Effect of High-Dose Vitamin D Supplementation During Pregnancy on Offspring Risk of Asthma, Lung Function, Bronchial Responsiveness, and Allergy Outcomes by the Age of 6 Years

	High-Dose Vitamin D		Placebo			
	Cases	Total No.	Cases	Total No.	Estimate (95% CI)	*P* Value
Primary Outcome						
Asthma at the age of 6 y, No. (%)						
Unadjusted analysis	23 (8)	274	18 (7)	268	OR: 1.27 (0.67 to 2.42)	.46
Adjusted analysis[a]	22 (8)	272	18 (7)	267	AOR: 1.21 (0.63 to 2.32)	.57
Secondary Outcomes						
Lung function, mean (SD)						
FEV_1, L	1.33 (0.16)	224	1.34 (0.17)	213	MD: −0.01 (−0.04 to 0.02)	.44
MMEF, L/s	1.66 (0.33)	224	1.69 (0.42)	213	MD: −0.03 (−0.10 to 0.04)	.37
FEV_1:FVC ratio	0.93 (0.05)	224	0.92 (0.06)	213	MD: 0.004 (−0.01 to 0.01)	.49
Specific airway resistance, kPa/s	1.09 (0.03)	233	1.09 (0.03)	230	MD: 0.001 (−0.04 to 0.06)	.69
Bronchial responsiveness, geometric mean (SD)						
PD20, μmoL	1.17 (3.93)	211	1.11 (3.52)	207	GMD: 0.94 (−0.73 to 1.22)	.66
Airway inflammation, geometric mean (SD)						
FeNO, ppb	6.4 (2.2)	177	6.5 (1.8)	163	GMD: −1.0 (−1.2 to 0.9)	.72
Allergy outcomes, No. (%)						
Sensitization, specific IgE	68 (29)	231	55 (25)	223	OR: 1.27 (0.84 to 1.93)	.25
Sensitization, skin prick test	21 (9)	226	11 (5)	214	OR: 1.89 (0.89 to 4.02)	.10
Allergic rhinitis	22 (8)	227	16 (6)	269	OR: 1.36 (0.70 to 2.66)	.36

Abbreviations: AOR, adjusted odds ratio; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GMD, geometric mean difference; MD, mean difference; MMEF, maximal mid-expiratory flow; OR, odds ratio; PD20, provocative dose of methacholine resulting in a 20% decrease in FEV_1 from baseline.

[a] Adjusted for sex, season of birth, randomization group of concomitant randomized clinical trial of n-3 long-chain polyunsaturated fatty acids, and maternal serum vitamin D level at time of randomization.

follow-up were of lower socioeconomic status and more likely to smoke. Asthma was diagnosed in 23 of 274 children (8%) in the high-dose vitamin D group compared with 18 of 268 children (7%) in the placebo group (odds ratio [OR], 1.27 [95% CI, 0.67-2.42], $P = .46$; adjusted OR, 1.21 [95% CI, 0.63-2.32], $P = .57$). An analysis of the yearly prevalence of persistent wheeze or asthma through the age of 6 years also showed no effect of the supplementation (OR, 0.87 [95% CI, 0.59-1.28], $P = .48$; **Figure**).

No significant differences were observed for lung function outcomes, bronchial reactivity, fractional exhaled nitric oxide concentration, allergic sensitization, or rhinitis by the age of 6 years (**Table**).

Discussion | High-dose compared with standard-dose vitamin D supplementation during pregnancy was not associated with the child's risk of asthma by the age of 6 years, at which time a diagnosis can be established using traditional measures. There also were no associations with lung function or bronchial hyperreactivity, which are key elements in asthma pathogenesis, and no association with allergy outcomes, suggesting that a benefit was not overlooked. The possible clinically important protective effect of vitamin D on persistent wheeze at the age of 3 years was not found at the age of 6 years.

The main limitations of the study are reduced statistical power, evidenced by the wide 95% CIs because the target sample was not reached, and the potential information bias from unblinding at the age of 3 years.

Future studies should investigate whether the effect of prenatal vitamin D supplementation is modified by environmental, dietary, or genetic factors.

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Accepted for Publication: January 4, 2019.

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Author Contributions: Dr Bisgaard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All coauthors have contributed substantially to the analyses of data, interpretation of the data, or both and have provided important intellectual input and approval of the final version of the manuscript.
Concept and design: Brustad, Stokholm, Bønnelykke, Bisgaard, Chawes.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Brustad, Bønnelykke, Chawes.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Brustad, Eliasen, Stokholm, Chawes.
Obtained funding: Bønnelykke, Bisgaard, Chawes.
Administrative, technical, or material support: Brustad.
Supervision: Brustad, Bønnelykke, Bisgaard, Chawes.

Conflict of Interest Disclosures: Dr Bisgaard reported receiving grants from the Lundbeck Foundation, Danish State Budget, Danish Council for Strategic Research, Danish Council for Independent Research, and the Capital Region Research Foundation during the conduct of the study and receiving personal fees from Chiesi outside the submitted work. No other disclosures were reported.

Funding/Support: Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) is funded by private and public research funds listed on http://www.copsac.com/. The Lundbeck Foundation, Danish State Budget, Danish Council for Strategic Research, Danish Council for Independent Research, and The Capital Region Research Foundation have provided core support for COPSAC.

Role of the Funders/Sponsors: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

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COMMENT & RESPONSE

Excess Deaths After Hurricane Maria in Puerto Rico

To the Editor Drs Santos-Lozada and Howard[1] estimated 1139 excess deaths in Puerto Rico from Hurricane Maria, which made landfall on September 20, 2017. They found that the observed death toll for September through November 2017 fell outside the 95% CIs of the mean death counts.

Given the destructive effect of Hurricane Maria, it is understandable that these months would be outliers from the historical patterns observed on the island. However, we have concerns that their method might be flawed and their estimation inaccurate.

The authors established expected monthly deaths and historical variability (95% CIs) based on summary statistics of the death counts from 2010 through 2016. Excess deaths were calculated by comparing observed counts with the upper 95% CI bound. This approach did not account for long-term trends and seasonal patterns, which can have significant effects on mortality rates.[2] It also did not account for the significant changes in population size that have occurred in Puerto Rico over the past 3 decades.[3]

As seen in the Table in the article,[1] this method was not able to accurately predict the observed prehurricane deaths during 3 months in 2017. In January, there were 2894 deaths, higher than the upper bound of 2739. In July, there were 2367 deaths, lower than the lower bound of 2413. In August, there were 2321 deaths, lower than the lower bound of 2370.

Prior to a natural disaster, we would expect a monthly death count outside the 95% CI to be a rare event. However, in the study,[1] in 3 of 8 months (37.5% of the time) the observed death counts were outside the 95% CI. If their method based on the historical patterns was not able to accurately predict 2017 deaths prior to the hurricane, how can we be confident that the results for 2017 deaths after the hurricane are correct?

Recently, the Puerto Rican government used a similar method to compare average deaths during the 4 posthurricane months of 2017 with the average from the previous 4 years. The government acknowledged that the official toll of 64 deaths was an underestimation and there might have been 1427 more deaths after the hurricane.[3]

Although we agree that the original count was a significant underestimation, we are concerned by the use of this method for estimating excess deaths. The accurate reporting of hurricane-related deaths is difficult but important for recovery efforts.

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Conflict of Interest Disclosures: None reported.

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In Reply The arguments presented by Drs Cruz-Cano and Mead are mistaken in some important conceptual, empirical, and methodological aspects. We stated in our Research Letter that the estimates were conservative and that they did not consider population denominators.[1]

Cruz-Cano and Mead state that the methodology "did not account for long-term trends and seasonal patterns, which can have significant effects on mortality rates." However, our method[1] accounted for seasonal patterns because it modeled each individual month's expected deaths as the mean over the previous 7 years, and the variability in this series accounted for the uncertainty around it. When we analyzed a longer series of data going back to the year 2000, the results are similar.[2]

The letter writers argue that our method did not account for changes in population size. We conducted a correlation analysis of the number of deaths and US Census Bureau population estimates, which showed no association between the number of deaths and population estimates in Puerto Rico from 2000 through 2016 (Pearson correlation coefficient = −0.26; $P = .32$). In fact, the number of deaths has remained stable over the last 10 or more years, ranging between 30 346 deaths in 2014 and 28 411 deaths in 2015.