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Associations between maternal vitamin D levels during pregnancy and allergic outcomes in the offspring in the first 5 years of life

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Keywords

maternal vitamin D; eczema; allergic outcomes; family history of allergy

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Competing interests

Chong YS has received reimbursement for speaking at conferences sponsored by Abbott Nutrition, Nestle, and Danone. Godfrey KM has received reimbursement for speaking at conferences sponsored by Nestle and Shek LP has received reimbursement for speaking at conferences sponsored by Danone and Nestle and consulting for Mead Johnson and Nestle.
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To the Editor

There is increasing evidence to support the Developmental Origins of Health and Disease (DOHaD) concept that fetal life and early life exposures are important determinants of fetal immune regulation and the development of disorders in later life, including allergies (1). Among the early life exposures, maternal vitamin D [25(OH)D] status during pregnancy, in particular 25(OH)D insufficiency (25(OH)D concentration of 50-75nmol/l) and/or 25(OH)D deficiency (25(OH)D concentration <50nmol/l) has been associated with allergic outcomes such as eczema, asthma and rhinitis in their offspring (2).

Vitamin D in humans is largely derived from the synthesis of 7-dehydrocholesterol in the skin from UVB solar radiation or ingestion via the gastrointestinal tract through food and supplements. It is converted to 25-hydroxy vitamin D in the liver and undergoes hydroxylation in the kidney, by the enzyme 25-hydroxyvitamin D-1 α-hydroxylase, into 1, 25-dihydroxyvitamin D – the active form of Vitamin D(3). Vitamin D receptors have an ubiquitous expression and can be found on keratinocytes and immune cells such as dendritic cells and natural killer cells which are able to modulate cytokine responses, which in turn influence the development of allergic outcomes (4). It has also been postulated that increasing sedentary indoor lifestyle and decreasing exposure to sunlight may be responsible for the prevalence of Vitamin D deficiency seen in developed countries today. In addition, other factors such as maternal vitamin D intake, age and body mass index also affect maternal vitamin D status during pregnancy.

Predictive markers of allergic diseases are evident even in early life. Differing levels of cord blood 25-hydroxyvitamin D3 levels have been associated with differences in allergen triggered cytokine responses and clinical eczema at 6 and 12 months of age (5), raising the question of whether factors much earlier in fetal life may modulate this risk. Current studies regarding the relationship between maternal vitamin D status, or antenatal Vitamin D supplementation, and offspring allergic outcomes have demonstrated conflicting results – whilst some data suggests a negative association, others have shown no significant link or even a positive relationship between maternal 25(OH)D levels and atopic outcomes. One study suggested a beneficial effect of prenatal 25(OH)D consumption on offspring allergic outcomes such as asthma (2), however others such as the World Health Organization Guidelines for Allergic Disease Prevention (GLAD-P) study did not find sufficient evidence to support recommending prenatal 25(OH)D supplementation for the prevention of allergic diseases in offspring (6).

Our study aimed to examine possible associations between maternal 25(OH)D levels and specific allergic outcomes in their offspring up to 5 years of age in the prospective mother-offspring cohort study Growing Up in Singapore Towards Healthy Outcomes (GUSTO). Evidence indicates that maternal serum and fetal cord blood 25(OH)D levels are closely correlated and assessment of maternal 25(OH)D status in the third trimester would thus be a good reflection of the infant's 25(OH)D status at birth and hence its potential influences on immunomodulation and infant allergic outcomes.

The methodology of the GUSTO study has been described previously(7). Briefly, we recruited healthy pregnant mothers who agreed to enroll their offspring for future follow-up. Interviewers gathered information on demographics, family history of allergy, social data and lifestyle factors. Definitions of allergic outcomes were standardized in the questionnaires administered at 3, 6, 9, 12, 15 18, 24, 36, 48 and 60 months to ensure consistency during interviews and home visits. Ethics approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth. Conduct of this study was based on the guidelines in the Declaration of Helsinki.

Parental report of physician-diagnosed eczema was based on a positive answer to the written question: “Has your child ever been diagnosed with eczema?” “Wheezing” was based on positive answers to the written questions “Has your child ever wheezed?” and “Has your child ever been prescribed with nebulizer/inhaler?”, while “rhinitis” was based on a positive response to the question “Has your child ever had sneezing, running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?” Study team members called the subjects who reported rhinitis to collect information on the number of episodes of rhinitis and the duration of each episode. A case prior to 18 months required a single episode that lasted for at least 4 weeks or two or more episodes each lasting at least 2 weeks. New cases of rhinitis after 18 months were defined by one or more episodes lasting at least 2 weeks.

For allergic outcomes (eczema, rhinitis, wheeze and use of nebulizer) by 18 months, the allergic outcome was classified as absent when the answers for the visits and/or at 18 month were “no.” For allergic outcomes (eczema, rhinitis, wheeze and use of nebulizer) by 36 months, the allergic outcome was classified as absent when the answers for the visits were “no” for the first 18 months and subsequent time points. For allergic outcomes (eczema, rhinitis, wheeze and use of nebulizer) by 60 months, the allergic outcome was classified as absent when the answers for the visits were “no” for the first 18 months and at least 75% of subsequent timepoints. Family history of allergy was defined as positive if the mother, father or an older sibling ever had eczema, asthma or allergic rhinitis.

Allergen sensitization was determined by skin prick testing. Skin prick testing (SPT) to inhalant allergens (house dust mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* and *Blomia tropicalis*) and food allergens (egg, peanut and cow’s milk) was carried out at 18, 36 and 60 months. At 60 months, skin prick testing was also carried out to shrimp and crab allergens. All of the allergens for skin prick testing were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis*, which was obtained from our laboratory. All tests were interpreted as positive if the wheal was at least 3 mm, and a child was considered as SPT-positive if any one or more of the individual tests was positive with a positive reaction to the positive control (histamine) and a negative reaction to the negative control (saline).

Fasting blood samples were obtained from subjects at 26 weeks pregnancy and isotope-dilution liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) was used to analyse plasma 25(OH)D levels as 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 (8).

The detection limit was <4nmol/l for both metabolites. Women were categorized as having 25(OH)D sufficiency (25(OH)D ≥ 75nmol/l), insufficiency (25(OH)D concentration of 50-75nmol/l) and/or 25(OH)D deficiency (25(OH)D concentration below 50nmol/l).

Comparison between demographic variables and maternal 25(OH)D status was performed using Pearson's Chi Square tests and the strength of associations between maternal 25(OH)D status and allergen sensitization, eczema, rhinitis and wheeze were assessed using multivariable logistic regression (adjusting for sex, ethnicity, maternal education levels, maternal age, maternal BMI during pregnancy, family history of allergy, total energy intake during pregnancy and vitamin D supplementation.), using a p value of < 0.05 as significant; we report adjusted odds ratios with exact 95% confidence intervals.

After exclusion of participants who dropped out of the study in early pregnancy, 925 (85.3%) had maternal 25(OH)D data. Out of these 925 participants, 557 (60.2%) had adequate 25(OH)D levels ≥75 nmol/l, 246 (26.6%) had insufficient 25(OH)D levels between 50nmol/l and 75nmol/l while 122 (13.2%) had deficiency in 25(OH)D levels ≤50nmol/l. There were differences in ethnicity, maternal age, maternal education levels, maternal BMI during pregnancy, total energy intake and vitamin D supplementation among the groups. There were more participants of Malay and Indian ethnicity and maternal BMI during pregnancy was higher in the 25(OH)D deficient group (Table 1). In addition, there were more participants with lower maternal education levels and vitamin D supplementation in the 25(OH)D deficient group. The mean maternal age and total energy intake were also lower in the 25(OH)D deficient group. We did not observe any significant associations between maternal 25(OH)D levels and allergic outcomes in the first 5 years of life (Table 2 and 3).

In our study, we found no significant associations between maternal vitamin D levels with allergic outcomes in the first 5 years of life. This is in line with current evidence provided by other cohort studies such as the Southampton Women's Survey which involved the measurement of serum 25-hydroxyvitamin D at 34 weeks gestation from the mothers of 860 full term children and found no link between maternal vitamin D levels and asthma, wheeze or atopy at age of 6 years (9). Levels of maternal and cord vitamin D levels are known to be correlated, further evidence is provided by the EDEN birth cohort which involved a follow up of 239 newborns to age of 5 years that showed no associations between cord serum vitamin D and allergic rhinitis (10). Besides this, supporting evidence is provided by a randomized controlled trial involving180 pregnant women at 27 weeks gestation who were randomized to receive either no vitamin D, 800 IU ergocalciferol or single oral bolus of 200000 IU cholecalciferol and no differences in atopy, eczema and lung function between the supplemented groups and control was observed in the offspring at the age of 3 years (11).

However, there are other studies such as that in Finland which involved 1669 children with HLA-DQB1-conferred susceptibility for type 1 diabetes that have reported an inverse association between higher maternal intake of vitamin D during pregnancy and rhinitis in children by age of 5 years (2).

Vitamin D in humans is largely derived from the cutaneous synthesis of 7-dehydrocholesterol in the skin by UVB solar radiation. Seasonal variability in serum Vitamin D levels has been shown to be paralleled by changes in peripheral blood adaptive immunity,(12) which may in turn influence allergic predisposition in populations which experience seasonal solar variability.(13) However, as Singapore is a tropical country with no seasonal sunlight variability, the majority of the mothers in our study would have been exposed to constant levels of UVB radiation throughout the year, thus this and the low numbers of vitamin D deficient mothers in our cohort could account for the lack of any observed associations between maternal vitamin D deficiency and allergic outcomes in their offspring in this study.

The strengths of our study are the regular collection of data at multiple time points which enable us to pick up atopic outcomes in a timely manner. In addition, antenatal 25(OH)D levels were objectively measured from maternal serum levels, compared to other studies which used maternal dietary intake of 25(OH)D as a surrogate measure of 25(OH)D status. However, we acknowledge that there are limitations to our study. Parental reporting of allergic outcomes may be subjected to recall and reporting bias. A single measurement of serum maternal vitamin D levels may not be an accurate representation of the vitamin D levels throughout pregnancy or the vitamin D status of their offspring between birth and the time at which outcomes were assessed. Varying vitamin D levels in early childhood with rapid growth and dietary changes may further impact upon the risk of developing allergic disorders in later childhood. Data on pre-pregnancy maternal vitamin D levels and the doses of antenatal vitamin D supplements consumed by individual mothers during pregnancy were also not available in our cohort, which limited our ability to perform secondary analyses based on these factors. The Vitamin D Antenatal Asthma Reduction Trial (VDAART)(14) and the Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) clinical trial(15) separately showed trends towards a reduced risk of asthma or persistent wheezing in offspring of mothers receiving antenatal Vitamin D_3 supplementation, but which did not reach statistical significance due to underpowering. Combined secondary analyses from both cohorts, however, later demonstrated a significant protective effect of antenatal vitamin D supplementation against asthma/recurrent wheeze in the offspring, an effect which was more pronounced in women with higher 25(OH)D levels (>30ng/ml) at trial entry.(16, 17) Multiple measurements of vitamin D levels during pregnancy and in the first few years of life alongside detailed capture of maternal and offspring vitamin D supplementation in future studies would allow for more detailed subgroup analyses.

In conclusion, we found no associations between maternal 25(OH)D deficiency and allergic outcomes in the first 5 years of life.

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Table 1

Comparison of demographic variables across the 25(OH)D groups

	N(%)			
	25(OH)D sufficiency (≥75nmol/l) N = 557	**25(OH)D insufficiency (≥50nmol/l and <75nmol/l)) N = 246**	**25(OH)D deficiency (<50nmol/l) N = 122**	**p-value**
Sex				
Male	303 (54.4)	116 (47.2)	65 (53.3)	0.2
Female	254 (45.6)	130 (52.8)	57 (46.7)	
Ethnicity				
Chinese	390 (70.0)	96 (39.0)	26 (21.3)	<0.01
Malay	91 (16.3)	92 (37.4)	60 (49.2)	
Indian	76 (13.6)	58 (23.6)	36 (29.5)	
Maternal education levels <12 years	213 (38.7)	101 (41.6)	61 (51.3)	0.04
Maternal education levels ≥ 12 years	337 (61.3)	142 (58.4)	58 (48.7)	
Maternal age (mean±standard deviation)	31.3 ± 5.0	29.7 ± 5.0	29.0 ± 5.3	<0.01
Maternal BMI during pregnancy (mean ± standard deviation)	23.2 ± 4.3	24.0 ± 4.9	24.6 ± 5.0	<0.01
Total energy intake during pregnancy (mean ± standard deviation)	1888.2 ± 555.8	1839.9 ± 549.4	1738.7 ± 608.8	0.03
No vitamin D supplementations during pregnancy	69 (13.3)	41 (19.0)	35 (35.7)	<0.01
Taken vitamin D supplementations during pregnancy	449 (86.7)	175 (81.0)	63 (64.3)	
Do not smoke during pregnancy	537 (96.9)	242 (98.8)	117 (96.7)	0.3
Smoke during pregnancy	17 (3.1)	3 (1.2)	4 (3.3)	

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Table 2

Numbers of subjects with allergic outcomes across the 25(OH)D groups

	25(OH)D sufficiency (≥ 75nmol/l)	25(OH)D insufficiency (≥50 nmol/l and <75 nmol/l)	25(OH)D deficiency (<50 nmol/l)
Outcomes by month 18	**N(%)**	**N(%)**	**N(%)**
Allergen sensitization	59 (13.5)	24 (12.5)	16 (17.6)
Eczema	103 (21.1)	37 (17.5)	19 (19.4)
Rhinitis	72 (18.0)	36 (21.8)	14 (21.2)
Wheeze and use nebulizer	56 (14.3)	26 (15.9)	11 (15.5)
Outcomes by month 36			
Allergen sensitization	110 (25.1)	36 (18.4)	24 (17.0)
Eczema	119 (26.6)	47 (24.2)	23 (27.4)
Rhinitis	157 (40.7)	68 (43.6)	33 (50.8)
Wheeze and use nebulizer	91 (24.7)	34 (22.4)	13 (21.7)
Outcomes by month 60			
Allergen sensitization	157 (38.2)	55 (31.4)	24 (30.0)
Eczema	126 (27.6)	48 (24.9)	25 (30.1)
Rhinitis	154 (41.6)	66 (44.3)	27 (46.6)
Wheeze and use nebulizer	108 (29.3)	46 (30.3)	20 (31.2)

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Table 3

Associations between maternal 25(OH)D levels and allergic outcomes (odds ratio and 95% confidence intervals)

	25(OH)D sufficiency (≥ 75nmol/l) OR (95% CI)*	25(OH)D insufficiency (≥50 nmol/l and <75 nmol/l) OR (95% CI)*	25(OH)D deficiency (<50 nmol/l) OR (95% CI)*
Outcomes by month 18			
Allergen sensitization	Ref	0.7 (0.3-1.3)	1.2 (0.5-2.6)
Eczema	Ref	0.9 (0.5-1.6)	1.4 (0.7-2.9)
Rhinitis	Ref	0.9 (0.5-1.6)	0.9 (0.4-2.1)
Wheeze and use nebulizer	Ref	0.7 (0.3-1.5)	0.7 (0.3-1.8)
Outcomes by month 36			
Allergen sensitization	Ref	0.6 (0.3-1.1)	1.2 (0.6-2.5)
Eczema	Ref	1.0 (0.6-1.8)	1.5 (0.8-3.1)
Rhinitis	Ref	1.1 (0.7-2.0)	1.3 (0.6-2.8)
Wheeze and use nebulizer	Ref	0.6 (0.3-1.2)	0.5 (0.2-1.3)
Outcomes by month 60			
Allergen sensitization	Ref	0.7 (0.4-1.1)	0.9 (0.4-1.8)
Eczema	Ref	1.1 (0.6-1.8)	1.6 (0.8-3.2)
Rhinitis	Ref	1.2 (0.7-2.1)	1.3 (0.6-2.7)
Wheeze and use nebulizer	Ref	1.0 (0.6-1.7)	0.9 (0.4-1.9)

*Adjusted for sex, ethnicity, maternal education levels, maternal age, maternal BMI during pregnancy, family history of allergy, total energy intake during pregnancy and vitamin D supplementation.