Associations of maternal vitamin D intake during pregnancy with asthma and other allergies in Japanese infants

Kozue Nakamura

Abstract

Vitamin D is known to have an immunological effect and may play an important role in allergic diseases. We investigated the associations of maternal intake of vitamin D during pregnancy with the risks of allergies in infants. Subjects were from a birth cohort constructed prenatally. Maternal intake of vitamin D during pregnancy was evaluated using a 5-day dietary record. After birth, 312 children were followed for physician-diagnosed allergic diseases until the ages of approximately 3 and 5 years old. As compared with the lowest, the highest maternal vitamin D intake from diet plus supplements during pregnancy was significantly associated with a reduced risk of physician-diagnosed asthma in children younger than 3 years of age after controlling for potential confounders. Statistically significant trends were also observed (p=0.006). Relative to the lowest, the highest maternal vitamin D intake was associated with an increased risk of eczema in children under 3 years old. The results of this study suggest that the maternal intake of vitamin D during pregnancy is inversely associated with asthma and positively associated with atopic eczema in infants.

Keywords : maternal vitamin D intake, pregnancy, children's asthma, children's allergies

Introduction

Events and exposures during pregnancy may crucially affect fetal growth and health status and disease susceptibility after birth. An increase in allergic disease in early childhood, as well as differences in immune reaction, may be attributed to antenatal events, including a mother's lifestyle and diet during pregnancy (1). Since vitamin D (VD) has been reported to have important effects on the immune system (2), it has been thought that VD deficiency may be associated with cancers and many immune-mediated disorders (3, 4). VD has also been shown to be essential for fetal lung development (4). Thus, interest in the relationship between VD status during pregnancy and children's asthma has been increasing. It is also possible that the intake of VD during pregnancy is associated with allergies other than asthma in children, such as atopic eczema and allergic rhinitis (5).

To our knowledge, only four prospective studies have assessed the association between VD intake during pregnancy and asthmatic symptoms in children (6-9). All of these studies demonstrated that a low intake of VD during pregnancy was associated with a high risk of wheezing in offspring. However, only one study repeatedly evaluated the association between maternal VD intake during pregnancy and wheezing in children at 2 and 5 years of age (7). Although the associations between VD intake during pregnancy and allergies other than asthma, such as atopic eczema and allergic rhinitis, have also been evaluated in these studies, the results have been inconsistent (6, 8, 9).

In the present study, we prospectively assessed the associations between consumption of VD in the third trimester of pregnancy and physician-diagnosed asthma, atopic eczema, allergic rhinitis, and food allergy in Japanese children by the age of 3 and 5 years.

Materials and Methods

Study population and measurement

Subjects were mother-child pairs who participated in the previous study on the associations between maternal lifestyle factors during pregnancy, maternal and umbilical hormones, and gestational and neonatal outcomes (10). Initially, early gestational women were recruited from the obstetric clinic in Gifu, Japan, from May 2000 to October 2001. Women from whom we obtained informed consent responded to a self-administered questionnaire seeking demographics and details with regard to smoking, medical, and reproductive histories at the time of enrollment when they were in early pregnancy. At time of the 10^{th} and 29^{th} weeks of gestation and of delivery, the clinic provided medical records and auxological data for the mothers and the babies. Maternal diet during pregnancy was assessed using a 5-day self-administered dietary record prior to consultation at the 29^{th} week of pregnancy. The supplements taken during these 5 days were also recorded. Individual intakes of nutrients, including VD, were estimated based on the dietary records using the Japanese Standard Tables of Food Composition, 5^{th} revised and enlarged edition, published by the Science and Technology Agency of Japan. A total of 535 women gave birth between December 2000 and June 2002. After excluding 6 mothers who had twins (n=3) and fetal anomalies (n=3), 529 mother-child pairs were enrolled in the study in 2003. During the follow-up between 2003 and 2007, we annually mailed mothers a brief questionnaire to obtain information regarding the allergy status of the children as our primary outcomes. Their allergy status was determined by questioning whether the children or mothers had ever been confirmed by a physician as having asthma, atopic eczema, allergic rhinitis, or a food allergy. When their reply to the question was affirmative, they were defined as having had asthma or the indicated allergies. Age when the child was diagnosed was also reported by the mothers and defined as the onset of each allergy. We also obtained information regarding the children's weight and height at each survey and an allergy history of the mothers. We mailed out all questionnaires at the same time each year. We could not reach 69 mother-child pairs because 68 had moved away, and one child had died before 2003. Among the remaining 460 mother-child pairs, a total of 313 (68.0%) replied to our questionnaires to evaluate the relationship between VD and allergies in children before the age of 3 years. During the survey from 3 to 5 years of age, we could not reach 11 mother-child pairs who had moved away. Of the remaining 449 mother-child pairs, 281 (62.6%) comprised the analysis for maternal VD intake and the allergy status of their children before 5 years of age. One mother had become pregnant twice during the recruitment period. Her two babies were followed, but only the oldest sibling was included in the analysis. Thus, ultimately we included 312 mother-child pairs for the follow-up of children until 3 years of age and 280 pairs for the follow-up until 5 years of age. Mothers gave their informed consent for the follow-up study each time they responded to the questionnaire. This follow-up study was approved by the ethics board of Gifu University Graduate School of Medicine.

Statistical method

We compared baseline data during pregnancy and at delivery between respondents and non-respondents to the present study using χ^2 test or ANOVA. To evaluate the relationship between maternal intake of VD during pregnancy and the offspring's asthma and other allergies after birth, we computed the ORs and 95 % CIs using a logistic regression model. The risk of asthma and other allergies from birth until ages 3 and 5 was assessed separately to observe any changes in the association over time. VD intake of mothers during pregnancy was adjusted for individual total energy intake after log-transformation based on the residual method proposed by Willett (11). The energy-adjusted VD intake was categorized

into tertiles on the basis of its distributions among all the subjects. The lowest category was defined as a reference. Crude ORs of the offspring's asthma and allergies were calculated for each intake category in comparison with the reference (Model 1). Non-nutritional variables, including children's gender, children's birth weight, maternal age, maternal education level, maternal history of allergies, maternal smoking habit, children's age, and body mass index at the time of the follow-up survey, were included in the model as covariates (Model 2). As maternal intakes of polyunsaturated fatty acids and vitamin E during pregnancy have been associated with allergies (12, 13), we performed additional adjustments for these nutritional factors (Model 3). The trend of association was tested on continuous values of each nutrient or food group. All statistical analyses were performed using the SAS software version 9.2 (SAS Institute, Inc., Cary, NC). Significance was defined as two-sided $p < 0.05$.

Table1
Characteristics of mothers and children participating the follow-up study (312 pairs)

	[1]			
Maternal characteristics				
Age when having child (yrs)	30.2	(	3.6	)
Years of education over 13 yrs	187	(	60.9	)
Current smokers	5	(	1.6	)
Former smokers	58	(	19.1	)
Use of supplements during pregnancy	31	(	9.9	)
Use of supplements containing vitamin D during pregnancy	10	(	3.2	)
Maternal diet at 29th week of gestation				
Total energy (kcal)	1862	(	293	)
Vitamin D without supplements (μg)	6.0	(	3.6	)
Vitamin D with supplements (μg)	6.1	(	3.6	)
Maternal past history of allergy				
Any type of allergy	150	(	48.1	)
Children's characteristics				
Boys	159	(	51.0	)
Birth weight (g)	3111	(	374	)
Fetal age (wks)	39.4	(	1.1	)
At the survey around at age 3 ys				
Age (y)	3.4	(	0.3	)
Body mass index [2]	15.7	(	1.59	)
At the survey around at age 5 ys				
Age (y)	5.5	(	0.3	)
Body mass index [2]	15.2	(	1.4	)

[1] Values are means (SD) or numerals (percentages).

[2] Body mass index=Body weight (kg)/ Height(m^2)

[3] 36 pairs were lost due to moving from this area and canceling their participation.

Results

Table 1 presents the characteristics of mother-infant pairs who participated in the present study. Most mothers abstained from smoking during pregnancy. The proportions of current and former smokers during pregnancy were 1.6% and 19.1%, respectively. The percentages of children who had been diagnosed with asthma, atopic eczema, allergic rhinitis, or food allergy by 3 years of age were 23 (7.3%), 51 (16.3%), 52 (16.6%), and 38 (12.1%), respectively. The corresponding values for the occurrence before 5 years of age were 34 (12.1%), 63 (22.5%), 94 (33.6%), and 44 (15.7%), respectively.

Participant mothers (n=312) were more likely to have had a high level (over 13 years) of education (60.9% vs. 45.4%) and less likely to be current smokers (1.6% vs. 6.4%) when compared with the mother-child pairs who dropped out of the study before the 3 years of follow-up (n=147) were complete. There were no differences in maternal VD intake during pregnancy, children's sex ratio, birth weight, or gestational age. Similar differences in characteristics between respondent (n=280) and non-respondent mothers (n=168) were observed at the time of the 5-year

Table 2
Odds ratios and 95% confidence intervals of prevalence of children's asthma when they were 3 / 5 years old according to maternal intake of Vitamin D during pregnancy.

	3 years old						5 years old					
			Model 1	Model 2	Model 3			Model 1	Model 2	Model 3		
	Cases	Subjects	Crude OR (95% CIs)	Multivariate[1] OR (95% CIs)	Multivariate[2] OR (95% CIs)	Cases	Subjects	Crude OR (95% CIs)	Multivariate[1] OR (95% CIs)	Multivariate[2] OR (95% CIs)		
Vitamin D from diet and supplements (μg)												
Q1	14	103	1.00	1.00	1.00	14	92	1.00	1.00	1.00		
Q2	6	103	0.39 (0.15-1.07)	0.34 (0.12-0.97)	0.34 (0.11-0.94)	9	92	0.60 (0.25-1.48)	0.59 (0.24-1.46)	0.56 (0.23-1.41)		
Q3	3	102	0.19 (0.05-0.69)	0.15 (0.04-0.58)	0.15 (0.03-0.52)	11	92	0.76 (0.32-1.77)	0.72 (0.30-1.74)	0.67 (0.27-1.66)		
P for trend [3]			0.01	0.005	0.006			0.52	0.43	0.33		
Vitamin D from diet (μg)												
Q1	13	103	1.00	1.00	1.00	15	92	1.00	1.00	1.00		
Q2	6	103	0.43 (0.16-1.18)	0.40 (0.14-1.12)	0.40 (0.14-1.13)	7	92	0.42 (0.16-1.09)	0.41 (0.16-1.07)	0.39 (0.15-1.04)		
Q3	4	102	0.28 (0.09-0.90)	0.23 (0.07-0.77)	0.24 (0.07-0.80)	12	92	0.77 (0.34-1.75)	0.72 (0.30-1.69)	0.68 (0.28-1.62)		
P for trend [3]			0.02	0.01	0.01			0.52	0.44	0.37		

[1] Adjusted for mother's age at delivery, children's sex, birthweight, mother's allergic history, maternal smoking habit, maternal education level, children's body mass index at each survey, and children's age at each survey.

[2] Adjusted for covariates used in Model 2 and individual intake of polyunsaturated fatty acid and vitamin E .

[3] P for trend across continuous values of each nutrient.

follow-up.

ORs and 95% CIs for the risk of doctor-diagnosed asthma until 3 years old according to maternal VD intake during pregnancy are presented in **Table 2**. Whether or not VD intake from supplements was considered, the highest category of maternal VD intake was significantly associated with a decreased risk of children's asthma, compared with the lowest category, after controlling for non-dietary covariates. The trend of the risk of asthma on VD was statistically significant. After additional adjustment for lifestyle and nutrient factors, the association between VD intake during pregnancy and children's asthma remained significant. At 5 years of age, children born to mothers with the highest intake of VD from diet or supplement plus diet during pregnancy had about a 30% reduction of cumulative risk of asthma, but this trend was not statistically significant **(Table 2)**.

We calculated the risks of atopic eczema, allergic rhinitis, and food allergy according to the maternal VD intake during pregnancy in the same manner (**Table 3**). High VD intake from diet as well as diet plus supplements was significantly and positively associated with eczema in children before age 3. The trend of the risk of atopic eczema had statistical significance. About a two-fold increased OR of eczema for the highest tertile of maternal VD intake from diet plus supplements was observed at the age of 5 years, compared with the lowest tertile ($p<0.05$). Compared with the lowest intake, the highest intake of maternal VD

Associations of maternal VD intake during pregnancy with asthma/other allergies in infants

Table 3
Odds ratios and 95% confidence intervals of prevalence of offspring's eczema, rhinitis, and food allergy around 3 / 5 years old according to maternal intake of Vitamin D during pregnancy.

	3 years old					5 years old				
			Model 1	Model 2	Model 3			Model 1	Model 2	Model 3
	Cases	Subjects	Crude OR (95% CIs)	Multivariate[1] OR (95% CIs)	Multivariate[2] OR (95% CIs)	Cases	Subjects	Crude OR (95% CIs)	Multivariate[1] OR (95% CIs)	Multivariate[2] OR (95% CIs)
Eczema										
Vitamin D from diet and supplements (μg)										
Q1	11	103	1.00	1.00	1.00	16	93	1.00	1.00	1.00
Q2	13	103	1.21 (0.51-2.84)	1.16 (0.48-2.76)	1.13 (0.47-2.72)	20	92	1.34 (0.64-2.78)	1.35 (0.64-2.86)	1.34 (0.63-2.85)
Q3	27	102	3.01 (1.40-6.47)	3.33 (1.51-7.35)	3.44 (1.54-7.68)	27	92	2.00 (0.99-4.03)	2.02 (0.97-4.20)	2.12 (1.01-4.45)
P for trend [3]			0.03	0.02	0.02			0.16	0.22	0.18
Vitamin D from diet (μg)										
Q1	13	103	1.00	1.00	1.00	18	93	1.00	1.00	1.00
Q2	11	103	0.83 (0.35-1.94)	0.77 (0.32-1.83)	0.76 (0.31-1.82)	18	92	1.01 (0.49-2.10)	0.96 (0.46-2.02)	0.95 (0.45-2.02)
Q3	27	102	2.49 (1.20-5.17)	2.71 (1.27-5.79)	2.80 (1.30-6.04)	27	92	1.73 (0.88-3.43)	1.69 (0.83-3.43)	1.75 (0.85-3.59)
P for trend [3]			0.03	0.02	0.02			0.13	0.18	0.14
Rhinitis										
Vitamin D from diet and supplements (μg)										
Q1	21	103	1.00	1.00	1.00	38	92	1.00	1.00	1.00
Q2	17	103	0.77 (0.38-1.57)	0.70 (0.33-1.49)	0.70 (0.33-1.48)	28	92	0.62 (0.34-1.14)	0.55 (0.28-1.08)	0.56 (0.28-1.10)
Q3	14	103	0.61 (0.29-1.29)	0.53 (0.24-1.17)	0.52 (0.23-1.15)	28	92	0.62 (0.34-1.14)	0.55 (0.28-1.09)	0.51 (0.25-1.03)
P for trend [3]			0.71	0.62	0.62			0.15	0.10	0.05
Vitamin D from diet (μg)										
Q1	20	103	1.00	1.00	1.00	40	92	1.00	1.00	1.00
Q2	17	103	0.82 (0.40-1.67)	0.78 (0.37-1.66)	0.78 (0.37-1.65)	24	92	0.46 (0.25-0.85)	0.38 (0.19-0.77)	0.38 (0.19-0.77)
Q3	15	103	0.71 (0.34-1.47)	0.66 (0.30-1.43)	0.65 (0.29-1.44)	30	92	0.63 (0.35-1.15)	0.60 (0.30-1.17)	0.56 (0.28-1.11)
P for trend [3]			0.63	0.54	0.54			0.09	0.06	0.03
Food allergy										
Vitamin D from diet and supplements (μg)										
Q1	14	103	1.00	1.00	1.00	16	92	1.00	1.00	1.00
Q2	6	103	0.39 (0.15-1.07)	0.35 (0.13-0.98)	0.35 (0.13-0.97)	9	92	0.52 (0.22-1.23)	0.50 (0.21-1.22)	0.51 (0.21-1.25)
Q3	18	102	1.26 (0.64-2.91)	1.44 (0.65-3.15)	1.44 (0.65-3.19)	19	92	1.24 (0.59-2.59)	1.57 (0.71-3.46)	1.53 (0.69-3.42)
P for trend [3]			0.72	0.59	0.62			0.93	0.58	0.69
Vitamin D from diet (μg)										
Q1	14	103	1.00	1.00	1.00	17	92	1.00	1.00	1.00
Q2	5	103	0.32 (0.11-0.94)	0.29 (0.10-0.86)	0.29 (0.10-0.86)	7	92	0.36 (0.14-0.92)	0.36 (0.14-0.92)	0.36 (0.14-0.93)
Q3	19	102	1.46 (0.69-3.09)	1.53 (0.70-3.35)	1.56 (0.71-0.86)	20	92	1.23 (0.60-2.53)	1.52 (0.71-3.28)	1.49 (0.68-3.24)
P for trend [3]			0.54	0.45	0.47			0.72	0.41	0.51

[1] Adjusted for mother's age at delivery, children's sex, birthweight, mother's allergic history, maternal smoking habit, maternal education level, children's body mass index at each survey, and children's age at each survey.

[2] Adjusted for covariates used in Model 2 and individual intake of polyunsaturated fatty acid and vitamin E .

[3] P for trend across continuous values of each nutrient.

from supplements plus diet was associated with a nearly 50% reduced OR of allergic rhinitis in children by both 3 and 5 years of age, although these associations were not statistically significant. Associations between maternal intake of VD and food allergy were not observed in children at 3 or 5 years of age.

Foods such as fish, eggs, meat, and mushrooms are rich in VD. There were no significant relationships between maternal consumption of these foods during pregnancy and asthma, eczema, rhinitis, or food allergy in their children (data not shown).

Discussion

In this prospective cohort study, we found that a high maternal intake of VD during pregnancy was significantly associated with a reduced risk of physician-diagnosed asthma in offspring by the age of 3 years old. The relationship was observed regardless of the intake of VD supplements. At the children's age of 5 years, the magnitude of the inverse associations was weakened.

Among the four previous prospective studies (6-9), Devereux et al. assessed offspring's wheezing twice during the follow-up period, at ages 2 and 5. The highest category of maternal VD intake had significant risk reduction of wheezing for the first 5 years, compared with the lowest intake of VD (OR, 0.48; 95 % CI, 0.25, 0.91), and no association was shown at 2 years of age (7). The results suggested that a preventive effect of VD on asthma was greater in children 5 years of age than in those 2 years of age. However, our study showed that the risk reduction of asthma was greater at 3 years of age than at 5 years of age, suggesting that an effect of VD was attenuated after 3 years of age. Risk reduction of children's asthma/wheeze according to maternal VD intake during pregnancy has been reported at 3 years of age (6, 9) and 5 years of age (8). However, these studies assessed infantile allergy only once. Larger and longer longitudinal studies are needed to investigate the time-dependent change of the effect of maternal VD intake during pregnancy on offspring's asthma.

Experimental studies have reported that VD has immunological effects and improved inappropriate allergic responses (4, 5). Considering that, it seems biologically plausible that maternal dietary VD during pregnancy is associated with children's allergies. VD has also been reported to be essential for maintaining a normal respiratory system in adults (14) and fetuses (15-18). Such effects of VD may have also contributed to the observed inverse association between high VD consumption during pregnancy and children's asthma in the present study.

We found that increased VD intake during pregnancy was significantly associated with a decreased OR of allergic rhinitis before the age of 5 years. Erkkola et al. also reported an inverse association between VD intake and the risk of allergic rhinitis (OR, 0.85; 95% CI, 0.75, 0.97) (8). However, epidemiological and clinical data on VD and allergic rhinitis are scarce. Allergic rhinitis and asthma, which occur in upper and lower airways, respectively, have been reported to be caused by common airway conditions (19). We speculate that mechanisms for potential allergy-suppressive effects of VD may be similar between rhinitis and asthma (5).

In contrast, we observed that infantile atopic eczema was positively and significantly associated with higher maternal VD intake during pregnancy. Previous observational studies have shown conflicting results: one observed a risk increase according to the increased serum VD level during pregnancy (OR 3.26) (20); two studies indicated inverse associations (OR 0.64-0.80) (8, 9); and one reported no association (6). The pathology of atopic eczema of the skin may be different from that of a respiratory tract allergy (21). Benson et al. reported that VD decreased T helper type 1 (Th1) cells and subsequently increased T helper type 2 (Th2) cells, resulting in a worsening skin allergy (22). The observed positive association between maternal VD intake and children's eczema may be due to the Th1/Th2 imbalance induced by high intake of VD.

Hens' eggs and fish are common foods that trigger allergies among Japanese infants (23). These foods are rich in VD. Some atopic pregnant women may have avoided such foods to prevent their children from having allergies, which might have resulted in the observed inverse association between VD intake during pregnancy and the risk of children's asthma. If this is true, the association between VD intake and atopic eczema should also be inverse. However, the observed association between maternal VD intake and children's eczema was positive in the present study. In addition, no

differences in egg and fish intake were observed between allergic mothers and healthy mothers in this cohort.

An advantage of the present study is its prospective design, which can verify a causal inference between maternal diet and offspring's allergic diseases and reduce recall bias. However, several limitations should be considered. Owing to the relatively low participation rate and small number of allergy cases, the present study lacks statistical power. We also have to consider the possibility that the low participation rate might have induced a selection bias. However, it is unlikely that mothers with high VD intake during pregnancy were less likely to attend the study when their children had asthma or more likely to attend when their children had atopic eczema. A dietary record for 5 days was conducted only once during pregnancy to estimate the maternal intake of VD. To assess the association of maternal VD intake during pregnancy and allergic disease in children, we should have considered children's current VD status. Sun exposure is fundamental for VD production (3, 4). However, neither the children's dietary survey nor a sunlight exposure measurement was conducted.

In summary, we presented the association between high intake of VD during pregnancy and reduced risk of physician-diagnosed asthma before 3 years of age in children. This observed association decreased with offspring growth. We also found that maternal VD intake during pregnancy was significantly and positively associated with offspring's atopic eczema. Maternal VD intake might have a possible role in the development of children's allergies. Further and longer studies are required to examine how long maternal VD intake during pregnancy would potentially influence the risk of each type of allergy among children.

Acknowledgments

The author is very grateful to Ms. Yoko Kurisu for her valuable technical contributions in the present study.

Literature Cited

1. Prescott S L. Allergic disease: understanding how in utero events set the scene. Proc Nutr Soc. 2010; 69: 366-72.
2. Griffin MD, N Xing, and R Kumar. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr. 2003; 23: 117-45.
3. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 2004; 79: 362-71.
4. Lange NE, *Litonjua A, Hawrylowicz CM, Weiss* S. Vitamin D, the immune system and asthma. Expert Rev Clin Immunol. 2009; 5: 693-702.
5. Searing DA, Leung DY. Vitamin D in atopic dermatitis, asthma and allergic diseases. Immunol Allergy Clin North Am. 2010; 30: 397-409.
6. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr. 2007; 85: 788-95.
7. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, Helms PJ, Seaton A, Weiss ST. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr. 2007; 85: 853-9.
8. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, Veijola R, Pekkanen J, Ilonen J, Simell O, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clin Exp Allergy. 2009; 39: 875-82.

9. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. Eur Respir J. 2010; 35: 1228-34.
10. Nagata C, Iwasa S, Shiraki M, Sahashi Y, Shimizu H. Association of maternal fat and alcohol intake with maternal and umbilical hormone levels and birth weight. Cancer Sci. 2007; 98: 869-73.
11. Willett W, Stampfer M. Implication of total energy intake for epidemiological analysis. 2nd. Ed. In: Willett W, ed. Nutritional epidemiology. New York, NY: Oxford University Press, 1998: 273-301.
12. Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, Helms PJ, Seaton A. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. Am J Respir Crit Care Med. 2006; 174: 499-507.
13. Black PN, Sharpe S. Dietary fat and asthma: Is there a connection? Eur Respir J. 1997; 10:6-12.
14. Iqbal SF, Freishtat RJ. Mechanism of action of vitamin D in the asthmatic lung. J Investig Med. 2011; 59: 1200-2.
15. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. Curr Opin Allergy Clin Immunol 2009; 9: 202-7.
16. Marin L, Dufour ME, Nguyen TM, Tordet C, Garabedian M. Maturational changes induced by 1 alpha, 25-dihydroxyvitamin D3 in type II cells from fetal rat lung explants. Am J Physiol. 1993;2 65: L45–52.
17. Marin L, Dufour ME, Tordet C, Nguyen M. 1,25(OH)2D3 stimulates phospholipid biosynthesis and surfactant release in fetal rat lung explants. Biol Neonate. 1990; 57: 257–260.
18. Nguyen M, Trubert CL, Rizk-Rabin M, Rehan VK, Besancon F, Cayre YE, Garabedian M. 1,25-Dihydroxyvitamin D3 and fetal lung maturation: immunogold detection of VDR expression in pneumocytes type II cells and effect on fructose 1,6 bisphosphatase. J Steroid Biochem Mol Biol. 2004; 89-90: 93-7.
19. Meltzer EO. The relationships of rhinitis and asthma. Allergy Asthma Proc. 2005; 26: 336-40.
20. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, Godfrey KM, Cooper C; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr. 2008; 62: 68-77.
21. Leung DY. Pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 1999; 104:S99-108.
22. Benson AA, Toh JA, Vernon N, Jariwala SP. The role of vitamin D in the immunopathogenesis of allergic skin diseases. Allergy. 2012; 67: 296-301..
23. Mukoyama T, Nishima S, Arita M, Ito S, Urisu A, Ebisawa M, Ogura H, Kohno Y, Kondo N, Shibata R, et al.; Food Allergy Committee, Japanese Society of Pediatric Allergy and Clinical Immunology. Guidelines for diagnosis and management of pediatric food allergy in Japan. Allergol Int. 2007; 56

（提出日　平成 28 年 1 月 5 日）