



The Link between Serum Vitamin D Level, Sensitization to Food Allergens, and the Severity of Atopic Dermatitis in Infancy

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Objective To investigate the association between serum vitamin D levels, sensitization to food allergens, and the severity of atopic dermatitis in infants.

Study design We investigated serum 25-hydroxyvitamin D (25[OH]D) and specific immunoglobulin E levels to common or suspected food allergens in 226 infants with atopic dermatitis or food allergy. The severity of atopic dermatitis by the Scoring Atopic Dermatitis index and amount of vitamin D intake was measured in subcohort children. Sensitization to food allergen was categorized by the number (non-, mono-, and poly-) of sensitized allergens and the degree (undetected-, low-, and high-level) of sensitization.

Results Significant differences in 25(OH)D levels were found between groups on number ($P = .006$) and degree ($P = .005$) of food sensitization. The polysensitization group had significantly lower levels of 25(OH)D than the non-sensitization ($P = .001$) and monosensitization ($P = .023$) group. High-level sensitization group had significantly lower 25(OH)D levels compared with undetected ($P = .005$) and low-level ($P = .009$) sensitization group. Vitamin D deficiency increased the risk of sensitization to food allergens (OR 5.0; 95% CI 1.8-14.1), especially to milk (OR 10.4; 95% CI 3.3-32.7) and wheat (OR 4.2; 95% CI 1.1-15.8). In addition, the Scoring Atopic Dermatitis index was independently related to 25(OH)D levels after adjusting for the level of sensitization (adjusted $R^2 = 0.112$, $P = .031$).

Conclusions Our results suggest that vitamin D deficiency increases the risk of sensitization to food allergens and that atopic dermatitis may be more severe in infants with vitamin D deficiency. (*J Pediatr* 2014;165:849-54).

Sensitization to food allergen is a precursor and a risk factor for the development of allergic diseases later in life^{1,2}; therefore, early detection and modification of risk indicators for food allergen sensitization might prevent the development of allergic diseases.³

Vitamin D is a hormone with multiple physiologic actions and has been reported to influence the regulation of the immune system.^{2,4,5} It has been reported that the vitamin D status is linked with the development of allergic disease including asthma in children⁶ and that vitamin D deficiency is associated with the severity of atopic dermatitis.⁷ Vitamin D deficiency is considered an important risk factor for food allergy,⁸ and increased maternal vitamin D intake reduced allergic sensitizations in the offspring.²

The symptoms of atopic dermatitis do not always coincide with the levels of sensitization, and factors influencing the skin barrier function, such as filaggrin mutations⁹ and local antimicrobial defense,^{10,11} also are related with the severity of atopic dermatitis. To date, the detailed mechanism of how the vitamin D status is related with the development of atopic dermatitis remains unclear. The aim of this study was to investigate whether the vitamin D status is related with sensitization to food allergens, and whether the severity of atopic dermatitis is influenced by the vitamin D status in infants.

Methods

This is a cross-sectional study in which subjects were recruited consecutively between January 2011 and December 2012 at the CHA Bundang Hospital, Korea (located at latitude 37° 26'N). The inclusion criteria were children aged 3-24 months with atopic dermatitis or suspected food allergy, who had not been on vitamin supplementation for at least 1 month prior to the study. Exclusion criteria were children with suspected chronic diseases or congenital anomaly, those with previous history of hospital admissions, and those treated with systemic corticosteroid for 7 days or more in the preceding month. Two hundred twenty-six infants (168 infants with atopic

25(OH)D	25-hydroxyvitamin D
IgE	Immunoglobulin E
SCORAD	Scoring atopic dermatitis
Treg	Regulatory T cell

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dermatitis [74.3%] and 58 with suspected food allergy without atopic dermatitis [25.7%]) were enrolled.

The parents answered structured questionnaires regarding the family history of allergy, housing, and environmental conditions such as secondhand smoking and pet ownerships. Participation in the study was voluntary, and informed consent was obtained from all participants. The study was approved by the Ethics Committees of the CHA University.

Assessment and Definition of Allergic Disease

Infants were defined as having atopic dermatitis if they have ever had a doctor's diagnosis of atopic dermatitis or evidence of typical skin lesions. Subjects were considered to have suspected food allergy if there was a history of acute allergic reaction to known food allergen, combined with food specific immunoglobulin E (IgE) ≥ 0.35 kU/L to the relevant food, or if any food specific IgE $> 95\%$ predictive decision points, regardless of symptom provocation to the relevant food.¹² Of the patients with atopic dermatitis 88 infants were evaluated for the severity of atopic dermatitis by one physician based on the scoring atopic dermatitis (SCORAD) index.

Specific IgE Test and Total IgE

Total IgE, as well as specific IgE to food allergens, were measured by using ImmunoCAP (Phadia AB, Uppsala, Sweden). We chose the most prevalent food allergens such as milk, egg, wheat, soybean, and peanut.^{9,10} Also, suspected food allergens were selected based on the parents' report.

Sensitization to food allergens was defined as at least 1 specific IgE > 0.35 kU/L.¹³ Sensitization was categorized into 3 groups based on the number of sensitized food allergens (non-sensitization, mono-sensitization, or polysensitization [≥ 2 food allergens]), and based on the degree of sensitization (undetected- [highest specific IgE level < 0.2 kU/L],¹⁴ low-level [IgE level 0.2-2 kU/L], or high-level [1 or more IgE level > 2 kU/L]).

Levels of Vitamin D

The serum 25-hydroxyvitamin D (25[OH]D) levels were measured by a chemiluminescence immunoassay Liaison (DiaSorin, Stillwater, Minnesota) with sensitivity of 4 ng/mL, linearity 150 ng/mL, and intra-assay coefficient of variation $\pm 10\%$. The participants were categorized into 3 groups by their serum 25(OH)D levels: < 20.0 ng/mL (deficiency), 20.0-29.0 ng/mL (insufficiency), and ≥ 30.0 ng/mL (sufficiency).¹⁵

Nutritional Assessment

A nutritionist evaluated the nutritional intake of 28 patients with atopic dermatitis who had removed the suspected foods from their diet. During the hospital visit, the nutrient intakes of the infants were assessed using a 24-hour recall method and a validated quantitative food frequency questionnaire by food record. This record was evaluated as the mean values of a 3-day food record using Computer Aided Nutritional Analysis Program for Professionals v 2.0 (CAN-Pro 2.0;

Korean Nutrition Society, Seoul, Korea). Based on these data, the daily intake of energy, protein, calcium, phosphorus, iron, zinc, folate, and vitamin D was estimated and compared with dietary intake file of the 8th Dietary Reference Intakes for Koreans.¹⁶

Statistical Analyses

Total and specific IgE levels and 25(OH)D levels were not normally distributed; therefore, means were compared by using the Mann-Whitney *U* test or Kruskal-Wallis 1-way ANOVA and are presented as medians with IQR, and these variables were \log_{10} -transformed before they underwent regression analysis.

Bivariate relationships between 2 variables were assessed using the Spearman rank correlation. Furthermore, post-hoc analyses (the least significant difference test) for Kruskal-Wallis rank sum test were used after transformation of the serum 25(OH)D levels into mean rank. The association between categories of vitamin D concentrations and clinical characteristics were evaluated using the χ^2 test, Fisher exact test, and Kruskal-Wallis rank sum test, as appropriate. Multivariable logistic regression was performed to estimate the factors independently related with SCORAD index. The variables were entered into the model to adjust for potential confounding variables such as age, sex, month of the test, season of birth (spring-winter/summer-fall), season of the test, weight gain ([current weight-birth weight]/age [month]), current dietary restriction (yes/no), exclusive breast-feeding during the first 3 months of life (yes/no), pet ownership, exposure to secondhand smoke, and parental history of asthma.

To demonstrate the compound relationship between the serum 25(OH)D levels, degree of sensitization, and the severity of atopic dermatitis, we used the online repository of open source software Scatterplot3d package on the R programming language (R v 3.0.1. <http://www.r-project.org/>) for the 3-dimensional plot. All statistical analyses were performed by using SPSS software (v 19 for IBM; SPSS Inc, Chicago, Illinois), and *P* values of $< .05$ were considered to be significant.

Results

The characteristics of the study population are shown in the **Table**. The prevalence of exclusively breast-fed infants until 3 and 6 months of age was 61.5% and 48.9%, respectively. The median serum 25(OH)D level was 18.1 ng/mL (IQR 4.7-28.9 ng/mL).

Factors Related with Vitamin D Levels

The serum 25(OH)D levels were lower in winter (5.3 ng/mL, IQR 4.0-20.4) and spring (17.1 ng/mL, IQR 4.0-28.9), than in summer (23.2 ng/mL, IQR 11.1-31.2) and fall (22.2 ng/mL, IQR 13.4-36.2), respectively (all $P < .001$) (**Figure 1**; available at www.jpeds.com). The infants who were born in summer and fall had higher serum 25(OH)D levels compared with those born in spring and winter ($P = .022$);

Table. Clinical characteristics of the participants (n = 226) and comparison of the subcohort of atopic dermatitis (n = 168) and those with suspected food allergy (n = 58)

Characteristics	Total (n = 226)	Atopic dermatitis (n = 168)	Suspected food allergy (n = 58)
25(OH)D*	18.1 (4.7-28.9)	18.3 (4.1-28.8)	20.0 (7.6-30.8)
Age (mo) evaluated†	8.44 (7.8-9.0)	7.96 (7.3-8.7)	9.83 (8.7-11.0)‡
Sex, male (%)	149 (65.9)	114 (67.9)	35 (60.3)
Season of birth, n (%)			
Winter-spring	95 (42.0)	63 (37.5)	32 (55.2)‡
Summer-fall	131 (58.0)	105 (62.5)	26 (44.8)‡
Birth weight (kg)†	3.36 (3.3-3.4)	3.37 (3.28-3.45)	3.33 (3.22-3.43)
Body weight (kg)†	8.93 (8.7-9.2)	8.74 (8.51-8.96)	9.50 (9.00-10.00)‡
Weight gain (kg)/mo†	0.78 (0.74-0.81)	0.80 (0.75-0.84)	0.70 (0.64-0.76)‡
Exclusively breast milk feeding >3 mo	139 (61.5)	99 (59.3)	40 (69.0)
Parental history			
Asthma (%)	8 (3.5)	6 (3.6)	2 (3.4)
Allergic rhinitis (%)	104 (46.0)	72 (42.9)	32 (55.2)
Atopic dermatitis (%)	33 (14.6)	25 (14.9)	7 (13.8)
Prematurity or LBW, n (%)	3 (1.3)	3 (1.8)	0 (0.0)
Wheezing episode, n (%)	27 (12.0)	14 (8.4)	13 (22.4)‡
Secondary smoking, n (%)	109 (48.4)	79 (47.3)	30 (51.7)
Pet in house, n (%)	8 (3.5)	7 (4.2)	1 (1.7)
Current diet restriction, n (%)	109 (48.2)	75 (44.6)	34 (58.6)
Hematologic profile*			
Eosinophils	6.0	6.3 (3.0-8.0)	5.3 (2.0-6.5)
IgE	113.4	96.6 (9.3-65.3)	160.8 (10.5-125.6)
Alkaline phosphatase	722.5	729.4 (568.0-803.0)	702.5 (542.0-867.0)
Iron	47.2	48.0 (33.0-62.0)	44.6 (25.5-62.8)

LBW, low birth weight.

Bold means $P < .05$.

Current dietary restriction was only applied to the foods that were not necessary to growth.

*Median (IQR) was expressed.

†Mean (95% CI) was expressed.

‡ $P < .05$ vs atopic dermatitis.

however, these association did not remain significant after adjusting for the season of the test ($P = .150$).

The serum 25(OH)D level showed a significant association with the amount of vitamin D intake ($r = 0.490$, $P = .008$) (Figure 2; available at www.jpeds.com) and iron intake ($r = 0.420$, $P = .026$), but not with total calorie intake or other nutritional contents (data not shown).

Vitamin D Levels and Allergen Sensitization

IgE-mediated sensitization to food allergens was detected in 130 infants; 94/168 (56.0%) in atopic dermatitis group and 36/58 (62.1%) in suspected food allergy group, respectively ($P = .417$). Egg was the most common allergen affecting 45.9% (60/130) of infants tested, followed by milk, wheat, peanut, and soybean affecting 36.8%, 19.4%, 15.6% and 12.7% of infants, respectively (Figure 3; available at www.jpeds.com).

We found a significant difference in serum 25(OH)D levels among the nonsensitization (median 26.2 ng/mL, IQR 17.8-34.2), monosensitization (median 22.7 ng/mL, IQR 8.6-30.7) and polysensitization groups (median 14.5 ng/mL, IQR 5.5-26.2, $P = .001$ vs nonsensitization group and $P = .023$ vs monosensitization group) ($P = .002$; Figure 4, A).

Furthermore, there was a significant difference in serum 25(OH)D levels in the 3 groups classified by the degree of allergen sensitization ($P = .005$). The infants in the high level sensitization group had lower serum 25(OH)D levels (median 14.5 ng/mL, IQR 5.5-28.2) than those in the low level sensitization (median 24.0 ng/mL, IQR 10.4-29.8, $P = .009$

vs high-level group) and the undetected group (median 25.7 ng/mL, IQR 18.1-33.8, $P = .005$ vs high-level group) (Figure 4, B).

Multivariate regression analyses adjusted for known risks and possible confounding factors showed that the low serum 25(OH)D level (OR 5.0, 95% CI 1.8-14.1, $P = .002$) was independently associated with an increased risk for food allergen sensitization. The low 25(OH)D levels were associated with sensitization to milk (OR 10.4, 95% CI 3.3-32.7, $P < .001$) and wheat (OR 4.2, 95% CI 1.1-15.8, $P = .034$), but not to egg, soybean, or peanut. Neither total IgE nor total eosinophils showed a significant association with serum 25(OH)D levels.

Link between the Severity of Atopic Dermatitis, Allergen Sensitization, and Vitamin D Levels

The median SCORAD index was 27.9 (IQR, 16.5-37.7). The SCORAD index was significantly correlated with the total eosinophil count ($r = 0.407$, $P < .001$). The correlation between the SCORAD index and \log_{10} transformed total IgE was of borderline significance ($r = 0.201$, $P = .053$) possibly because of fewer children for whom the SCORAD index was measured.

In the overlaying plots of 25(OH)D levels, the sensitization levels (expressed as the \log_{10} -transformed specific IgE levels) correlated with the SCORAD index ($r = 0.268$, $P = .009$), and the serum 25(OH)D levels were inversely related with the sensitization levels ($r = -0.181$, $P < .007$) and with the SCORAD index ($r = -0.196$, $P = .043$) (Figure 5).

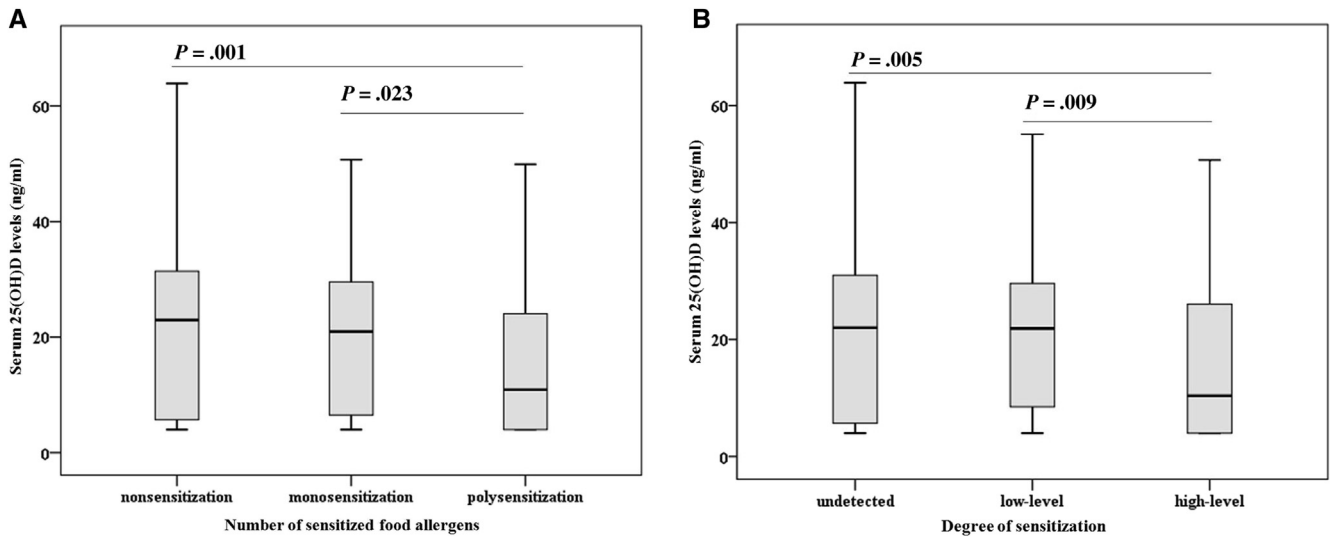


Figure 4. Serum vitamin D levels in the groups classified by **A**, the number of sensitized food allergens and **B**, the degree of sensitization. **A**, The serum 25(OH)D level was significantly lower in the polysensitization group than that in the monosensitization group and that in the nonsensitization group. **B**, The serum 25(OH)D level was significantly lower in the high-level sensitization group than that in the low-level sensitization group and that in the undetected group.

The linear regression analyses revealed that the serum 25(OH)D ($P = .031$), and the sensitization levels ($P = .008$) were independently associated with the SCORAD index (adjusted $R^2 = 0.112$).

Discussion

This study suggests that low 25(OH)D levels increase the risk of food allergen sensitization and are associated with the

severity of atopic dermatitis. The severity of atopic dermatitis was independently influenced by the serum 25(OH)D levels and by food allergen sensitization. This report indicates the relationship between the vitamin D status in infancy (not cord blood levels), the degree of sensitization, and the severity of atopic dermatitis.

In line with previous studies, the dietary vitamin D intake also was related with the serum vitamin D levels. Of note, the serum vitamin D level did not correlate with total calorie intake, suggesting that the composition, not the amount, of food is important for the vitamin D status in infants. The major source of vitamin D in infancy is a dietary supplement with vitamin D.^{5,17} This may be ascribed to the fact that infants spend greater time indoors, and parents tend to keep their children away from direct sunlight exposure,¹⁸ resulting in a low cutaneous vitamin D production.⁵ However, there was a seasonal variation in vitamin D levels in the present study, suggesting that sunlight exposure also might be related with serum vitamin D levels in infants. It is also possible that seasonal variations may present in the vitamin D concentrations in the breast milk, which can be influenced by maternal sunlight exposure.

The present study found that the 25(OH)D levels have a significant impact on allergen sensitizations in infancy and that the serum 25(OH)D levels correlate well with the number and the degree of allergen sensitization. Previous studies suggested that the cord blood vitamin D levels may predict the later development of allergen sensitization,^{13,19} whereas others did not.^{10,20,21} The cord blood vitamin D levels, which strongly correlate with maternal vitamin D levels,¹³ do not correlate with the mononuclear cells cytokines in responses to various stimuli,²² and the cord blood IgE was not a useful tool in predicting allergen sensitization at 6 months of age.²³

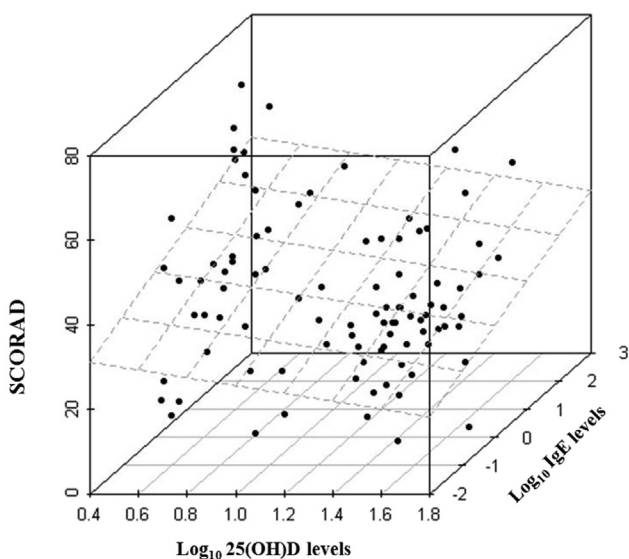


Figure 5. How the serum 25(OH)D levels and the degree of sensitization to food allergens affect the SCORAD index.

Sensitization to food allergens, as measured by specific IgE, fluctuates greatly in infancy¹⁴ and the vitamin D levels during this critical period, rather than antenatal vitamin D status, may be more directly related with the development of allergen sensitization. This interpretation is supported by the observation that infants born in the fall, whose cord blood vitamin D levels tend to be higher and experience the winter season during early infancy, have an increased risk for food allergy^{24,25} and atopic dermatitis.²⁶

There are a few previous reports focusing on the relationship between vitamin D levels and the severity of atopic dermatitis. The cord blood vitamin D levels,¹⁰ maternal vitamin D levels,²⁷ and season of birth, a surrogate marker for sunlight exposure,^{25,26} were suggested to be related with the risk of atopic dermatitis. The serum vitamin D levels inversely correlated with the severity of atopic dermatitis⁷ and eczema²⁸ in children. The present study reports on the relationship between the vitamin D status and the severity of atopic dermatitis as assessed by the SCORAD index in infants. The finding that low serum vitamin D levels are associated with higher SCORAD index corresponds well with previous studies in older children.^{7,10}

There are 2 pathophysiologic mechanisms in the development of atopic dermatitis: (1) the immunologic mechanism that modulate the regulatory T cell (Treg) capacity²⁹ and Th1/Th2 adaptive immune responses⁴; and (2) disruption of the skin barrier function that is influenced by the local antimicrobial defense mechanism, such as cathelicidin.^{10,11} It can be hypothesized that vitamin D can influence both pathways. Vitamin D seems to have a protective role against the development of IgE-mediated food allergen sensitization. The degree and prevalence of food allergen sensitization increased in infants with vitamin D deficiency in the present study. Vitamin D also is important in maintaining skin barrier function, and vitamin D deficiency can directly aggravate atopic dermatitis by impairing the local antimicrobial defense mechanism. It was reported that vitamin D deficiency is associated with decreased cathelicidin expression, an important local defense mechanism in the skin barrier.^{10,11}

Some investigators reported that serum vitamin D level is not related with the development of IgE-mediated allergic diseases such as allergic rhinitis and bronchial asthma,²⁸ suggesting that non IgE-mediated direct mechanism might be more important in the link between vitamin D deficiency and atopic dermatitis. Our results imply that a low vitamin D level may lead to a higher degree of allergen sensitization, as well as directly influencing the severity of atopic dermatitis, regardless of the degree of sensitization.

On the other hand, some researchers suggested that higher vitamin D levels could be related with the development of food allergy or atopic dermatitis. Higher maternal or cord blood vitamin D levels were related with higher risk for food allergy during the first 2 years of life.^{13,30} Higher serum 25(OH)D3 concentrations were associated with increased risk for flexural dermatitis and wheezing in children.³¹ The relationship between serum 25(OH)D and

allergic disease seems to be nonlinear. Both low and high levels of cord blood 25(OH)D were associated with increased aeroallergen sensitization in children.¹⁹ In a large British cohort, IgE concentrations were lowest in those with 25(OH)D 100-125 nmol/L,^{19,32} suggesting that both low and high levels of vitamin D can be related with the development of allergic diseases.

Vitamin D receptors are identified on almost all cells of the immune system. According to in vitro studies, vitamin D induces the development of Tregs whereas it suppresses the development of Th17 cells.³³ Vitamin D also has been reported to promote Th1 to Th2 shift by reducing the production of Th1 cells.³⁴ Taken together, it can be hypothesized that vitamin D can decrease allergic response by promoting Treg and suppressing Th17 cells, whereas high vitamin D levels may also be associated with allergic diseases by inducing allergy-associated Th2 cell proliferation.

The present study is limited by its cross-sectional design, and the vitamin D deficiency in infants with food allergen sensitization might be a consequence that is related with systemic inflammatory response,³⁵ not a cause. Although the variables related to dietary restriction were adjusted as confounding factors, there is still a possibility that restricted diet may have resulted in vitamin D deficiency.

In conclusion, our results suggest that the severity of atopic dermatitis is independently associated with the serum vitamin D status and the degree of allergen sensitization, and that low serum vitamin D levels are associated with increased food allergen sensitization. Further investigations are required to verify the possible nonlinear relationship between vitamin D status and atopic dermatitis. ■

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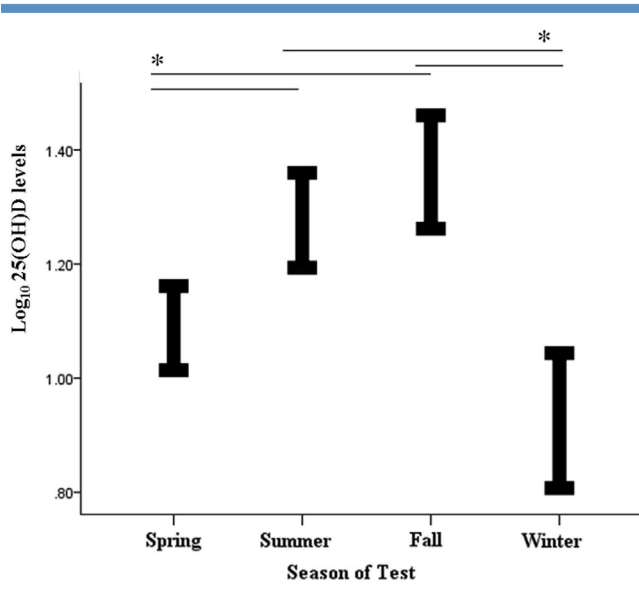


Figure 1. Comparison of the serum 25(OH)D levels according to the seasons when the test was performed. There is a difference in the serum 25(OH)D levels between spring and summer ($P = .023$) and fall ($P = .022$), and between winter and summer ($P < .001$) and fall ($P < .001$).

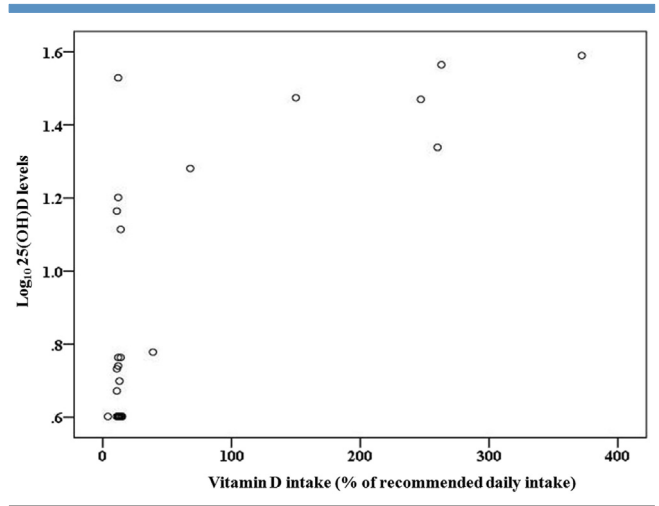


Figure 2. Correlations between the log₁₀-transformed 25(OH)D levels and the vitamin D intake. The X axis shows the amount of vitamin D intake expressed as a percentage of vitamin D recommended by the Korean Nutrition Society. The vitamin D intake correlated with the serum 25(OH)D levels ($r = 0.490$, $P = .008$).

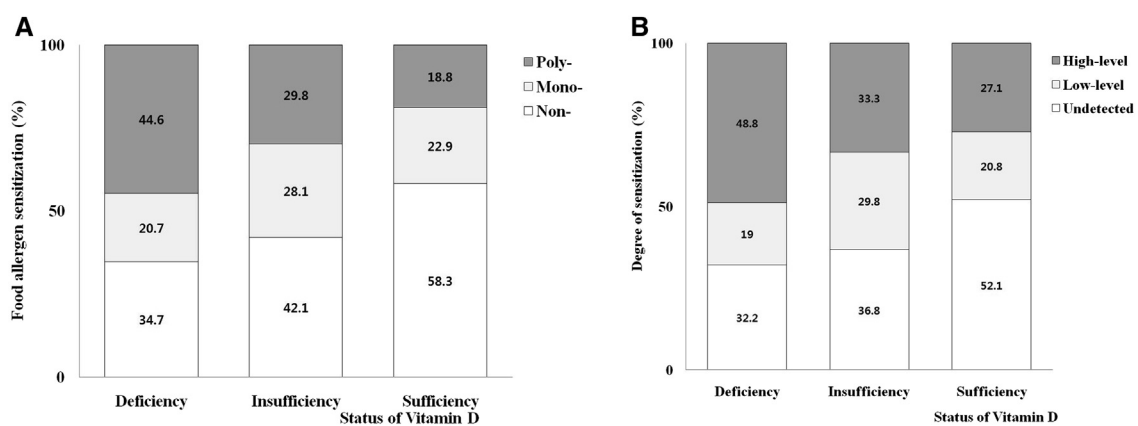


Figure 3. Comparison of **A**, the food allergen sensitization and of **B**, the degree of sensitization.