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Original article

Exposure amount and timing of solar irradiation during pregnancy and the risk of sensitization in children

Hyun Yong Koh^a, Eunhae Cho^a, So-Yeon Lee^b, Woo Kyung Kim^c, Yong Mean Park^d, Jihyun Kim^{e,f}, Kangmo Ahn^{e,f}, Seung Won Lee^a, Mi Ae Kim^g, Myung-Il Hahm^h, Yoomi Chaeⁱ, Kee-Jae Lee^j, Ho-Jang Kwon^k, Man Yong Han^{l,*}

^a CHA University School of Medicine, Seongnam, South Korea^b Department of Pediatrics, Childhood Asthma Atopy Center, Environmental Health Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea^c Department of Pediatrics, Inje University College of Medicine, Seoul, South Korea^d Department of Pediatrics, Konkuk University Hospital, Konkuk University School of Medicine, Seoul, South Korea^e Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea^f Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, South Korea^g Department of Medicine, CHA University School of Medicine, Seongnam, South Korea^h Department of Health Administration and Management, College of Medical Science, Soonchunhyang University, Asan, South Koreaⁱ Department of Medical Education, Dankook University College of Medicine, Cheonan, South Korea^j Department of Information and Statistics, Korea National Open University, Seoul, South Korea^k Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, South Korea^l Department of Pediatrics, CHA University School of Medicine, Seongnam, South Korea

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25(OH)D3 25-hydroxyvitamin D

ISAAC the International Study of Asthma

and Allergies in Childhood

aORs Adjusted odds ratios

DLNM distributed lag non-linear models

ABSTRACT

Background: Solar irradiation affects sensitization to aeroallergens and the prevalence of allergic diseases. Little is known, however, about how the time and amount of solar irradiation during pregnancy affects such risks in children. We aimed to find out how solar irradiation during pregnancy affects sensitization to aero-allergens and the prevalence of allergic diseases in children.

Methods: This population-based cross-sectional study involved 7301 aged 6 years and aged 12 years children. Maternal exposure to solar irradiation during pregnancy was evaluated using data from weather stations closest to each child's birthplace. Monthly average solar irradiation during the second and third trimesters was calculated with rank by quartiles. Risks of allergic sensitization and allergic disease were estimated.

Results: Relative to the first (lowest) quartile, the adjusted odds ratio (aOR) for allergic sensitization in the fourth (highest) quartile was lowest within solar irradiation during pregnancy months 5–6 (aOR = 0.823, 95% CI 0.720–0.942, $p < 0.05$). During months 9–10, the aOR for allergic sensitization for the fourth was higher than the first quartile of solar irradiation (aOR = 1.167, 95% CI 1.022–1.333, $p < 0.05$). Similar results were observed when solar irradiation was analyzed as a continuous variable during months 5 (aOR = 0.975, 95% CI 0.962–0.989, $p < 0.001$) and month 9 (aOR = 1.018, 95% CI 1.004–1.031, $p = 0.003$). Increased solar irradiation during months 7–8 increased the risk of asthma (aOR = 1.309, 95% CI 1.024–1.674, $p = 0.032$).

Conclusions: Maternal exposure to solar irradiation during the second trimester of pregnancy associated with reduced aeroallergen sensitization, whereas solar irradiation during the third trimester was related to increased sensitization to aeroallergens.

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Introduction

Atopic sensitization to aeroallergens and food allergens can result in the development of asthma,¹ allergic rhinitis² and food hypersensitivity³ in children. Such atopic sensitization and allergic

* Corresponding author. Department of Pediatrics, CHA University School of Medicine, 351 Yatap-dong, Bundang-gu, Seongnam, Gyeonggi-do 463-712, South Korea.

E-mail address: drmesh@gmail.com (M.Y. Han).

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disease result from the combined interactions of genetic and environmental factors. Gestational environment *in utero* during fetal organogenesis^{4,5} may influence the development of immunomodulating diseases, such as multiple sclerosis, type I diabetes and rheumatoid arthritis.⁶ Similarly, allergic diseases^{4,7} and sensitization are programmed *in utero* and these are affected by fetus size, maternal exposure to allergens and smoking, as well as by maternal nutrition and vitamin D status.^{5,8} Postnatal solar irradiation can affect allergic sensitization,⁹ asthma and anaphylaxis,¹⁰ but there has been little to no research into temporal relationship between prenatal solar irradiation and the incidence of child's allergic sensitization or allergic disease afterbirth. Because immune response and epigenetic mechanism involved in allergic sensitization starts from early perinatal period as in developmental origins of health and disease (DOHaD) theory,¹¹ the solar irradiation controlled by maternal behavior which affects to environment *in utero* might have an influence to postnatal allergic sensitization susceptibility. In this instance, the fact that allergic disease susceptibility affected by gestational period should be helpful to plan the antepartum care.

The relationship between vitamin D levels during pregnancy and the risk of sensitization to foods and aero-allergens remains unclear. Lower 25(OH)D3 (25-hydroxyvitamin D) levels in cord blood have been associated with a higher risk of sensitization to foods and aero-allergens,^{12–15} whereas other studies have failed to observe these correlations.^{8,16–21} These discrepancies may be due to the biphasic effect of cord blood vitamin D levels on serum IgE concentrations²² and to differences in genetic backgrounds of the participants.^{14,23} Vitamin D concentrations at different time points during pregnancy may differ in their effects on allergic sensitization, as both the first fetal reactions to allergen exposure and T cell maturation occur during the second trimester.^{4,24}

Exposure to sunlight exposure, not dietary vitamin D, is the major contributor to changes in 25(OH)D levels,^{17,18,25,26} which in turn is associated with allergen sensitization. This study was therefore designed to investigate the relationship between the timing and amount of solar irradiation during pregnancy and the offsprings' sensitization to aeroallergens and development of allergic diseases.

Methods

Subjects

This cross-sectional study in Korean assessing the prevalence of allergic diseases among school aged children in 2010 involved 4003 subjects born in 2002–2003 (aged 6 years) and 4112 subjects born in 1997–1998 (aged 12 years) in 40 schools in 30 representative cities of Korea.²⁷ Participants were selected by a stratified, multiple-staged and countrywide probability sampling. The inclusion criteria were children born in 2002–2003 and born in 1997–1998 who were in school and completely replied to the questionnaire and allergic skin test. To remove selection bias, the number of students were enrolled in proportion to the population density of city where school was located on. Of the 7714 children who completed both the skin test and the questionnaire, 7301 were selected, 3613 children born in 2002–2003 and 3688 children born in 1997–1998. 413 children who had a disagreement or turned examination down were excluded. All of the children underwent skin tests for 18 types of aero-allergens and their parents completed questionnaires on basic demographic information and risk factors associated with allergic diseases.²⁸ The study design and protocol were approved by a Dankook University in Cheonan institutional review board (IRB approval number: DKUH IRB 2010-09-0260), and all participants provided a written consent.

Questionnaire

Parents completed standardized questionnaires that contained the International Study of Asthma and Allergies in Childhood (ISAAC) core health questions,²⁷ in addition to 27 items regarding general information, 29 items regarding living space and habits and 5 items assessing pre- and post-pregnancy socio-economic status, as well as current socio-economic status. For assessing allergic rhinoconjunctivitis, asthma and eczema with ISSAC questionnaire, we defined symptoms suggestive of allergic diseases as follows: those who had experienced itchy eczema episodes, or a problem with nasal symptoms or wheezing unrelated to a cold within 12 months of the survey.²⁷

Solar irradiation and other climate information

Data on solar irradiation (MJ/m²) and other climate information (temperature and humidity) in Korea, measured at 22 weather stations in April 2002–December 2003 and April 1997–December 1998, were obtained from the data archives of the Korea Meteorological Agency. The intensity of ultraviolet-B radiation was measured as minimal erythral doses every 10 min using UV-biometers (Solar light, USA), with the highest intensity of each day regarded as the daily intensity. Monthly intensity was calculated as the average of the highest daily intensities. All participants were matched to one of the 22 weather stations closest to their place of birth. Daily levels of solar irradiation measured at the nearest weather station were approximated to solar irradiation exposure throughout the whole pregnancy period.

Skin prick test and total IgE measurement for allergic sensitization

All subjects were tested for atopic sensitization to 18 aero-allergens, i.e. *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), *Tyrophagus putrescentiae* (Tyr p), cockroach, cat, dog, alder, birch, oak, Japanese cedar, orchard grass, bermuda grass, timothy, mugwort, ragweed, Japanese hop, alternaria, and *Aspergillus fumigatus* (Allergopharma, Reinbeck Germany). Details on the skin test protocol have been described previously.²⁸ In the skin prick test (SPT), a test was regarded as positive if a wheal was ≥ 3 mm and controls showed adequate reactions. Non sensitization was defined participant who has no any reaction in SPT about all aeroallergen types. Mono- and polysensitization were single and multiple sensitization to aero-allergen panels, respectively. The amount of total IgE was measured using patient's serum by the IgE ImmunoCAP. High value of total IgE was defined if it was ≥ 100 .²⁷

Potential confounding factors

Potential confounding factors on univariate analysis included factors with a known risk for sensitization and those showing statistically significant differences. Factors associated with environment during pregnancy and infancy included maternal smoking during pregnancy, pets in the household before age 1 year, breast feeding history, number of siblings, remodeling or moving to a new house within 1 year, and age at first presentation to a childcare center. Factors associated with current status included monthly income, exposure to second-hand cigarette smoking, location of living space within a building, terms of the building, presence of a fabric sofa, and purchase of new furniture within 1 year. Other potential confounders of outcome included gender, Z scores of current BMI calculated for the Korean population,²⁹ and birth weight.

Statistical analysis

Continuous variables were compared using ANOVA, with Tukey–Kramer adjustments for multiple comparisons. Categorical variables were compared using χ^2 -tests, with Bonferroni corrections for multiple testing. Multivariable logistic regression analysis was used to examine the risk of sensitization phenotype, current allergic disease, total IgE level and total eosinophil count after adjusting for other significant risk factors including gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. Adjusted odds ratios (aORs) for sensitization relative to monthly, bimonthly and trimester exposure to solar irradiation were calculated using logistic regression. All the above statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA).

Risks of sensitization to aeroallergens during the second and third trimesters were calculated using the R package of distributed lag non-linear models (DLNM), version 2.0.6. DLNM was used to explore the non-linear and delayed effects of solar irradiation expressed as lag days, simultaneously. The model using these variables can be described by the equation, $E(Y_t) = s(SS, df, lag, df) + \varepsilon$, where the subscript t denotes the time (month) of observation; $E(Y_t)$ denotes the expected sensitization to allergen on month t ; ε is the error term; s denotes the natural cubic spline regression function for non-linear solar irradiation³⁰; and df , or degrees of freedom, set as 2, was used to assess non-linear effects and the effect of lag time on solar irradiation. In all statistical analyses, a p value < 0.05 was considered statistically significant.

Results

Demographic characteristics and exposure to solar irradiation

The average age of children born in 1997–1998 was 12-year-old (SD, 0.31 years) and that of children born in 2002–2003 was 6-year-old (SD, 0.28 years). Therefore, we described the group of children born in 1997–1998 as group aged 12 years and that of children born in 2002–2003 as group aged 6 years. The daily median amount of solar irradiation during the last 6 months of pregnancy among all women was 12.44 MJ/m². Table 1 shows the characteristics of the study population stratified into four quartiles based on exposure to solar irradiation during one month before birth. Solar irradiation varied significantly according to season of birth ($p < 0.001$), and year of birth ($p < 0.001$). Allergic morbidity, family history and other conditions of the two groups of samples at the time of the study are shown in Table 2.

Aeroallergen sensitization and solar irradiation

To assess which gestational month's solar irradiation exposure influences prevalence of aeroallergen sensitization, each monthly aOR was calculated after adjusting for confounding factors (Fig. 1). As solar irradiation increased, risk of sensitization to aeroallergens during the fifth month of pregnancy decreased (aOR = 0.975, 95% CI 0.962–0.989, $p < 0.001$), but gradually increased during the tenth month of pregnancy, which is the period for delivery (aOR = 1.017, 95% CI 1.003–1.030, $p = 0.014$). Although the aOR was statistically significant at the end of the first trimester during the fourth month

Table 1

The characteristics of the study population stratified by the quartile of maternal exposure to solar irradiation.

Offspring characters	Overall [‡]	The estimated amount of maternal solar irradiation at birth [†]				P value*
		<25 Quartile <9.70 MJ/m ²	25–50 Quartile 9.70–12.65 MJ/m ²	50–75 Quartile 12.66–14.95 MJ/m ²	>75 Quartile ≥14.96 MJ/m ²	
Average SI (MJ/m ²)						<0.001
Aged 6 years	3,613	3.58	9.12	14.39	21.37	
Aged 12 years	3,688	3.99	9.67	14.96	21.56	
Gender						0.257
Male	3,638 (49.8)	943 (25.9)	884 (24.3)	911 (25.0)	900 (24.7)	
Female	3,663 (50.2)	879 (24.0)	943 (25.7)	914 (25.0)	927 (25.3)	
Season of birth						<0.001
Spring	1,946 (26.7)	394 (20.2)	222 (11.4)	451 (23.2)	879 (45.2)	
Summer	1,738 (23.8)	305 (17.5)	303 (17.4)	368 (21.2)	762 (43.8)	
Fall	1,777 (24.3)	406 (22.8)	499 (28.1)	695 (39.1)	177 (10.0)	
Winter	1,840 (25.2)	717 (39.0)	803 (43.6)	311 (16.9)	9 (0.5)	
Siblings [§]						0.587
0	4,195 (57.5)	1,050 (25.0)	1,081 (25.8)	1,020 (24.3)	1,044 (24.9)	
1	2,136 (29.3)	525 (24.6)	517 (24.2)	559 (26.2)	535 (25.0)	
≥2	970 (13.3)	247 (25.5)	229 (23.6)	246 (25.4)	248 (25.6)	
Birth weight						0.513
<3.0 kg	2,315 (32.0)	588 (25.4)	578 (25.0)	573 (24.8)	576 (24.9)	
3 ~ 4 kg	4,663 (64.5)	1,156 (24.8)	1,172 (25.1)	1,163 (24.9)	1,172 (25.1)	
≥4.0 kg	254 (3.5)	58 (22.8)	55 (21.7)	78 (30.7)	63 (24.8)	
Smoking						
During pregnancy	33 (0.6)	9 (27.3)	8 (24.2)	7 (21.2)	9 (27.3)	0.954
<1 year afterbirth	33 (0.6)	8 (24.2)	8 (24.2)	6 (18.2)	11 (33.3)	0.676
Income						0.641
<\$2,897	2,571 (36.0)	632 (24.6)	637 (24.8)	666 (25.9)	636 (24.7)	
\$2,897 ~ \$4,834	2,973 (41.7)	743 (25.0)	775 (26.1)	723 (24.3)	732 (24.6)	
\$4,835	1,588 (22.3)	396 (24.9)	382 (24.1)	397 (25.0)	413 (26.0)	
Pet [§]	387 (5.4)	92 (5.1)	90 (23.3)	91 (23.5)	114 (29.5)	0.232

SI, solar irradiation.

*P values were calculated using the χ^2 test for categorical variables, with a significant difference defined as a P value less than 0.05.

[†] Birth cohorts divided by the quartiles of maternal exposure to sunshine during the last month of pregnancy.

[‡] Values are numbers (percentages).

[§] Siblings: the number of children aged ≤17 years who lived with a child in the same house during the first year of infancy. Pet: the presence of a pet in the household during pregnancy or the first year of life.

Table 2

The characteristics of allergic disease and sensitization test features of children in both groups.

Features	Aged 12 years (n = 3,688)	Aged 6 years (n = 3,613)	P value
Allergic disease features			
Allergic rhinoconjunctivitis (%)	695 (19.4)	632 (18.0)	0.118
Asthma (%)	298 (8.2)	350 (9.7)	0.024
Eczema (%)	471 (13.0)	743 (20.6)	<0.001
Family history			
Parental asthma (%)	128 (3.5)	166 (4.6)	0.015
Parental allergic rhinitis (%)	1,109 (39.9)	1,667 (46.1)	<0.001
Parental atopic eczema (%)	212 (6.7)	354 (10.9)	<0.001
Skin test			
Nonsensitization (%)	1,698 (46.0)	2,140 (59.2)	<0.001
Mono-sensitization (%)	1,061 (28.8)	981 (27.2)	
Poly-sensitization (%)	929 (25.2)	492 (13.6)	
IgE (IU/ml)			
Log IgE level (SD)	0.67 (0.01)	0.69 (0.01)	0.018
% Total IgE ≥ 100	1,794 (49.3)	1,664 (47.1)	0.064
Eosinophil count in blood			
Eosinophil % (SD)	3.20 (0.04)	4.07 (0.06)	<0.001
% TEC > 4%	825 (22.7)	1,089 (30.9)	<0.001
Obesity			
BMI z score	−0.12 (0.02)	−0.16 (0.02)	<0.001
Number of obese patients	83 (2.4)	101 (3.5)	0.008

SD, standard deviation; TEC, total eosinophil count; BMI, body mass index.

Asthma: 'yes' response to the question: "In the past 12 months, has your child experienced wheezing or whistling in the chest?"

Allergic rhinoconjunctivitis: 'yes' response to the question: "In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?"

Eczema: 'yes' response to the question: "In the past 12 months, has your child had an itchy rash?"

of pregnancy (aOR = 0.979, 95% CI 0.966–0.994, $p = 0.001$), it had no significance much earlier months (Fig. 1). The lowest aOR was reported in the fifth month of pregnancy (aOR = 0.975, 95% CI 0.962–0.989, $p = 0.001$).

Bimonthly analysis showed that in comparison to the first (lowest) quartile of exposure to solar irradiation, the aOR of sensitization to aeroallergens in the fourth (highest) quartile was 0.823 (95% CI 0.720–0.942, $p = 0.005$) during months 5–6 of pregnancy. In contrast, aOR for the fourth quartile to the first quartile of solar

irradiation was high during months 9–10 (aOR = 1.167, 95% CI 1.022–1.333, $p = 0.023$) (Table 3).

In the analysis of multiple sensitization, the results were similar to previous skin sensitization, but it remarkably appeared in 6-year-old children (Fig. 2). In the 6-year-old subjects, the lowest aOR in both mono and poly sensitizations appeared in the fifth trimester of pregnancy (for monosensitization, aOR = 0.952, 95% CI 0.927–0.978, $p < 0.001$; for polysensitization, aOR = 0.933, 95% CI 0.901–0.967, $p < 0.001$). In the case of polysensitization, the aOR was gradually increased from this point, indicating a high aOR at 9 months of gestation (aOR = 1.037, 95% CI 1.004–1.072, $p = 0.028$). However, there was no statistical significance in the 12-year-old children, only the tendency.

Analysis of the lag influence of solar irradiation on relative risk of allergic sensitization is shown in Figure 3. Use of DLNM showed that exposure to a lower level of solar irradiation, less than 12.44 MJ/m², during the fifth month of pregnancy significantly increased the risk for allergic sensitization in subjects aged 6 years, but not in those aged 12 years.

Relationships between exposure to solar irradiation during pregnancy with TEC and total IgE

Increased exposure to solar irradiation during months 5–6 of pregnancy was associated with a lower concentration of total IgE (aOR = 0.980, 95% CI 0.966–0.995, $p = 0.010$). In subjects aged 6 years, increased exposure to solar irradiation during months 5–6 of pregnancy was associated with lower TEC (aOR = 0.954, 95% CI 0.927–0.981, $p = 0.001$), whereas increased exposure to solar irradiation during months 9–10 was associated with higher TEC (aOR = 1.044, 95% CI 1.017–1.072, $p = 0.002$) (Table 4). However, for aged 12 years' children, solar irradiation had no significance in both TEC and total IgE count.

Links to allergic diseases

During 7–8 months of pregnancy, we found that the risk for asthma was significantly higher (aOR = 1.309, 95% CI 1.024–1.674, $p = 0.032$) for those in the highest to the lowest quartile of solar irradiation, with similar results observed when solar irradiation

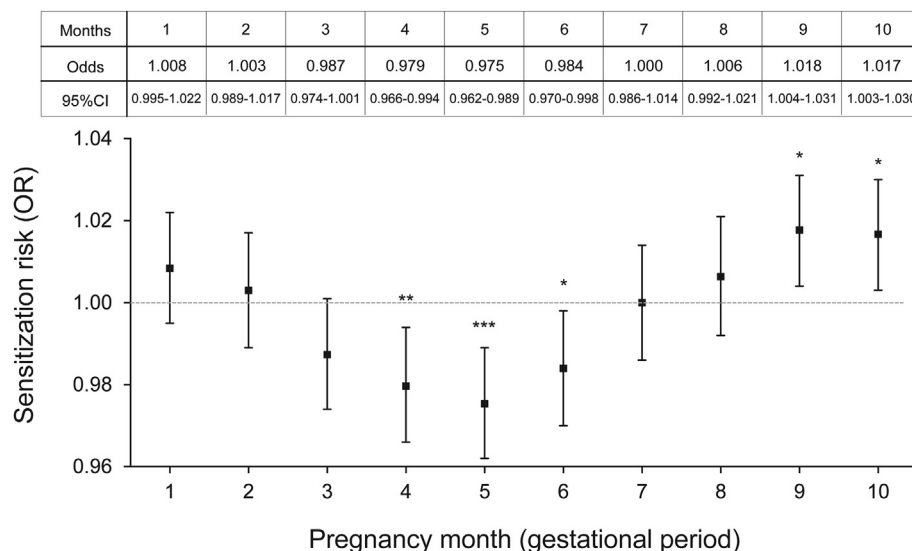


Fig. 1. Odd ratios of allergic sensitization in children aged 6 years and 12 years according to months of pregnancy and adjusting for confounding variables. Solar irradiation during the second trimester associated with reduced sensitization, whereas solar irradiation during the third trimester related to the high risk of sensitization. The adjusting factors include the following gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 3

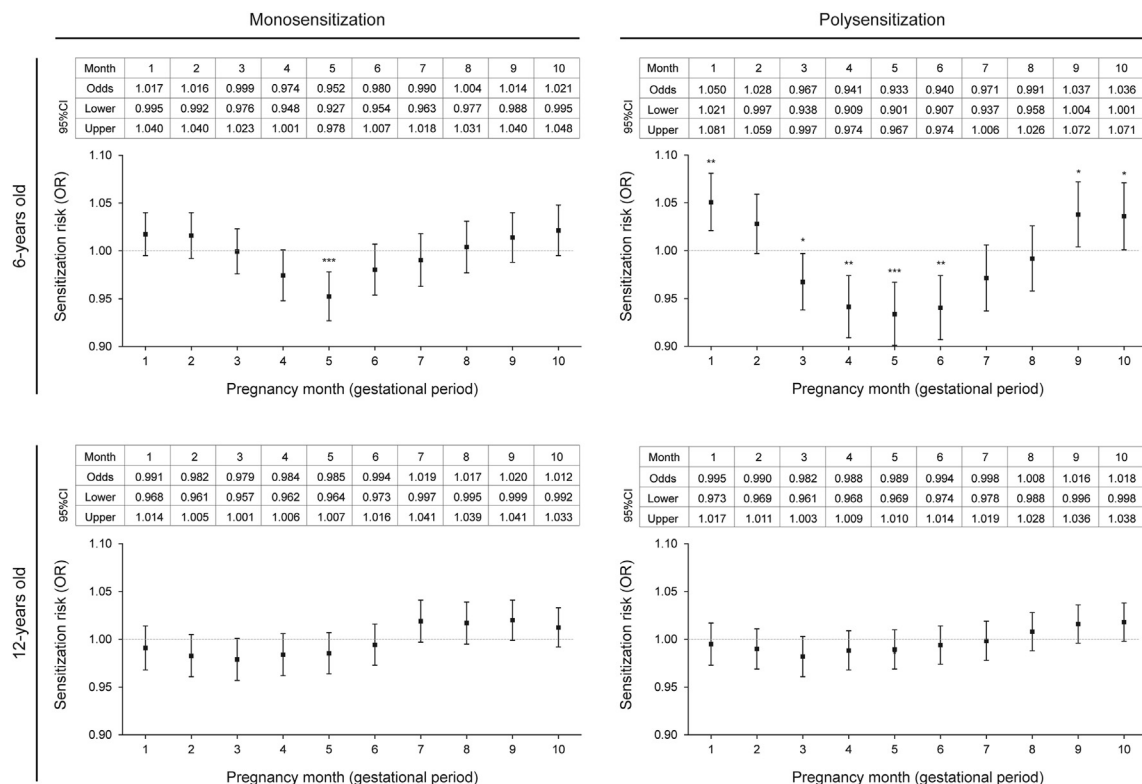
The multivariable logistic regression analysis of bimonthly solar irradiation during the pregnancy as a predictor of aeroallergen sensitization in offspring.

SI (MJ/m ²)	5–6 months of pregnancy			7–8 months of pregnancy			9–10 months of pregnancy		
	aOR	95% CI	P value	aOR	95% CI	P value	aOR	95% CI	P value
<9.70	1 (ref)			1 (ref)			1 (ref)		
9.70–12.64	0.994	0.867–1.140	0.936	1.056	0.779–1.432	0.555	1.006	0.877–1.154	0.937
12.65–14.95	0.831	0.730–0.946	0.005	0.933	0.820–1.062	0.293	1.074	0.946–1.220	0.272
≥14.96	0.823	0.720–0.942	0.005	1.011	0.884–1.157	0.872	1.167	1.022–1.333	0.023
			0.002*			0.395*			0.091*
	0.972	0.958–0.985	<0.001**	0.999	0.985–1.013	0.850**	1.020	1.007–1.034	0.003**

SI, solar irradiation; aOR, adjusted odds ratio; CI, confidential interval.

*P value for the crossover analysis of solar irradiation quartiles set during each bimonthly period.

**P value for the effect of amount of each exposure to solar irradiation as a continuous variable on aeroallergen sensitization within each bimonthly period, after adjustment for potential confounding factors to analyze in solar irradiation quartiles in each bimonthly period. The adjusting factors include the following gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. The figures in bold indicate P value <0.05.

**Fig. 2.** Odd ratios of allergic mono- or poly-sensitization in children aged 6 years and 12 years according to months of pregnancy and adjusting for confounding variables. The adjusting factors include the following gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

was analyzed as a continuous variable (aOR = 1.032, 95% CI 1.004–1.060, $p = 0.023$). Significant relationship between solar irradiation level and asthma risk was only found in aged 6 years children (for highest solar irradiation quartile, aOR = 1.609, 95% CI, 1.089–2.376, $p = 0.017$; for continuous variable analysis, aOR = 1.076, 95% CI, 1.030–1.125, $p = 0.001$), but not in aged 12 years children (for highest solar irradiation quartile, $p = 0.240$) (Table 5).

Discussion

We found that greater exposure to solar irradiation during months 5–6 of pregnancy was associated with the protection offspring against sensitization to aeroallergens, whereas solar irradiation during months 9–10 was inversely related to aeroallergen sensitization. These outcomes remained strong even when

birth season was included as a confounding factor, and were more apparent in subjects aged 6 years than 12 years children. Similar patterns were observed between sensitization risk and total eosinophil count and IgE. Current asthma, but not allergic rhinitis or atopic eczema, in school-aged children showed a correlation with solar irradiation during pregnancy. Taken together, these findings indicate that the timing and the amount of exposure to solar irradiation during pregnancy affected sensitization to aeroallergens and asthma morbidity at school age.

Several studies have analyzed the relationship between vitamin D concentration and sensitization, but most of these studies were performed using cord blood samples,^{12,13,17,18,20–22} or were limited to the third trimester of pregnancy.^{8,15,19} As the half-life of vitamin D in the body is about 8 weeks,³¹ assays of cord blood samples can determine only the effects of solar irradiation during the third trimester on vitamin D levels. Neonate born from healthy pregnant

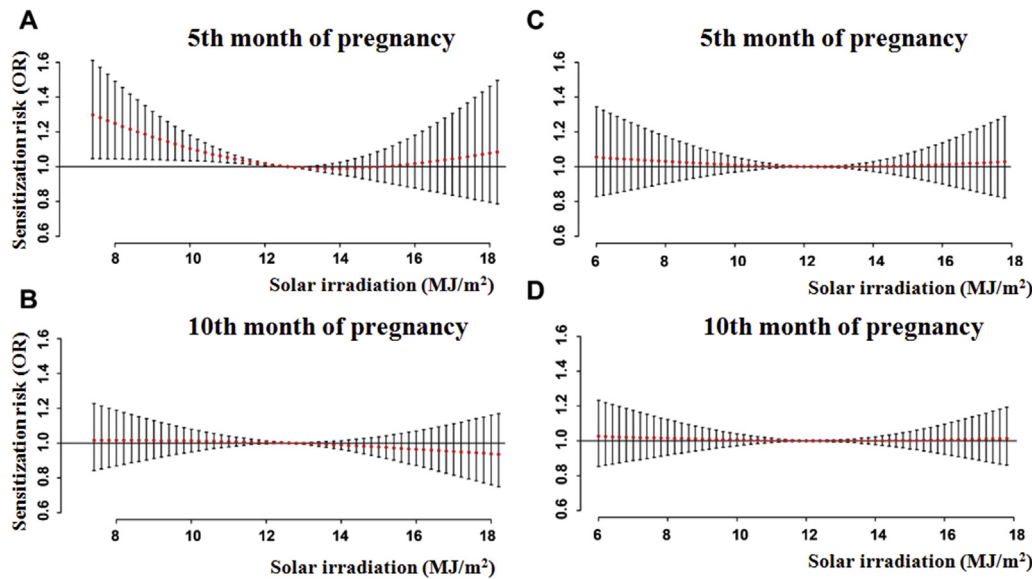


Fig. 3. Odds ratio of allergic sensitization according to solar irradiation during the fifth (A, C) and tenth (B, D) month of pregnancy in children aged 6 years (A, B) and 12 years (C, D). The odds ratio of allergic sensitization increased as solar irradiation decreased during the fifth month of pregnancy in both sets of subjects. This was statistically significant only in aged 6 years children. Solar irradiation during the tenth month of pregnancy did not significantly affect allergic sensitization in either cohort.

Table 4

The multivariable regression analysis of bimonthly solar irradiation during pregnancy as a predictor of total eosinophil counts and total IgE concentration in offspring.

SI	5–6 months of pregnancy			7–8 months of pregnancy			9–10 months of pregnancy		
	aOR	95% CI	P value	aOR	95% CI	P value	aOR	95% CI	P value
TEC > 4%	0.986	0.969–1.003	0.112*	0.997	0.980–1.014	0.724*	1.010	0.994–1.027	0.216*
(Aged 6 years)	0.954	0.927–0.981	0.001	1.003	0.975–1.031	0.838	1.044	1.017–1.072	0.002
(Aged 12 years)	1.011	0.989–1.034	0.328	1.004	0.982–1.026	0.736	0.995	0.974–1.016	0.645
Total IgE >100	0.980	0.966–0.995	0.010*	0.988	0.973–1.002	0.099*	0.994	0.980–1.008	0.433*
(Aged 6 years)	0.963	0.939–0.989	0.005	1.003	0.997–1.029	0.838	1.012	0.988–1.037	0.323
(Aged 12 years)	0.991	0.973–1.010	0.365	0.984	0.966–1.003	0.992	0.987	0.970–1.004	0.137

SI, solar irradiation; TEC, total eosinophil count; aOR, adjusted odds ratio; CI, confidential interval.

Blood eosinophil count and total IgE levels were logarithmically transformed.

*P value for the logistic regression analysis of the effect of amount of solar irradiation on outcomes.

**P value for the linear regression models of each exposure to solar irradiation and outcomes within each bimonthly period, after adjustment for potential confounding factors to analyze solar irradiation quartiles in each bimonthly period. The adjusting factors include the following gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. The figures in bold indicate P value <0.05.

women could be depleted of vitamin D by the age of 2 months.³² This is reasonably supported by a previous study that investigated influence of UVB during gestation on offspring's health.⁶ In addition, we showed that increased exposure to solar irradiation towards the second trimester associated with reduced the risk of sensitization, decreasing in magnitude as children was older.

Interestingly, this study showed that the quantity of solar irradiation has different associations during each gestational period.⁶ The amount of solar irradiation during the second trimester, which is the period of immunological development *in utero*, has been shown to affect sensitization to aeroallergens.³³ Indeed, the second trimester of pregnancy is believed to be critical for immune modulation and aero-allergen sensitization. T cell priming to allergens²⁴ and the production of IgE antibodies occur during the second trimester,^{4,33} and various immune-mediated diseases that occur in offspring later in life are influenced by exposure of the mother to solar irradiation during the second trimester.⁶ This may be due to Th2 skewing, in that vitamin D deficiency may reduce the function of regulatory T cells even in school-aged children.^{23,34} The fact that the total IgE and the total eosinophil count increased during month 5–6 of pregnancy in the aged 6 years and total IgE

increased when solar irradiation decreased in the aged 12 years children is consistent with the immunological basis behind solar irradiation during 5–6 months of pregnancy.³⁵

Although a causal relationship has not been clarified, sunlight might affect allergic sensitization by various mechanisms, such as melatonin,³⁶ nitric oxide³⁷ or season behavior change. Even these previous studies, however, have lacked intensive and well-constructed methods of measuring vitamin D level in each gestational point³⁵ and the amount of exposure in UVA and UVB,⁶ leaving the detailed mechanism to be further investigated. While our study is logically based on characteristics and physiology of vitamin D, the lack of quantitative measurement of vitamin D remains one of our limitations.

Clinical application of the results will be challenging. Although there have been no well-controlled studies to date on the vitamin D status of pregnant Korean women, 80% of Asian women of child-bearing age have been reported to be vitamin D-deficient.³⁸ Moreover, exposure to solar irradiation cannot be equated with vitamin D level, since exposure is dependent on location, season, time of day, and weather conditions. Phenotypic presentation of atopic sensitization is heterogeneous and can be initiated as

The characteristics of the study population stratified for exposure to solar irradiation at birth.

Group	Amount of SI at birth (MJ/m ²)	5–6 months of pregnancy adjusted OR (95% CI)	P value	7–8 months of pregnancy adjusted OR (95% CI)	P value	9–10 months of pregnancy adjusted OR (95% CI)	P value	
Asthma within one year								
Whole	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.116 (0.859–1.449)	0.412	0.849 (0.651–1.107)	0.227	1.151 (0.886–1.496)	0.291	
	3rd quartile (12.65–14.95)	0.960 (0.747–1.234)	0.752	0.973 (0.760–1.245)	0.827	1.291 (1.013–1.644)	0.039	
	4th quartile (≥14.96)	1.268 (0.989–1.627)	0.062	1.309 (1.024–1.674)	0.032	1.046 (0.806–1.357)	0.736	
			0.116*		0.009*		0.165*	
Aged 6 years		1.014 (0.987–1.042)	0.301**	1.032 (1.004–1.060)	0.023**	1.016 (0.990–1.042)	0.226**	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.009 (0.69–1.475)	0.963	0.895 (0.612–1.31)	0.568	1.187 (0.816–1.727)	0.371	
	3rd quartile (12.65–14.95)	1.012 (0.704–1.455)	0.950	1.202 (0.841–1.717)	0.312	1.363 (0.958–1.939)	0.085	
	4th quartile (≥14.96)	1.577 (1.066–2.332)	0.023	1.609 (1.089–2.376)	0.017	1.316 (0.881–1.967)	0.180	
Aged 12 years			0.042		0.015		0.351	
		1.032 (0.988–1.078)	0.158	1.076 (1.030–1.125)	0.001	1.039 (0.997–1.084)	0.069	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.292 (0.888–1.879)	0.857	0.738 (0.494–1.103)	0.139	1.225 (0.84–1.785)	0.291	
	3rd quartile (12.65–14.95)	0.947 (0.667–1.345)	0.235	0.815 (0.577–1.152)	0.247	1.177 (0.836–1.656)	0.351	
	4th quartile (≥14.96)	1.031 (0.737–1.444)	0.630	1.038 (0.750–1.436)	0.823	0.890 (0.625–1.266)	0.516	
			0.426		0.240		0.276	
		0.995 (0.961–1.03)	0.768	0.999 (0.965–1.033)	0.940	1.000 (0.968–1.032)	0.984	
	Allergic rhinoconjunctivitis within one year							
	Whole	1st quartile (<9.69)	1		1		1	
2nd quartile (9.70–12.64)		1.113 (0.917–1.350)	0.278	0.932 (0.769–1.129)	0.469	0.888 (0.733–1.077)	0.228	
3rd quartile (12.65–14.95)		1.098 (0.917–1.314)	0.311	1.049 (0.877–1.255)	0.601	0.966 (0.810–1.153)	0.704	
4th quartile (≥14.96)		0.978 (0.809–1.183)	0.818	0.966 (0.799–1.167)	0.721	0.847 (0.703–1.020)	0.080	
			0.451*		0.629*		0.280*	
Aged 6 years		0.999 (0.980–1.019)	0.929**	1.001 (0.981–1.020)	0.960**	0.987 (0.969–1.005)	0.165**	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.016 (0.813–1.269)	0.892	1.054 (0.849–1.308)	0.636	1.173 (0.922–1.493)	0.194	
	3rd quartile (12.65–14.95)	1.096 (0.885–1.356)	0.400	1.223 (0.989–1.512)	0.063	1.027 (0.809–1.305)	0.825	
	4th quartile (≥14.96)	1.135 (0.884–1.459)	0.320	1.024 (0.797–1.314)	0.855	1.123 (0.892–1.414)	0.324	
Aged 12 years			0.670		0.222		0.483	
		1.015 (0.988–1.042)	0.282	1.012 (0.985–1.039)	0.379	0.989 (0.964–1.014)	0.386	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.078 (0.868–1.34)	0.495	0.952 (0.766–1.184)	0.660	0.994 (0.823–1.2)	0.949	
	3rd quartile (12.65–14.95)	0.996 (0.822–1.206)	0.965	1.022 (0.843–1.24)	0.823	1.013 (0.818–1.255)	0.905	
	4th quartile (≥14.96)	0.96 (0.796–1.158)	0.670	0.996 (0.824–1.204)	0.967	0.917 (0.759–1.107)	0.365	
			0.774		0.937		0.756	
		0.996 (0.977–1.016)	0.707	1.002 (0.983–1.021)	0.857	0.997 (0.979–1.015)	0.753	
	Atopic eczema within one year							
	Whole	1st quartile (<9.69)	1		1		1	
2nd quartile (9.70–12.64)		1.015 (0.828–1.244)	0.888	0.940 (0.769–1.148)	0.542	0.838 (0.686–1.024)	0.084	
3rd quartile (12.65–14.95)		1.153 (0.954–1.393)	0.142	1.163 (0.965–1.402)	0.112	0.988 (0.823–1.186)	0.896	
4th quartile (≥14.96)		1.169 (0.959–1.426)	0.123	1.075 (0.880–1.313)	0.479	0.929 (0.765–1.129)	0.462	
			0.252*		0.143*		0.299*	
Aged 6 years		1.017 (0.997–1.039)	0.102**	1.018 (0.997–1.039)	0.093**	0.999 (0.980–1.019)	0.932**	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	0.938 (0.719–1.225)	0.639	0.884 (0.683–1.144)	0.347	0.883 (0.681–1.146)	0.349	
	3rd quartile (12.65–14.95)	0.997 (0.774–1.285)	0.981	1.03 (0.803–1.322)	0.813	0.957 (0.748–1.224)	0.725	
	4th quartile (≥14.96)	1.025 (0.762–1.378)	0.872	0.847 (0.626–1.145)	0.279	0.986 (0.742–1.31)	0.921	
Aged 12 years			0.929		0.420		0.798	
		1.002 (0.97–1.034)	0.918	0.996 (0.965–1.028)	0.791	0.999 (0.969–1.029)	0.936	
	1st quartile (<9.69)	1		1		1		
	2nd quartile (9.70–12.64)	1.143 (0.824–1.585)	0.423	0.9 (0.645–1.256)	0.535	0.703 (0.505–0.977)	0.036	
	3rd quartile (12.65–14.95)	1.332 (1.007–1.764)	0.045	1.253 (0.949–1.655)	0.111	1.015 (0.776–1.327)	0.912	
	4th quartile (≥14.96)	1.295 (0.984–1.704)	0.065	1.227 (0.932–1.617)	0.145	0.851 (0.649–1.116)	0.243	
			0.172		0.103		0.100	
		1.027 (0.999–1.057)	0.058	1.031 (1.003–1.06)	0.031	0.999 (0.973–1.025)	0.939	

**P* value for the crossover analysis of solar irradiation quartiles set for each bimonthly period.

*P value for the linear regression models of solar irradiation and allergic disease prevalence within each bimonthly period, after adjustment for potential confounding factors to analyze solar irradiation quartiles in each bimonthly period. The adjusting factors include the following gender, BMI, paternal asthma, maternal asthma, paternal rhinitis, maternal rhinitis and socioeconomic status. The figures in bold indicate P value <0.05.

early as infancy, although it usually manifests during childhood and adolescence.³⁹

Interestingly, unlike 2nd trimester, increased aeroallergen sensitization was associated with the high amount of solar irradiation during 3rd trimester. This result was correlated to previous study that the rate of aeroallergen and food allergen sensitization was increased when cord blood vitamin D level was high.^{15,22} These

results suggested that high vitamin D level as well as low vitamin D level could induce allergic sensitization. Previously, the association of cord blood vitamin D and IgE level had U-shaped rather than non-linear relationships. In that study, both high (>40 ng/ml) and low (<20 ng/ml) vitamin D levels were associated with high total IgE and IgE specific to certain inhalant allergens. This may be caused by low number of regulatory T cells in cord, which was

negatively related to high intensity of solar irradiation.²² In addition, we showed that association between the different level of solar irradiation during pregnancy and allergic sensitization has close connection with each time point of gestational period. Reduced relationship between solar irradiation and allergic sensitization in more aged children is also consistent with studies showing an association between allergic sensitization and vitamin D levels in cord blood.²² This may be due to subsequent exposure to other factors that influence allergic sensitization.³⁹

The difference of solar irradiation effectiveness in allergic sensitization and asthma prevalence could be explained with lung development that starts from 25 weeks to 34 weeks of pregnancy accompanying rapid alveolization⁴⁰ and characteristics of complicated phenotype. This result was consistent with previous results, showing that vitamin D level during pregnancy influences pulmonary function later on in life.^{8,40,41} Although our data could not show the same pattern as in the previous study, there may be a critical period in terms of higher solar irradiation in the 3rd trimester that may induce increased susceptibility to asthma. This may be attributed to environmental factors other than vitamin D that can affect the prevalence of allergic rhinitis and atopic dermatitis,^{8,20,42,43} or to the limitations of questionnaire-based research.

The strengths of the present study are its population-based approach, the use of a validated questionnaire, and large, unbiased sample groups that represent a national cohort of children of the same age. This study, however, had several limitations, including its non-prospective design. Vitamin D levels were not measured during pregnancy. In addition, solar irradiation was estimated by meteorological data according to each individual's living place, but not directly measured with their life style. The degree of each outdoor activity for participants was not considered in this study. However, maternal serum 25(OH) D levels have been shown to correlate significantly with exposure to UV irradiation,²⁵ suggesting that exposure to solar irradiation is used to expect the vitamin D levels. The children enrolled were aged 6 years and 12 years, such that their environment at birth could have differed.

This study showed that the association of exposure to solar irradiation on allergen sensitization depended on both the timing and amount of exposure. Solar irradiation during the second trimester reduced the risk of allergen sensitization in school-aged children, whereas solar irradiation during the third trimester increased this risk. This relation tended to decrease in older age group. Determination of specific amounts of solar irradiation during particular periods of pregnancy and consequent removal of such risk factors may be effective in reducing the risk of allergen sensitization in their offspring.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HYK, EC, SWL, MAK and MYH contributed to conception, design, analysis, interpretation, and writing; SYL, WKK, YMP, JK and KA contributed to design and data collection; MIH, YC, KJL and HJK contributed to data collection, and analysis. The research project was conducted under the supervision of MYH.

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