学位論文

Maternal vitamin D intake during pregnancy is associated with allergic diseases in children at 3 years old: the Japan Environment and Children's Study

妊娠中の母親のビタミンD摂取量は子どもの3歳時点でのアレルギー疾患と関連する：

子どもの健康と環境に関する全国調査

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Abstract

Background: Vitamin D plays an important role in the immune system, and postnatal vitamin D insufficiency is one of the risk factors for the development of allergic disease. However, the effects of women's vitamin D intake during pregnancy on the prevalence of allergic disease in their children remain controversial.

Methods: From the Japan Environment and Children's Study, an on-going nationwide birth cohort study, I obtained information on maternal vitamin D intake determined using a food frequency questionnaire and parent-reported allergic diseases based on the ISAAC questionnaire in children at 3 years of age.

Results: From the full dataset of 103,060 pregnancies, I analyzed complete data for 73,309 mother–child pairs. The prevalence of current wheeze, current rhinitis, current rhino-conjunctivitis, current eczema, ever asthma, ever pollinosis, and ever atopic dermatitis in the children was 17.2%, 29.7%, 3.8%, 15.2%, 9.6%, 3.7%, and 11.0%, respectively. The ORs for current rhinitis were significantly lower in the third, fourth, and fifth quintiles than in the first quintile after adjustment for various covariates and showed a linear association. The ORs for ever pollinosis were significantly lower in the second, third, and fourth quintiles than in the first quintile, showing a U-shaped curve.

Conclusions: Maternal vitamin D intake during pregnancy is associated with the ORs for nasal allergies in children at the age of 3 years. Further studies are warranted to evaluate the appropriate intake dose of vitamin D for pregnant women to prevent the development of nasal allergies in their children.

Abbreviations

JECS, Japan Environment and Children's Study; FFQ, food frequency questionnaire; JPY, Japanese yen

Introduction

In recent years, the prevalence of allergic diseases has significantly increased worldwide. [1, 2] There are several hypotheses concerning the mechanisms underlying the development of allergic diseases, including the hygiene hypothesis[3] and dual allergen exposure theory. [4] It is also well known that nutrients can affect the development of various kinds of diseases, including allergic diseases. [5]

One such nutrient, vitamin D, which has been recognized as a crucial determinant of bone health, plays an important role in immune system function and regulation. Vitamin D insufficiency has been linked to susceptibility to the development of a variety of cancers and autoimmune diseases. [6] In addition, a lack of vitamin D after birth is one of the risk factors for the development of allergic diseases such as asthma and atopic dermatitis. [7, 8] However, the effects of maternal vitamin D status on the prevalence of allergic disease in children are controversial. I previously evaluated the relationship between women's vitamin D intake during pregnancy and the prevalence of allergic diseases in their children at the age of 1 year in a nationwide cohort, the Japan Environment and Children's Study (JECS). [9] Although there was no clear relationship between the two variables, I speculated that the difficult diagnosis of allergic diseases at this early age was one possible explanation for the negative results. In the present study, I attempted to determine if there is an association of maternal vitamin D status with the prevalence of allergic diseases at the age of 3 years, using the same cohort.

Methods

Study population

The JECS methods have been described in detail elsewhere. [10, 11] Briefly, the JECS is a nationwide, government-funded, birth cohort study that is evaluating the impact of various environmental factors on the health and development of children. The pregnant women who participated in the JECS were recruited from 15 areas in Japan between January 2011 and March 2014. This study is based on the jecs-ta-20190930 dataset, which was released in October 2019. The full dataset includes 103,060 pregnancies, 5,647, 948, and 3,520 of which I excluded because women participated multiple times in the study, had multiple pregnancies, or had miscarriages/still births, respectively (Figure 1). I also excluded data on 19,630 records due to missing information on vitamin D intake during pregnancy or missing information on children's allergy status; thus, 73,309 mother–child pairs were included in the final analysis. The study protocol was approved by the Japanese Ministry of the Environment's Institutional Review Board on Epidemiological Studies (authorization number: 100910001) and by the ethics committees of all participating institutions. Written informed consent was obtained from all participating women.

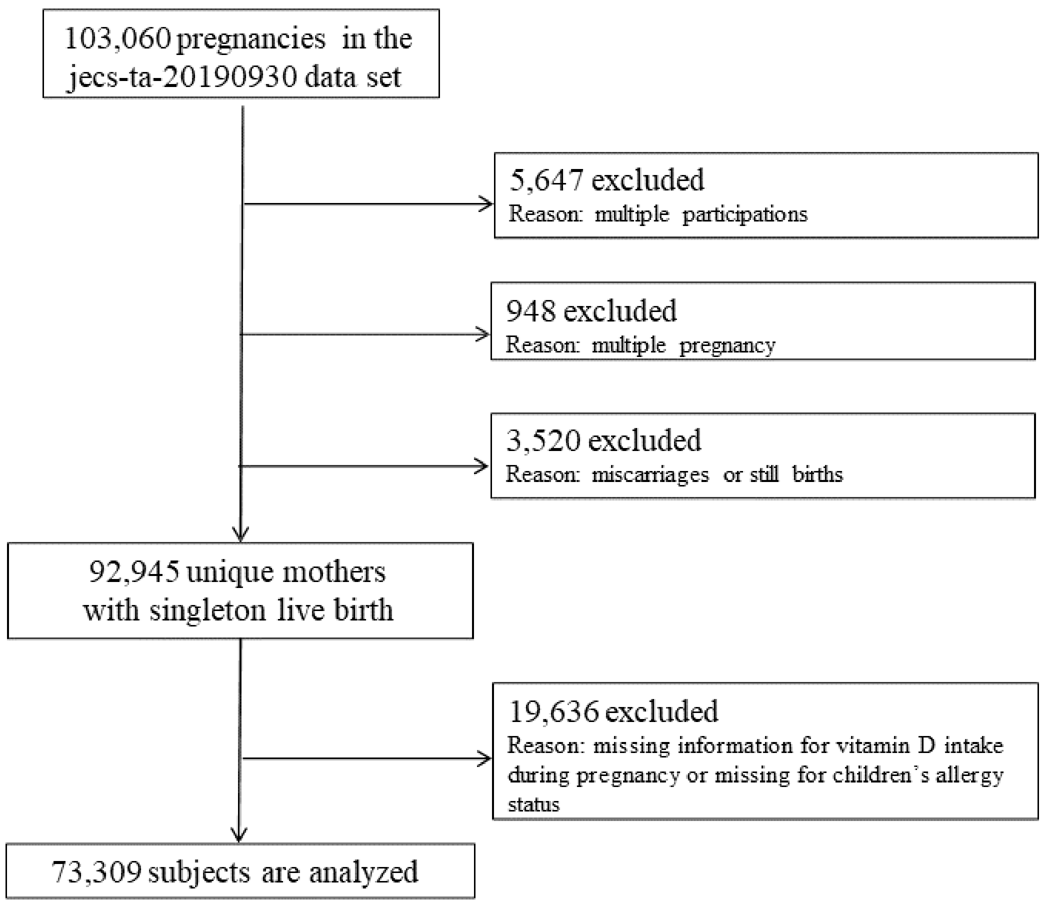

Fig. 1. Flow diagram of the recruitment and exclusion process for pregnant women in this study.

Measurements

A self-report questionnaire was administered to the pregnant women on two occasions—early and mid-late pregnancy—to collect data on demographics, medical and obstetric history, physical and mental health, lifestyle, occupation, and socioeconomic status. Information was also obtained from the medical records on gravidity and related complications, parity, maternal anthropometry, and other factors during early pregnancy and during delivery. After delivery, a self-report questionnaire was administered to the participants 1 month, 6 months, 12 months, 1.5 years, 2 years, 2.5 years, and 3 years after delivery to collect data on mothers' lifestyle and psychological condition and their children's health condition and neurodevelopmental status, among other factors. And of these, questionnaires for 1 month, 6 months, 12 months, and 3 years were used in the present study.

Dietary vitamin D intake was determined by using a food frequency questionnaire (FFQ), which is semi-quantitative and has been validated for use in large-scale epidemiological studies in Japan. [12] Serum 25-hydroxyvitamin D (25[OH]D) levels in pregnant women have also been correlated with vitamin D intake estimated using a FFQ. [13] Pregnant women were asked how often and how much of each food type they consumed during early pregnancy (also covering dietary intake in the previous year, i.e., the periconception period) and during mid-late pregnancy (covering dietary intake after they learned of the pregnancy). In the present study, I only analyzed the data from the mid-late pregnancy period.

Data on children's allergies were collected 3 years after delivery using a parent-completed questionnaire. The prevalence of wheeze, rhinitis, rhino-conjunctivitis, and eczema in children at 3 years of age was evaluated by using answers to questions based on the Japanese version of the ISAAC questionnaire (Table 1). [14]

Table 1. Allergic disease definitions based on the ISAAC questionnaire

Current wheeze	A positive answer to the following two questions: "Has your child ever had wheezing or whistling in the chest at any time in the past?"; "Has your child had wheezing or whistling in the chest in the last 12 months?"
Current rhinitis	A positive answer to the following two questions: "Has your child ever had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?"; "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?"
Current rhino-conjunctivitis	Among children with current rhinitis, a positive answer to the following question: "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?"
Current eczema	A positive answer to the following three questions: "Has your child ever had an itchy rash which was coming and going for at least 6 months?"; "Has your child had this itchy rash at any time in the last 12 months?"; "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"
Ever asthma	A positive answer to the following question: "Has your child ever had asthma?"
Ever pollinosis	A positive answer to the following question: "Has your child ever had pollinosis?"
Ever atopic dermatitis	A positive answer to the following question: "Has your child ever had atopic dermatitis?"

Statistical analysis

Data are expressed as means ± SDs, unless stated otherwise. To estimate the risk of allergic diseases for different levels of vitamin D intake, I categorized the subjects according to quintile. I then analyzed the data using a generalized linear mixed model, setting the regional and subregional centers with 19 levels as a random effect, to calculate ORs and their 95% CIs. Tests for trend involved the assignment of categorical numbers to quintile distributions for vitamin D intake and their evaluation as continuous variables. All analyses were adjusted for 23 covariates, including intake of calories, maternal age, marital status, annual household income, highest educational level, employment status for women during mid-late pregnancy, history of maternal allergy (asthma, allergic rhinitis/pollinosis, atopic dermatitis, allergic conjunctivitis, and/or food allergy), alcohol intake in mid-late pregnancy, active smoking status 1 month after delivery, passive smoking status 1 month after delivery, physical activity during mid-late pregnancy (yes or no), pre-pregnancy BMI, time spent outside during mid-late pregnancy, previous deliveries, mode of delivery (vaginal delivery or cesarean section), period of gestation, sex of the child, congenital anomaly of the child, birth season (spring, summer, fall, or winter), child's experience of communal life (yes or no), child's history of a physician-diagnosed upper or lower respiratory infection (yes or no), feeding method during the first month after birth, and the presence of any type of animal (dog, cat, cow, horse, pig, chicken, and/or others) at home (yes or no). This study defined infant's anomalies as 31 congenital anomalies that are easily detected at delivery and that generally require prompt medical attention after delivery. [15] Details regarding the re-categorization of choices for each factor were described in a previous study. [16] Re-categorizations that were not described in the previous study are as follows. For active smoking, there were six choices in the original questionnaire: 1=never, 2=previously did but quit before learning of the current pregnancy, 3=previously did but quit after find out about the current pregnancy, 4=still smoking (1-10 cigarettes per day), 5=still smoking (11-20 cigarettes per day), and 6=still smoking (21 cigarettes or more per day); the last choice (i.e., number 6) was merged with number 5. For passive smoking, the choices were as follows: 1=no one smoked, 2=someone smoked but not in the presence of the baby, and 3=someone smoked in the presence of the baby. Two-sided P values < 0.05 were considered to indicate statistical significance. Data were analyzed using SAS version 9.4 software (SAS Institute Inc., Cary, NC).

Results

Maternal characteristics according to quintile of dietary vitamin D intake during pregnancy are shown in Table 2. Compared with women who reported low vitamin D intake, those who reported higher vitamin D intake had a higher energy intake and were more likely to have a higher annual household income and a higher level of education. There was no clear association between the maternal history of allergies and dietary vitamin D intake during pregnancy. There were also no clear tendencies in the characteristics of children, such as mode of delivery and birth season, according to quintile of the mother's dietary vitamin D intake during pregnancy (Table 3).

Table 2. Maternal characteristics according to quintile of vitamin D intake during pregnancy (n=73,309)

	Quintile of vitamin D intake				
	1 (low) n=13,993	**2** n=15,155	**3** n=14,528	**4** n=14,890	**5 (high)** n=14,743
Mean intake of vitamin D, µg/day, mean (SD)	1.1 (0.5)	2.6 (0.4)	3.9 (0.4)	5.5 (0.6)	10.5 (5.5)
Mean intake of calories, kcal, mean (SD)	1,270 (478)	1,518 (467)	1,646 (460)	1,857 (532)	2,328 (1,005)
Age at mid-late pregnancy, years, mean (SD)	30.2 (5.2)	31.0 (4.9)	31.3 (4.8)	31.7 (4.8)	31.8 (4.8)
Physical activity during mid-late pregnancy, n (%)					
Yes	10,138 (73.1)	11,342 (74.9)	11,121 (76.6)	11,614 (78.1)	11,481 (78.0)
Pre-pregnancy BMI, kg/m^2, n (%)					
<18.5	2,327 (16.6)	2,501 (16.5)	2,380 (16.4)	2,377 (16.0)	2,266 (15.4)
18.5 to <25	10,180 (72.8)	11,153 (73.6)	10,868 (74.9)	11,114 (74.7)	10,908 (74.0)
>25	1,480 (10.6)	1,492 (9.9)	1,272 (8.8)	1,391 (9.4)	1,564 (10.6)
Time spent outside during mid-late pregnancy, hours, mean (SD)	1.8 (2.4)	1.6 (2.2)	1.6 (2.1)	1.7 (2.1)	1.8 (2.2)
Previous deliveries, mean (SD)	0.7 (0.9)	0.7 (0.9)	0.8 (0.9)	0.8 (0.9)	0.9 (0.9)
Marital status, n (%)					
Married	12,986 (93.6)	14,408 (95.8)	13,941 (96.6)	14,353 (97.1)	14,167 (96.8)
Single	730 (5.3)	518 (3.4)	417 (2.9)	349 (2.4)	387 (2.6)
Divorced or widowed	152 (1.1)	114 (0.8)	73 (0.5)	81 (0.6)	89 (0.6)
Annual household income, JPY, mean (%)					
<4 million	5,897 (46.1)	5,782 (40.8)	5,077 (37.1)	4,836 (34.4)	4,923 (35.5)
4-6 million	3,967 (31.0)	4,961 (33.1)	4,780 (34.9)	4,771 (34.0)	4,779 (34.5)
>6 million	2,928 (22.9)	3,700 (26.1)	3,846 (28.1)	4,438 (31.6)	4,169 (30.1)
Highest level of education, n (%)					
Junior high school or high school	5,845 (42.2)	5,308 (35.1)	4,605 (31.8)	4,314 (29.1)	4,463 (30.4)
Technical junior college, technical/vocational college, or associate degree	5,559 (40.2)	6,532 (43.2)	6,304 (43.5)	6,447 (43.4)	6,532 (44.5)
Bachelor's degree, postgraduate degree	2,434 (17.6)	3,271 (21.7)	3,576 (24.7)	4,091 (27.6)	3,683 (25.1)
Employed, n (%)					
Yes	7,904 (57.3)	8,172 (54.3)	7,733 (53.5)	7,964 (53.8)	7,853 (53.6)
Maternal history of allergy, n (%)					
Yes	6,697 (48.0)	7,580 (50.2)	7,403 (51.1)	7,587 (51.2)	7,330 (49.9)
Alcohol intake, n (%)					
Never	4,902 (35.4)	5,196 (34.5)	4,840 (33.6)	4,770 (32.3)	4,805 (32.8)
Quit before learning of pregnancy	2,119 (15.3)	2,414 (16.0)	2,333 (16.2)	2,460 (16.6)	2,639 (18.0)
Quit after learning of pregnancy	6,510 (47.0)	7,080 (47.0)	6,838 (47.5)	7,149 (48.3)	6,769 (46.1)
Current drinking	309 (2.2)	380 (2.5)	400 (2.8)	411 (2.8)	456 (3.1)
Active smoking status, n (%)					
Never	7,680 (55.4)	9,099 (60.5)	8,945 (62.0)	9,355 (63.3)	9,148 (62.5)
Quit before learning of pregnancy	3,042 (21.9)	3,357 (22.3)	3,238 (22.4)	3,403 (23.0)	3,406 (23.3)
Quit after learning of pregnancy	2,501 (18.0)	2,093 (13.9)	1,825 (12.6)	1,631 (11.0)	1,646 (11.3)
Current smoking ≤ 10 cigarettes	539 (3.9)	394 (2.6)	360 (2.5)	316 (2.1)	342 (2.3)
Current smoking > 10 cigarettes	114 (0.8)	108 (0.7)	72 (0.5)	79 (0.5)	85 (0.6)
Passive smoking status, n (%)					
No one smoked	6,160 (44.3)	7,348 (48.8)	7,278 (50.3)	7,869 (53.2)	7,505 (51.3)
Someone smoked but not in the presence of the baby	7,335 (52.8)	7,385 (49.1)	6,906 (47.8)	6,640 (44.9)	6,799 (46.5)
Someone smoked in the presence of the baby	399 (2.9)	318 (2.1)	275 (1.9)	290 (2.0)	316 (2.2)

JPY = Japanese yen

Table 3. Characteristics of children according to quintile of vitamin D intake during pregnancy (n=73,309)

	Quintile of vitamin D intake				
	1 (low) n=13,993	**2** n=15,155	**3** n=14,528	**4** n=14,890	**5 (high)** n=14,743
Mode of delivery, n (%)					
Cesarean section	2,591 (18.6)	2,763 (18.3)	2,621 (18.1)	2,710 (18.3)	2,836 (19.4)
Period of gestation, weeks, mean (SD)	39.3 (1.5)	39.3 (1.5)	39.3 (1.5)	39.3 (1.5)	39.2 (1.5)
Children sex, n (%)					
Female	6,764 (48.3)	7,348 (48.5)	7,132 (49.1)	7,244 (48.7)	7,256 (49.2)
Congenital anomaly, n (%)					
Yes	333 (2.4)	338 (2.2)	312 (2.2)	320 (2.2)	339 (2.3)
Birth season, n (%)					
Spring	3,273 (23.4)	3,553 (23.4)	3,308 (22.8)	3,500 (23.5)	3,379 (22.9)
Summer	3,767 (26.9)	3,996 (26.4)	3,865 (26.6)	4,006 (26.9)	3,927 (26.6)
Fall	3,929 (28.1)	4,298 (28.4)	4,014 (27.6)	3,986 (26.8)	3,984 (27.0)
Winter	3,024 (21.6)	3,308 (21.8)	3,341 (23.0)	3,398 (22.8)	3,453 (23.4)
Child's experience of communal life, n (%)					
Yes	1,065 (7.7)	965 (6.5)	900 (6.3)	783 (5.3)	915 (6.3)
Physician-diagnosed upper or lower respiratory tract infection, n (%)					
Yes	3,042 (22.3)	3,676 (24.7)	3,705 (25.9)	3,865 (26.5)	3,846 (26.6)
Feeding method during the first month after birth, n (%)					
Breast feeding only	5,533 (39.8)	6,233 (41.4)	6,251 (43.3)	6,521 (44.1)	6,407 (43.8)
Mixed feeding	8,105 (58.4)	8,632 (57.4)	8,045 (55.7)	8,105 (54.8)	8,065 (55.1)
Infant formula only	252 (1.8)	187 (1.2)	137 (1.0)	157 (1.1)	158 (1.1)
Having any type of animal, n (%)					
Yes	3,604 (26.3)	3,622 (24.3)	3,420 (23.9)	3,422 (23.4)	3,476 (24.0)

The prevalence of current wheeze, current rhinitis, current rhino-conjunctivitis, current eczema, ever asthma, ever pollinosis, and ever atopic dermatitis in the children was 17.2%, 29.7%, 3.8%, 15.2%, 9.6%, 3.7%, and 11.0%, respectively. Table 4 shows the crude and adjusted ORs with 95% CIs of the association between maternal vitamin D intake during pregnancy and the development of allergic diseases in children at 3 years of age. The ORs for current rhinitis were significantly lower in the third, fourth, and fifth quintiles than in the first quintile after the adjustment for various covariates, revealing a significant but somewhat vague linear association between the ORs of the disease and maternal vitamin D intake dose. The OR for current rhino-conjunctivitis was significantly lower in the third quintile than in the first quintile. Furthermore, the ORs for ever pollinosis were significantly lower in the second, third, and fourth quintiles than in the first quintile. However, there was no linear association between the ORs of the disease and the maternal vitamin D intake dose. Regarding current wheeze, current eczema, ever asthma, and ever atopic dermatitis, there were no clear tendencies between the ORs of the diseases and maternal vitamin D intake dose.

Table 4. ORs (95% CIs) for child's allergy at 3 years old according to quintile of vitamin D intake during pregnancy (n=73,309)

	Quintile of vitamin D intake					
	1 (low)	2	3	4	5	P value for trend
All subjects, n	13,993	15,155	14,528	14,890	14,743	
Current wheeze						
Case, n	2,373	2,608	2,422	2,533	2,659	
Crude OR	1.00	1.02 (0.96-1.08)	0.98 (0.92-1.04)	1.00 (0.94-1.07)	**1.08 (1.01-1.15)**	**0.047**
Adjusted OR†	1.00	1.07 (1.00-1.15)	0.98 (0.91-1.05)	1.03 (0.95-1.10)	1.07 (0.99-1.16)	0.319
Current rhinitis						
Case, n	4,377	4,527	4,109	4,362	4,404	
Crude OR	1.00	**0.94 (0.89-0.98)**	**0.87 (0.82-0.91)**	**0.91 (0.87-0.96)**	**0.94 (0.89-0.98)**	**0.006**
Adjusted OR†	1.00	0.95 (0.90-1.01)	**0.88 (0.83-0.94)**	**0.92 (0.86-0.98)**	**0.90 (0.84-0.96)**	**<0.001**
Current rhino-conjunctivitis						
Case, n	564	545	481	589	624	
Crude OR	1.00	0.89 (0.79-1.00)	**0.82 (0.72-0.92)**	0.98 (0.87-1.10)	1.05 (0.94-1.18)	0.110
Adjusted OR†	1.00	0.90 (0.78-1.03)	**0.81 (0.70-0.93)**	1.00 (0.87-1.14)	1.02 (0.89-1.18)	0.322
Current eczema						
Case, n	1,964	2,317	2,184	2,329	2,335	
Crude OR	1.00	**1.11 (1.04-1.18)**	**1.08 (1.02-1.16)**	**1.14 (1.06-1.21)**	**1.15 (1.08-1.23)**	**<0.001**
Adjusted OR†	1.00	1.06 (0.98-1.14)	1.00 (0.93-1.08)	1.04 (0.96-1.12)	1.03 (0.94-1.11)	0.774
Ever asthma						
Case, n	1,377	1,417	1,339	1,372	1,538	
Crude OR	1.00	0.95 (0.87-1.02)	0.93 (0.86-1.01)	0.93 (0.86-1.01)	1.07 (0.99-1.15)	0.158
Adjusted OR†	1.00	1.02 (0.93-1.11)	0.98 (0.89-1.08)	0.99 (0.90-1.09)	1.10 (1.00-1.22)	0.146
Ever pollinosis						
Case, n	576	485	502	532	635	
Crude OR	1.00	**0.77 (0.68-0.87)**	**0.83 (0.74-0.94)**	**0.86 (0.77-0.97)**	1.05 (0.93-1.18)	0.099
Adjusted OR†	1.00	**0.75 (0.65-0.87)**	**0.82 (0.71-0.94)**	**0.83 (0.72-0.96)**	0.94 (0.81-1.08)	0.939
Ever atopic dermatitis						
Case, n	1,490	1,626	1,600	1,637	1,734	
Crude OR	1.00	1.01 (0.94-1.09)	1.04 (0.96-1.12)	1.04 (0.96-1.12)	**1.12 (1.04-1.20)**	**0.002**
Adjusted OR†	1.00	0.98 (0.90-1.07)	1.01 (0.92-1.10)	1.00 (0.91-1.09)	1.08 (0.98-1.18)	0.109

Bold indicates significance ($P < 0.05$).

†Adjusted for intake of calories, maternal age, marital status, annual household income, highest educational level, employment status for women during mid-late pregnancy, history of maternal allergy (asthma, allergic rhinitis/pollinosis, atopic dermatitis, allergic conjunctivitis, and/or food allergy), alcohol intake in mid-late pregnancy, active smoking status 1 month after delivery, passive smoking status 1 month after delivery, physical activity during mid-late pregnancy (yes or no), pre-pregnancy BMI, time spent outside during mid-late pregnancy, previous deliveries (none, or one or more), mode of delivery (vaginal delivery or cesarean section), period of gestation, child's sex, any congenital anomaly of child, birth season (spring, summer, fall, or winter), child's history of physician-diagnosed upper or lower respiratory infection (yes or no), child's experience of communal life (yes or no), feeding method (breast feeding only/mixed/formula only), and the presence of any type of animal (dog, cat, cow, horse, pig, chicken, and/or others) at home (yes or no). n=60,660

Discussion

The present prospective cohort study showed that women's vitamin D intake during the mid-late pregnancy period reduced the risk of the development of nasal allergies in their children at the age of 3 years. This is consistent with a previous report showing that maternal vitamin D intake from foods in the late trimester of pregnancy was negatively associated with the risk of allergic rhinitis in children at the age of 5 years. [17] Another study [18] showed similar results, with the more vitamin D obtained by pregnant women from their diet during their first and second trimesters of pregnancy, the lower the ORs of allergic rhinitis in their school-aged children. Regarding the effects of supplement intake, there was no reported association between maternal supplemental vitamin D intake during pregnancy and allergic rhinitis in school-aged children. In contrast, in pregnant women with vitamin D insufficiency during the early term, vitamin D sufficiency in late pregnancy, primarily through the use of supplements, reduced the risk of allergic rhinitis with aeroallergen sensitization but not eczema in children at the age of 3 years. [19] There thus might be a time window of pregnancy during which maternal vitamin D status plays a key role in the development of allergic diseases in children.

The present study showed a U-shaped relationship between the maternal vitamin D intake dose and the risk of pollinosis in children at the age of 3 years. Although there are no similar results for nasal allergic diseases, a meta-analysis of prospective studies suggested a U-shaped relationship between maternal blood 25(OH)D levels and the risk of childhood asthma. [20] Regarding the serum 25(OH)D levels, one study showed that both high (>100 nmol/L) and low (<25-30 nmol/L) levels in mid-pregnancy were associated with an increased risk of asthma in children at the age of 18 months. [21] A possible explanation for the U-shaped effects of vitamin D is a complex immune response to vitamin D. Vitamin D participates in the Th1/Th2 balance by suppressing both components. [22] In this study, the mean vitamin D intake dose was 4.7 µg/day, which is much lower than the recommended dose in Japan (7 µg/day). [23] From the present results, it is difficult to show the appropriate intake dose of vitamin D for pregnant women to prevent the development of nasal allergies in their children.

Regarding other allergic diseases (e.g., asthma and atopic dermatitis), I found no association between maternal vitamin D intake and disease development. A meta-analysis including five cohort studies showed that higher intake of vitamin D in pregnant women reduced the risk of the development of wheeze in children, but not asthma and other atopic conditions. [24] Another meta-analysis including 15 prospective studies showed that higher 25(OH)D level in cord blood was associated with a lower risk of wheeze in children. [25] However, three randomized clinical trials failed to show protective effects of maternal supplemental vitamin D intake on the development of asthma in children at the age of 3 years. [26-28] Regarding eczema and atopic dermatitis, one meta-analysis identified an association between the maternal vitamin D level and the risk of eczema in children, [29] but another meta-analysis failed to find any association between them. [30] Regional differences in the amount of daylight time that is essential for the synthesis of active vitamin D and cultural differences in the consumption of foods containing vitamin D may contribute to these controversial results.

A strength of my study is the size of the cohort, because I enrolled about 74,000 mother–child pairs from a nationwide population. In addition, I controlled for numerous potential covariates in the analysis, such as birth season, time spent outside, feeding method, lifestyle, and physical and social factors. However, there are also some limitations. Most of the information was self-reported. I did not obtain information regarding atopic status such as sensitization to allergens or enough data regarding vitamin D intake in children. Furthermore, I did not measure serum vitamin D levels in pregnant women or children.

In conclusion, I showed that higher vitamin D intake in pregnant women might reduce the risk of allergic rhinitis in their children at the age of 3 years. Rhinitis in early life is a risk factor for later asthma. [31] Therefore, prevention of the development of rhinitis might interrupt future allergic march. Further studies are warranted to evaluate the mechanisms underlying how maternal vitamin D status affects the development of allergic diseases in children.

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