

Original Article

Increased food allergy and vitamin D: Randomized, double-blind, placebo-controlled trial

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Abstract **Background:** To elucidate whether maternal vitamin D supplementation during lactation improves infantile eczema and other subsequent allergic disorders, a randomized, double-blind, placebo-controlled trial was performed.

Methods: Mothers ($n = 164$) of infants with facial eczema at 1 month check-up were randomly assigned to receive vitamin D3 supplements ($n = 82$; 800 IU/day) or placebo ($n = 82$) for 6 weeks from May 2009 to January 2011. The primary outcome was infantile eczema quantified on Scoring Atopic Dermatitis (SCORAD) index at 3 month check-up, and the secondary outcomes were atopic dermatitis, food allergy, and wheeze diagnosed by doctors up to 2 years of age.

Results: There was no significant difference in SCORAD at 3 month check-up between the two groups. Doctor-diagnosed food allergy was significantly more common up to age 2 years in the vitamin D group (10/39, 25.7%) than in the placebo group (3/40, 7.5%; risk ratio (RR), 3.42; 95% confidence interval [CI]: 1.02–11.77; $P = 0.030$). Moreover, at least one secondary outcome was also significantly more common in the vitamin D group (17/39, 43.6%) than in the placebo group (7/40, 17.5%; RR, 2.49; 95%CI: 1.16–5.34; $P = 0.012$).

Conclusions: Vitamin D supplementation may not decrease the severity of infantile eczema at 3 months of age, but may rather increase the risk of later food allergy up to 2 years of age. Because a large number of subjects was lost to follow up, further study is needed to confirm the findings.

Key words food allergy, infantile eczema, prevention, randomized controlled trial, vitamin D.

The discovery that immune cells possess both the enzyme to activate 25-hydroxyvitamin D (25OHD), the major circulating form of vitamin D in serum, and its receptor within the cells^{1,2} has provided new insights into the immune function of this vitamin. Following extensive research in the field of immunology, active vitamin D was found to suppress dendritic cell maturation and consequent T-helper (Th) 1 cell development.³ It has been implied that delayed maturation of Th1-associated functions during early postnatal life increases the risk for sensitization to allergens, resulting in atopic disorders.⁴ Of interest, the time course of the vitamin D intervention policy for early infants to prevent rickets during the last 30 years runs in parallel with the increased prevalence of allergic diseases.⁵ Therefore, Wjst and Dold hypothesized that vitamin D supplementation either through cod oil or formula milk during early infancy may be a risk factor for atopic disorders later in life.^{6,7} Indeed, the UK long-term cohort study showed that children whose mothers had

25OHD concentration in pregnancy >30 ng/mL, which is considered within the normal range for adults, had an increased risk of eczema on examination at 9 months and of asthma at age 9 years compared with children whose mothers had a concentration <12 ng/mL.⁸ Moreover, a Finnish 30 year long-term cohort study demonstrated an association between vitamin D supplementation in infancy and an increased risk of atopic sensitization and allergic rhinitis later in life.⁹ In contrast, recent epidemiological studies are showing that vitamin D insufficiency has been widespread in the developed countries over the past few decades,¹⁰ and that higher vitamin D intake by pregnant mothers reduced the asthma risk by as much as 40% in children 3–5 years old.^{11,12} Therefore, Litonjua and Weiss hypothesized that, as populations grow more prosperous, more time is spent indoors, and there is less exposure to sunlight, leading to decreased cutaneous vitamin D production, coupled with inadequate intake from foods and supplements, which then leads to vitamin D deficiency, particularly in pregnant women, resulting in more asthma and allergy in their offspring.¹³

Thus, there are several observational studies showing the associations between vitamin D either in pregnancy or early infancy and allergic disorders during childhood or later in life, but the results of these studies are not always consistent. To clarify whether vitamin D supplementation during early postnatal life improves or worsens infantile eczema and whether it reduces

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or enhances the risks of allergies such as atopic dermatitis, food allergy, and wheeze, a randomized, double-blind, placebo-controlled trial using vitamin D3 supplements was conducted for pairs of lactating mothers and their breast-fed infants with eczema at 1 month of age.

Methods

Study design

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted by two hospitals and three doctors in the Departments of Pediatrics of Japanese General Hospitals from May 2009 to January 2011. The study protocol was reviewed and approved by the ethics committee of Jikei University School of Medicine and the clinical study committee of the Jikei Dai-San hospital, as well as the institutional review board of Fuji Chuo Hospital. The trial (number UMIN000001841) was registered with UMIN Clinical Trials Registry on 9 March 2009. The data monitoring center was at the Division of Molecular Epidemiology, Jikei University School of Medicine. The safety review board consisted of two physicians from Jikei University hospital who are not co-authors of this study. Both vitamin D3 (StatusD3®) and placebo were purchased from Zenyaku (Otsuka, Tokyo, Japan).

Subjects, eligibility, and consent

Mothers and their breast-fed infants were eligible. Selection criteria were: (i) exanthema on the face at 1 month check-up in the infants; (ii) exclusive breast-feeding or breast-feeding dominant; and (iii) provision of informed consent by the mothers. Exclusion criteria were: (i) vitamin D supplement or active vitamin D already being taken; (ii) past history of urinary tract stone or underlying disease related to calcium or bone in the mothers; (iii) allergy to food additives in the mothers (sesame oil, gelatin, D-sorbitol, Yellow No.5, titanium oxide, which were used in the StatusD3 and the placebo); and (iv) other difficulties judged by the pediatrician in charge.

Randomization, blinding, and intervention

A central computerized procedure created by MU was used to randomly assign mothers in permuted blocks of four to receive either vitamin D or placebo. Mothers were provided with two numbered bottles, each of which contained 90 tablets. One tablet contained 200 IU of vitamin D3 or placebo, and active and placebo tablets were identical in appearance. Participants were asked to take four tablets once daily (total 800 IU vitamin D3 or placebo). Blinding of the study was achieved by bottle numbering. Participants and doctors who saw these participants and evaluated primary and secondary outcomes (N.A., T.S., and H.T.) were blinded, whereas staff at the data monitoring center (C.N., H.M., H.I., and M.U.) had no contact with the mother–infant pairs and were not blinded.

Follow-up procedures and outcomes

After 6 weeks of taking the supplement, participants were asked to visit a doctor's clinic with their babies for a 3 month check-up.

Pediatricians (N.A., T.S., and H.T.) evaluated the Scoring Atopic Dermatitis (SCORAD) index as the primary outcome.¹⁴ For case identification, the study number was used, and private information such as names and addresses of participants was not disclosed to the data monitoring center. The pediatricians in charge were asked to send a fax to the data monitoring center to report the primary outcome at the 3 month check-up, as well as any cases of adverse events, including serious signs/symptoms of the mothers and their infants.

Information about children's allergic manifestations during the first 2 years of life was obtained from questionnaires filled out by the parents at entry (infants at 1 month of age) and annually thereafter (infants at 1 and 2 years of age). Secondary outcomes were defined as the doctor-diagnosed allergic incidents, including atopic dermatitis, food allergy with or without being positive for IgE food allergens, or wheeze or asthma with or without being positive for IgE inhaled allergens, by the time the infant was 2 years old.

Statistical analysis

At first, SCORAD was predicted to be 2 ± 3 in the placebo group. A 1 : 1 divided sample of 300 was calculated as being sufficient for the detection of a 50% reduction (1 ± 3) in outcome, with a type I error (two-sided) of 5% and a power of 80%, on the assumption of 6% loss to follow up. The SCORAD, however, was actually 4 ± 5 in the placebo group. Therefore, the sample size of 130 was calculated as being sufficient for the detection of a 50% reduction (2 ± 3) in outcome, with a type I error (two-sided) of 5% and a power of 80%. We decided to stop recruiting the participants in January 2011.

An intention-to-treat analysis was planned, which included all infants in the study even if their mothers did not take vitamin D for 6 weeks, independent of whether infants were taking formula milk after randomization. The incidences of both primary and secondary outcomes were compared in the two groups with the use of the risk ratio (RR) and the 95% confidence interval (95%CI). Mann–Whitney test was used to compare the total SCORAD between the vitamin D3 and placebo groups as well as between exclusively and partially breast-fed infants. All reported *P*-values are two-sided. $P < 0.05$ was considered significant. All analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX, USA).

Results

Participants

Mothers ($n = 196$) of infants with facial eczema and extensive breast-feeding or who were breast-feeding dominant at the 1 month check-up were asked to participate in this trial. As a result, 164 mothers agreed to participate in the trial and were randomly assigned to receive vitamin D3 supplements ($n = 82$; 800 IU/day) or placebo ($n = 82$) in a double-blind setting for 6 weeks from May 2009 to January 2011 (Fig. 1). One hundred and forty-six infants (89%) re-visited the hospitals for the 3 month check-up, and SCORAD was measured as the primary endpoint at the same time. Adherence to vitamin D supplements or placebo was

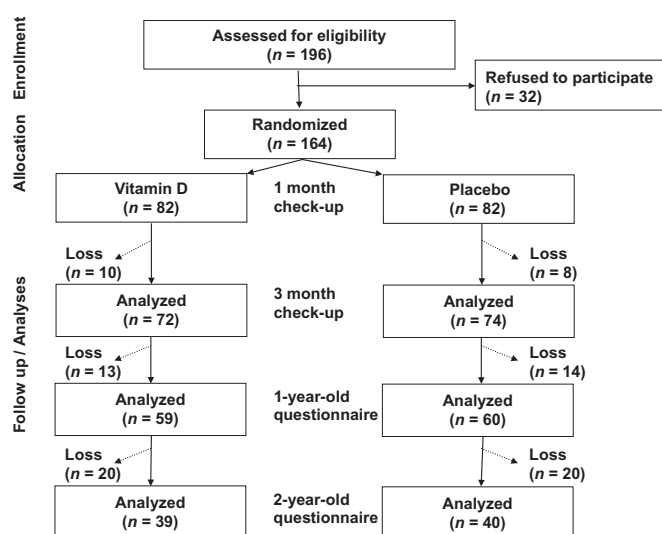


Fig. 1 Participant flow.

evaluated on the basis of the logs provided. A total of 96% of mothers took at least 90% of the supplement. One hundred and nineteen mothers, 82% of participants who came for the 3 month check-up, returned the questionnaires to the monitoring center at 1 year of age. Seventy-nine mothers, 66% of the participants who returned questionnaires at 1 year of age, returned the questionnaires to the monitoring center at 2 years of age.

Participant characteristics

The mean subject age was 31 years. The allergy status of participants' families, maternal smoking status, diet during pregnancy, skin reaction to sun exposure, and breast-fed versus formula-fed ratio at each month for 1–7 months were similar between the two groups (Table 1). These characteristics were also not different between participants who completed follow up to 2 years of age and those who were lost to follow up by 2 years of age. Furthermore, there were no significant differences in participant and infant characteristics between the vitamin D3 group and placebo group for those followed up to 2 years of age, except for frequencies of past smokers (Table 2).

Primary outcome

The primary outcome, SCORAD, was evaluated by pediatricians in a double-blind setting at the 3 month check-up. Mean $\pm$ SD of the total SCORAD was 4.75 ± 7.49 in the vitamin D3 group and 3.95 ± 5.36 in the placebo group, which were not significantly different (Fig. 2). Each score for extent, intensities, and subjective scales, was not different between the vitamin D3 group and the placebo group (data not shown). When the analysis was restricted only to exclusively breast-fed infants from 1 to 3 months of age, there were no significant differences between the two groups (data not shown). Next, the SCORAD were compared between infants who were followed up to 2 years of age and those who were lost to follow up at 2 years of age, and there were no significant differences (data not shown). Furthermore, among infants who were lost to follow up from the 3 month check-up to

2 years of age, there were no significant differences in SCORAD between the vitamin D group and the placebo group (data not shown).

Secondary outcomes

The secondary outcomes, three kinds of doctor-diagnosed allergic conditions (atopic dermatitis, food allergy, and wheeze up to 2 years of age), were evaluated in a double-blind setting and compared between the vitamin D group and the placebo group (Table 3). Food allergy occurred significantly more in the vitamin D group than in the placebo group (RR, 3.42; 95%CI: 1.02–11.77, $P = 0.030$). Moreover, at least one allergic condition was also observed significantly more in the vitamin D group than in the placebo group (RR, 2.49; 95%CI 1.16–5.34, $P = 0.012$).

Post-hoc analysis: Exclusive breast-feeding and allergic conditions

In addition to the initial protocol, associations between exclusive breast-feeding up to 3 months of age and allergic conditions were examined on post-hoc analysis. The mean total SCORAD was 2.33 ± 4.73 in the partially breast-fed infants and 5.93 ± 7.89 in the exclusively breast-fed infants, which were significantly different ($P = 0.0018$; Fig. 3). Each score for extent, intensities of erythema and excoriation and the visual analog scale of pruritus were significantly worse in exclusively breast-fed infants than in partially breast-fed infants (data not shown).

Safety

There were no reports of serious adverse events or hospital admissions in either participating mothers or their infants while mothers were taking the supplement.

Discussion

In this randomized, double-blind, placebo-controlled trial, daily supplementation with 800 IU of vitamin D3 for 6 weeks from 1 month after birth for breast-feeding mothers showed no significant effects on infantile eczema at the 3 month check-up, as quantified on SCORAD. Moreover, the incidence of atopic dermatitis up to 2 years of age was neither decreased nor increased by vitamin D supplementation. There is still no convincing evidence of the benefit of vitamin D supplementation during the perinatal period in preventing atopic eczema.^{15–17}

In this study, the incidence of food allergy up to 2 years of age was increased by vitamin D supplementation. A recent German prospective cohort study showed that high vitamin D levels in pregnancy and at birth may contribute to a higher risk for food allergy up to 2 years of age,¹⁸ which is consistent with the present results.

In this study, the incidence of wheezing was not significantly changed by vitamin D supplementation, although the incidence was twice as high in the vitamin D group as in the placebo group. Cord-blood 25OHD level has been reported to have an inverse association with risk of respiratory infection and of childhood wheezing, but no association with incident asthma.¹⁹ In contrast, no significant associations between maternal late-pregnancy 25OHD status and either asthma or wheeze at age 6 years were

Table 1 Subject characteristics

	Total vitamin D (<i>n</i> = 82) Placebo (<i>n</i> = 82) <i>n</i> (%) or mean $\pm$ SD		<i>P</i>	Followed up to 2 years of age (<i>n</i> = 79) <i>n</i> (%) or mean $\pm$ SD	Lost to follow up by 2 years of age (<i>n</i> = 85) <i>n</i> (%) or mean $\pm$ SD	<i>P</i>
Maternal age (years)	31.4 $\pm$ 5.4	30.5 $\pm$ 4.8	0.35 [†]	31.7 $\pm$ 5.1	30.1 $\pm$ 5.1	0.06 [†]
Boy	39 (48)	38 (46)	0.88 [‡]	39 (49)	38 (45)	0.55 [‡]
Birthweight (g)	2957 $\pm$ 340	2993 $\pm$ 381	0.56 [†]	2959 $\pm$ 371	2993 $\pm$ 349	0.58 [†]
Birth height (cm)	48.9 $\pm$ 1.8	49.2 $\pm$ 2.0	0.24 [†]	48.8 $\pm$ 2.0	49.3 $\pm$ 1.7	0.19 [†]
1 month weight (g)	4136 $\pm$ 512	4176 $\pm$ 503	0.50 [†]	4146 $\pm$ 521	4191 $\pm$ 491	0.69 [†]
1 month height (cm)	52.8 $\pm$ 2.2	53.4 $\pm$ 1.9	0.09 [†]	52.9 $\pm$ 2.1	53.3 $\pm$ 1.9	0.24 [†]
Maternal current allergy [§]						
Asthma	4	2	0.40 [‡]	4	2	0.51 [‡]
Atopic dermatitis	7	7	1.00 [‡]	8	6	0.78 [‡]
Sun allergy	3	1	0.31 [‡]	1	3	0.25 [‡]
Drug allergy	2	1	0.56 [‡]	2	1	0.65 [‡]
Food allergy	4	6	0.56 [‡]	5	5	0.81 [‡]
Metal allergy	14	8	0.16 [‡]	9	13	0.20 [‡]
Allergic rhinitis	33	29	0.50 [‡]	38	24	0.10 [‡]
Chemical sensitivity	1	0	0.22 [‡]	0	1	0.28 [‡]
Smoking status of mother						
Current smoker	3 (5)	1 (2)	0.34 [‡]	2 (3)	2 (3)	0.94 [‡]
Past smoker	24 (37)	26 (42)	0.56 [‡]	23 (34)	27 (44)	0.28 [‡]
Diet during pregnancy						
None/1–2/3–4/5–6/7 days per week						
Sun-dried shiitake mushrooms	50/13/0/1/0	61/7/0/0/0	0.13 [‡]	57/15/0/1/0	55/6/0/0/0	0.15 [‡]
Fresh shiitake mushrooms	33/29/3/1/1	38/28/2/0/0	0.63 [‡]	37/32/3/1/1	34/27/2/0/0	0.76 [‡]
Salmon	21/44/2/1/0	25/39/4/1/0	0.73 [‡]	26/45/2/2/0	20/40/4/0/0	0.41 [‡]
Sardines	55/11/2/0/0	62/5/1/0/0	0.22 [‡]	66/7/2/0/0	53/9/1/0/0	0.62 [‡]
Mackerel	41/27/0/0/0	46/23/0/0/0	0.44 [‡]	47/28/0/0/0	41/23/0/0/0	0.87 [‡]
Pacific saury	48/19/1/0/0	51/17/1/0/0	0.91 [‡]	56/18/1/0/0	45/18/1/0/0	0.85 [‡]
Tuna	14/46/8/0/0	18/45/6/0/0	0.67 [‡]	18/50/7/0/0	14/43/7/0/0	0.92 [‡]
Egg yolk	5/19/22/9/13	5/15/25/13/11	0.82 [‡]	8/20/25/12/10	2/15/23/10/14	0.35 [‡]
Vitamin D-intensified food	34/12/5/2/15	36/10/6/2/13	0.98 [‡]	35/12/6/4/18	35/10/5/1/11	0.64 [‡]
Cod-liver oil	67/0/1/0/0	65/3/0/0/1	0.70 [‡]	72/2/0/0/1	62/1/1/0/0	0.53 [‡]
Fast food	40/26/2/0/0	46/21/2/0/0	0.62 [‡]	48/24/3/0/0	40/23/1/0/0	0.64 [‡]
Hours of exposure to sunshine			0.14 [‡]			0.40 [‡]
>2 h/day	5	9		9	5	
1–2 h/day	25	13		23	15	
0.5–1 h/day	29	30		31	28	
<0.5 h/day	11	16		11	16	
Almost none	0	1		1	0	
Skin reaction to sun exposure			0.40 [‡]			0.99 [‡]
Sunburn but no suntan	11	5		8	8	
Sunburn, slight suntan, recover in winter	28	37		36	29	
Sunburn, average level of suntan	24	23		25	22	
No sunburn, always suntan	5	3		4	4	
				1	1	
Breast-fed vs formula fed at 3 months [¶]			0.41 [‡]			0.16 [‡]
Exclusively breast-fed	45 (77)	38 (67)		57 (76)	26 (65)	
Breast-fed dominant	12 (21)	15 (26)		17 (23)	10 (25)	
Half breast-fed and half formula fed	1 (2)	3 (5)		1 (1)	3 (8)	
Formula-fed dominant	0 (0)	1 (2)		0 (0)	1 (3)	
Exclusively formula fed	0 (0)	0 (0)		0 (0)	0 (0)	
Breast-fed vs formula fed at 7 months [¶]			0.21 [‡]			0.75 [‡]
Exclusively breast-fed	38 (66)	36 (63)		49 (66)	25 (63)	
Breast-fed dominant	10 (18)	10 (18)		12 (16)	8 (20)	
Half breast-fed and half formula-fed	3 (5)	0 (0)		1 (1)	2 (5)	
Formula-fed dominant	4 (7)	4 (7)		6 (8)	2 (5)	
Exclusively formula-fed	2 (4)	7 (12)		6 (8)	3 (8)	

[†]Student's *t*-test; [‡]chi-squared test. [§]Maternal past allergy, paternal current and past allergy, and siblings' current and past allergy were similarly compared, with no significant differences between the vitamin D and placebo groups. [¶]Ratios of breast-fed vs formula fed at 3 months and at 7 months are shown as representative values. The ratios at 1, 2, 4, 5, and 6 months were also not significantly different (data not shown).

reported.^{20,21} A U-shaped association between serum 25OHD and IgE has been observed in adults²² and a birth cohort.²³

Although formula milk was fortified with vitamin D, exclusively breast-fed infants had significantly worse SCORAD at the 3 month check-up than partially breast-fed infants. In a New

Zealand birth cohort, exclusively breast-fed infants had more atopic sensitization after 9 years of age and asthma after 13 years of age than those who were not.²⁴ The duration of breast-feeding was associated with an increased risk of atopic dermatitis in New Zealand.²⁵ Prolonged exclusive breast-feeding may be related to

Table 2 Subjects followed up to 2 years of age

	Total (<i>n</i> = 79) Vitamin D (<i>n</i> = 39) Placebo (<i>n</i> = 40) <i>n</i> (%) or mean $\pm$ SD		<i>P</i>
Maternal age (years)	32.6 $\pm$ 5.4	30.8 $\pm$ 4.6	0.11 [†]
Boy	18 (46)	21 (53)	0.57 [‡]
Birthweight (g)	2924 $\pm$ 348	2992 $\pm$ 394	0.43 [†]
Birth height (cm)	48.7 $\pm$ 1.9	49.0 $\pm$ 2.1	0.50 [†]
1 month weight (g)	4090 $\pm$ 480	4197 $\pm$ 557	0.39 [†]
1 month height (cm)	52.5 $\pm$ 2.2	53.3 $\pm$ 2.0	0.10 [†]
Maternal current allergy [§]			
Asthma	3	1	0.29 [‡]
Atopic dermatitis	4	4	1.00 [‡]
Sun allergy	1	0	0.31 [‡]
Drug allergy	2	0	0.15 [‡]
Food allergy	2	3	0.67 [‡]
Metal allergy	6	3	0.27 [‡]
Allergic rhinitis	20	18	0.56 [‡]
Chemical sensitivity	0	0	-
Smoking status of mother			
Current smoker	2 (6)	0 (0)	0.17 [‡]
Past smoker	8 (24)	15 (47)	0.047 [‡]
Diet during pregnancy			
None/1–2/3–4/5–6/7 days per week			
Sun-dried shiitake mushrooms	26/8/0/1/0	31/7/0/0/0	0.50 [‡]
Fresh shiitake mushrooms	16/17/2/1/1	21/15/1/0/0	0.54 [‡]
Salmon	12/23/1/1/0	14/22/1/1/0	0.98 [‡]
Sardines	32/4/1/0/0	34/3/1/0/0	0.91 [‡]
Mackerel	22/15/0/0/0	25/13/0/0/0	0.57 [‡]
Pacific saury	27/9/1/0/0	29/9/0/0/0	0.59 [‡]
Tuna	8/25/4/0/0	10/25/3/0/0	0.84 [‡]
Egg yolk	5/12/12/5/3	3/8/13/7/7	0.52 [‡]
Vitamin D-intensified food	16/6/3/2/10	19/6/3/2/8	0.98 [‡]
Cod-liver oil	37/0/0/0/0	35/2/0/0/1	0.22 [‡]
Fast food	23/12/2/0/0	25/12/1/0/0	0.82 [‡]
Hours of exposure to sunshine			0.64 [‡]
>2 h/day	3	6	
1–2 h/day	13	10	
0.5–1 h/day	16	15	
<0.5 h/day	5	6	
Almost none	0	1	
Skin reaction to sun exposure			0.35 [‡]
Sunburn but no suntan	6	2	
Sunburn, slight suntan, recover in winter	17	19	
Sunburn, average level of suntan	11	14	
No sunburn, always suntan	30	11	
Breast-fed vs formula-fed at 3 months [¶]			0.19 [‡]
Exclusively breast-fed	32 (84)	25 (68)	
Breast-fed dominant	6 (16)	11 (30)	
Half breast-fed and half formula fed	0 (0)	1 (3)	
Formula-fed dominant	0 (0)	0 (0)	
Exclusively formula fed	0 (0)	0 (0)	
Breast-fed vs formula-fed at 7 months [¶]			0.70 [‡]
Exclusively breast-fed	26 (70)	23 (62)	
Breast-fed dominant	5 (14)	7 (19)	
Half breast-fed and half formula fed	1 (3)	0 (0)	
Formula-fed dominant	3 (8)	3 (8)	
Exclusively formula-fed	2 (5)	4 (11)	

[†]Student's *t*-test; [‡]chi-squared test. [§]Maternal past allergy, paternal current and past allergy, and siblings' current and past allergy were similarly compared, with no significant differences between the vitamin D and placebo groups. [¶]Ratios of breast-fed vs formula fed at 3 months and at 7 months are shown as representative values. The ratios at 1, 2, 4, 5, and 6 months were also not significantly different (data not shown).

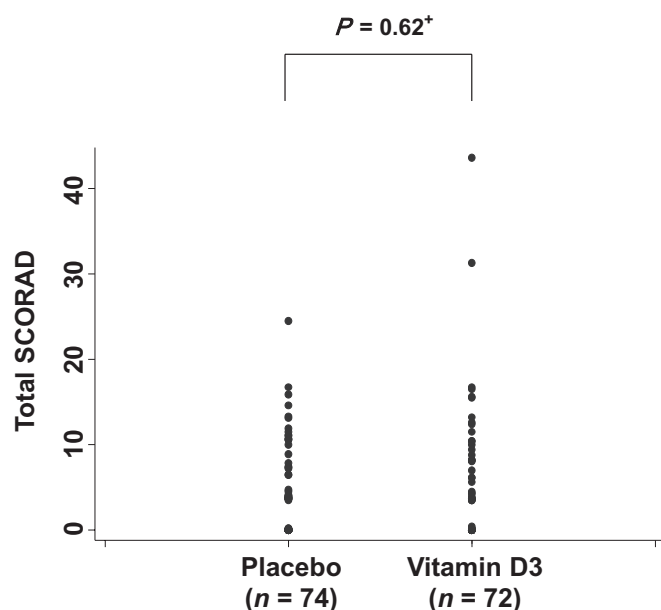


Fig. 2 Vitamin D3 supplementation and Scoring Atopic Dermatitis (SCORAD) as the primary outcome at 3 month check-up. Mean SCORAD: placebo group, 3.95 ± 5.36 ; Vitamin D3 group, 4.75 ± 7.49 . [†]Mann–Whitney test.

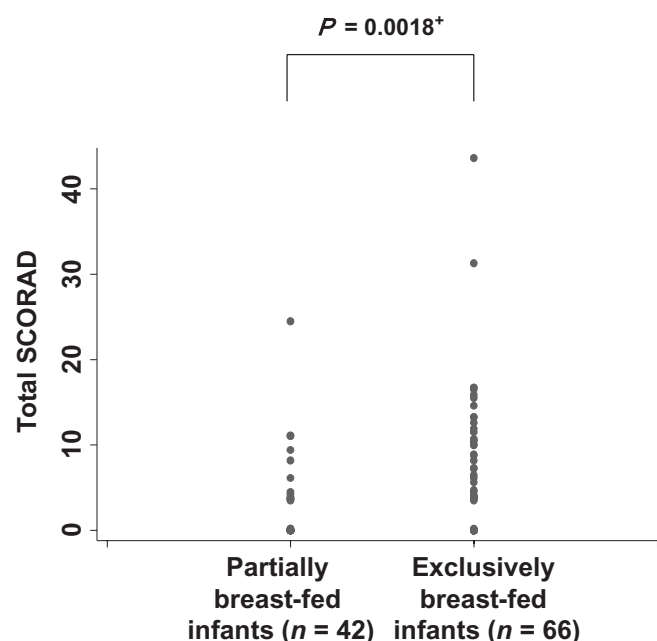


Fig. 3 Exclusive breast-feeding and Scoring Atopic Dermatitis (SCORAD) as the primary outcome at 3 month check-up. Mean SCORAD: partially breast-fed infants, 2.33 ± 4.73 ; exclusively breast-fed infants, 5.93 ± 7.89 . [†]Mann–Whitney test.

delayed weaning onto solid foods, which may increase the risk of food allergy;²⁶ and longer duration of total breast-feeding, rather than its exclusivity, was protective against the development of non-atopic but not atopic asthma.²⁷

The strength of the present study is that this is the first randomized, double-blind, placebo-controlled trial to examine whether postnatal vitamin D supplementation has an effect on allergic disorders up to 2 years of age, in contrast to the previous observational studies referred to here. The uniqueness of the present study is that it targeted 1-month-old, breast-fed infants, but there are several limitations to this study. First, a large number of subjects was lost during follow up. Participant characteristics and SCORAD, however, were not significantly different between the followed-up group and the group lost to follow up by 2 years of age. Within the group that was lost to follow up from 3 months to 2 years of age, there were no differences in SCORAD between the vitamin D group and the placebo group. In addition, there were no significant differences in the participant and infant characteristics between the vitamin D3 group and placebo group for those who were followed up to 2 years of age. This suggests that bias induced by loss to follow up may be not so

serious. Second, serum 25OHD level was not measured in either the mothers or the infants. Thus, whether 800 IU of vitamin D intake for 6 weeks was adequate to raise the serum 25OHD in the infants remains unknown. In a previous study, serum 25OHD increased around 5–10 ng/mL among nursing infants of mothers receiving 400 IU/day vitamin D3 during 3 months, but it did not increase much among the mothers themselves.²⁸ Third, the present results relate to infants who had exanthema on the face at the 1 month check-up. Moreover, in Japan, infants are seldom given vitamin D supplement, therefore the generalizability of this study to other countries may not be possible. Fourth, some mothers added formula milk to breast milk, which might dilute the effects of vitamin D supplementation, given that formula milk is fortified with vitamin D, although this occurred equally in both the vitamin D group and the placebo group.

Conclusion

Vitamin D supplementation may not decrease the severity of infantile eczema at 3 months of age, but it may rather increase the

Table 3 Vitamin D3 supplementation and secondary endpoints up to 2 years of age

	Vitamin D3 n/total (%)	Placebo n/total (%)	Relative risk	95%CI	Risk difference	95%CI	P
Atopic skin	4/39 (10.3)	2/40 (5.0)	2.05	0.40–10.56	0.05	–0.06 to 0.17	0.38
Food allergy	10/39 (25.6)	3/40 (7.5)	3.42	1.02–11.77	0.18	0.02 to 0.34	0.030
Wheeze	8/39 (20.5)	4/40 (10.0)	2.05	0.67–6.26	0.11	–0.05 to 0.26	0.19
Any allergic condition [†]	17/39 (43.6)	7/40 (17.5)	2.49	1.16–5.34	0.26	0.07 to 0.46	0.012

[†]At least one allergic condition among atopic skin, food allergy, and wheeze was diagnosed by a pediatrician. CI, confidence interval.

risk of later food allergy. Because a large number of subjects was lost to follow up, further study is needed to confirm the findings.

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