Original Article

Early Discontinuation of Cow's Milk Protein Ingestion Is Associated with the Development of Cow's Milk Allergy

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What is already known about this topic? Supplementing breast-feeding with cow's milk formula in the first few days of life can increase the risk of cow's milk allergy, but little is known about the effects of discontinuing cow's milk formula ingestion.

What does this article add to our knowledge? Early discontinuation of cow's milk formula ingestion, particularly in the first month of life, may increase the risk of cow's milk allergy in infants who received cow's milk formula in the first 3 days of life.

How does this study impact current management guidelines? Continuous cow's milk formula ingestion over the first month of life may represent a potential method for preventing cow's milk allergy development in early-exposed infants.

BACKGROUND: Although early supplementation with cow's milk formula (CMF) reportedly increases the risk of cow's milk allergy (CMA) in breast-fed infants, little is known about the association between the timing of CMF discontinuation and subsequent CMA development.
OBJECTIVE: To elucidate the relationship between the timing of CMF discontinuation and CMA development in infants who received CMF in the early days of life.
METHODS: Using data from a randomized controlled trial of a birth cohort from 4 Japanese hospitals, we performed a subgroup analysis of participants who ingested CMF in the first 3 days of life. We compared the proportions of participants who developed CMA at age 6 months in those who discontinued CMF ingestion before age 1 month ("DISC <1-month group"), during age 1 to 2 months ("DISC 1-2−month group"), and during age 3 to 5 months ("DISC 3-5−month group") with those who continued CMF ingestion until age 6 months ("continuous group"). The risk ratios (RRs) and 95% CIs for CMA development were calculated.
RESULTS: CMA incidence was significantly higher in the DISC <1-month group (n = 7 of 17, 41.2%; RR, 65.7; 95% CI, 14.7-292.5; $P < .001$), DISC 1-2−month group (n = 3 of 26, 11.5%; RR, 18.4; 95% CI, 3.2-105.3; $P = .003$), and DISC 3-5−month group (n = 7 of 69, 10.1%; RR, 16.2; 95% CI, 3.4-76.2; $P < .001$) than in the continuous group (n = 2 of 319, 0.6%).
CONCLUSIONS: Early CMF discontinuation, particularly in the first month of life, was associated with CMA development in infants who received CMF in the first 3 days of life. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: *Food allergy; Milk allergy; Prevention; Cow's milk; Randomized controlled trial; Birth cohort; Infant formula; Cow's milk formula; Discontinuation; Breast-feeding*

INTRODUCTION

IgE-mediated cow's milk allergy (CMA) is one of the most common food allergies in infants, and may lead to more severe conditions such as anaphylaxis. Observational studies have shown an association between early cow's milk protein introduction and a lower risk of CMA development,[1,2] but previous randomized controlled trials did not demonstrate the efficacy of early cow's milk protein exposure in preventing CMA development.[3-5] In contrast, other studies have reported that supplementing breast-feeding with cow's milk formula (CMF) in the first few days of life can increase the risk of CMA in infants.[5,6] Moreover, subsequent exclusive breast-feeding or small amounts of CMF intake may also increase the risk of CMA.[7]

In 2020, we reported on the findings of the Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study, which demonstrated that the continuous daily ingestion of greater than or equal to 10 mL of CMF between age 1 and 2 months prevented the development of

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No funding was received for this work.
The authors declare that they have no relevant conflicts of interest.
Received for publication March 30, 2021; revised July 27, 2021; accepted for publication July 28, 2021.
Available online ■■
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2213-2198

https://doi.org/10.1016/j.jaip.2021.07.053

Abbreviations used
CMA- Cow's milk allergy
CMF- Cow's milk formula
OFC- Oral food challenge
RR- Risk ratio
SPADE- Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy
SPT- Skin prick test

CMA.[8] In that study, none of the participants who avoided CMF for the first 3 days of life developed CMA. However, a portion of the participants had ingested CMF in the first few days of life to supplement breast-feeding, and discontinued CMF ingestion at different times thereafter. At present, little is known about the association between the timing of CMF discontinuation and CMA development.[9] This study aimed to elucidate this relationship in infants who had ingested CMF in the first 3 days of life through a subgroup analysis of the SPADE study.

METHODS

This analysis was conducted using SPADE study participants who had ingested CMF in the first 3 days of life because of their higher risk of CMA development.[5]

Study design of the SPADE study

The SPADE study was a multicenter, open-label randomized controlled trial that recruited newborns (≤5 days of birth) from 4 hospitals in Okinawa, Japan. Study participants ingested CMF as required to supplement breast-feeding before age 1 month, and underwent a screening oral food challenge (OFC) consisting of 20 mL of CMF at age 1 month. Participants with a negative result in the screening OFC were randomly assigned to either a CMF ingestion group (daily ingestion of ≥10 mL of CMF) or an avoidance group (avoidance of CMF). The intervention was performed between age 1 and 2 months. Participants who had ingested CMF in the first 3 days of life were selected for this subgroup analysis.

Next, open OFCs were performed at age 3 months (first OFC) and age 6 months (second OFC) to assess CMA development. After reaching age 3 months, the participants (with the exception of those with a positive first OFC result) ingested CMF on demand to supplement breast-feeding. Each participant's parent(s) or guardian(s) recorded the daily ingestion quantities of CMF in an event diary, which was checked by the attending physician every month for 6 months. For participants who discontinued CMF ingestion, the reasons for discontinuation were asked and recorded by the physicians. The reasons included, but were not limited to, infant's refusal and mother's desire to resume exclusive breast-feeding. The final date of CMF ingestion at home was regarded as the discontinuation date.

Skin prick tests

At age 3 months and 6 months, skin prick tests (SPTs) were performed to assess sensitization to cow's milk and other allergens. SPTs were performed using standard methods with commercial allergen extracts of cow's milk, egg white, wheat, and soy (Torii Pharmaceutical Co, Ltd, Tokyo, Japan). The positive and negative controls were histamine dihydrochloride (10 mg/mL) and 50% glycerol solution, respectively. A wheal diameter (that was) at least 3 mm more than that of the negative control or larger than half of the positive control was regarded as a positive response for sensitization.

Oral food challenges

The first OFC consisted of a cumulative dose of 50 mL of CMF, which was equivalent to 750 mg of cow's milk protein. Participants who developed a positive reaction to the cow's milk SPT were orally administered 5, 15, and 30 mL of CMF at 30-minute intervals. In contrast, participants with a negative reaction to the cow's milk SPT were orally administered 50 mL of CMF as a single dose. The second OFC consisted of a cumulative dose of 100 mL of CMF, which was equivalent to 1500 mg of cow's milk protein. Participants who developed a positive reaction to the cow's milk SPT were orally administered 5, 15, 30, and 50 mL of CMF at 30-minute intervals. In contrast, participants with a negative reaction to the cow's milk SPT were orally administered 100 mL of CMF as a single dose.

In accordance with the Japanese Guidelines for Food Allergy 2017,[10] OFC results were defined as positive for CMA if any of the following clinical reactions were observed: urticaria, angioedema, vomiting, diarrhea, continuous cough, wheezing, stridor, or a decrease in blood pressure.

Eczema control

All episodes of eczema were treated and controlled (without exacerbation) throughout the intervention period. Participants who developed moderate to severe eczema were proactively treated with topical corticosteroids until the eczema had cleared. Corticosteroids were then used intermittently to maintain remission. Monthly clinical assessments, including growth parameters and the presence of atopic eczema (based on the Japanese Guidelines for Atopic Dermatitis 2017[11]), were performed until age 6 months.

Definition of the discontinued and continuous groups

Among the participants who had ingested CMF in the first 3 days of life, we identified those who discontinued CMF ingestion at home before age 1 month (designated the "DISC <1-month group"), during age 1 to 2 months ("DISC 1-2—month group"), and during age 3 to 5 months ("DISC 3-5—month group"). We also identified participants who continued CMF ingestion until age 6 months ("continuous group"). Because some participants had inadequate adherence to the intervention regimen of the SPADE study, allocation to these discontinued and continuous groups was performed retrospectively on the basis of event diaries that recorded the daily CMF ingestion quantities.

The DISC <1-month group consisted of ingestion group participants who discontinued CMF before allocation and subsequently did not ingest CMF because of poor adherence during the intervention period, as well as avoidance group participants who discontinued CMF before allocation and subsequently did not resume CMF after the intervention period. The DISC 1-2—month group consisted of ingestion group participants who discontinued CMF during the intervention period (including some cases of inadequate adherence), as well as avoidance group participants who discontinued CMF during the intervention period (including some cases of inadequate adherence) and subsequently did not resume CMF after the intervention period. The DISC 3-5—month group consisted of ingestion group participants who discontinued CMF after the intervention period, as well as avoidance group participants who (with or without CMF ingestion during the intervention period) ingested CMF after age 3 months and subsequently discontinued CMF by age 6 months. The continuous group consisted of both ingestion and avoidance group participants who continued

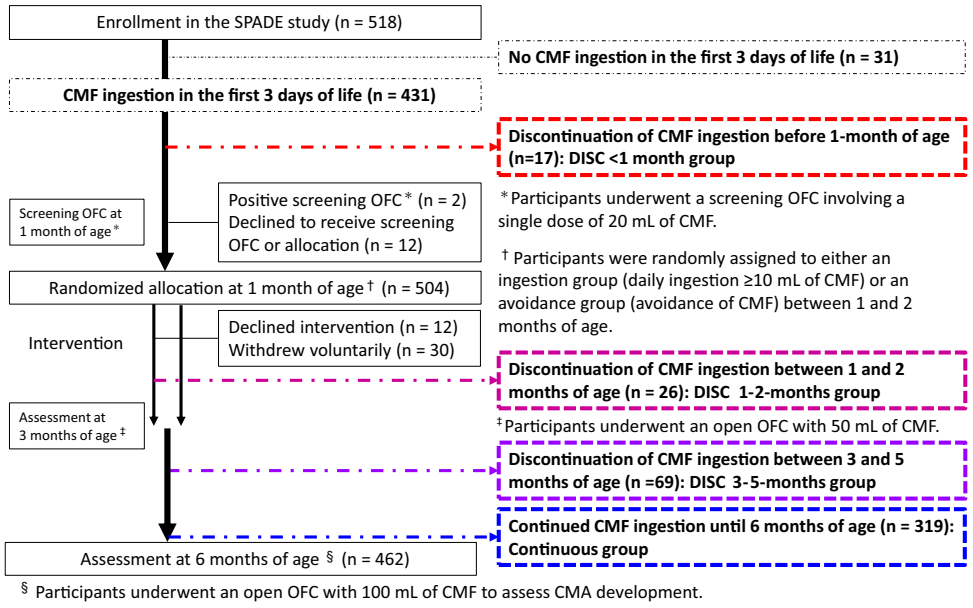

FIGURE 1. Study flow diagram.

TABLE I. Baseline characteristics of participants

Characteristic	Value				*P* value
	DISC <1-month group (n = 17)	DISC 1-2−month group (n = 26)	DISC 3-5−month group (n = 69)	Continuous group (n = 319)	
Male	5 (29.4)	11 (42.3)	32 (46.4)	183 (57.4)	.002
Cesarean section	3 (17.6)	8 (30.8)	17 (24.6)	80 (25.1)	.83
Season of birth: spring/summer	13 (76.5)	15 (57.7)	43 (62.3)	213 (6.8)	.55
Gestational age (wk)	40 (38-40)	38 (38-40)	39 (38-40)	39 (38-40)	.18
Birth weight (g)	3050 (2945-3158)	3053 (2862-3220)	3062 (2802-3265)	2998 (2772-3240)	.82
No siblings	6 (35.3)	7 (26.9)	26 (37.7)	135 (42.3)	.43
Maternal age (y)	35 (30-37)	33 (31-37)	32 (28-34)	32 (28-36)	.22
Maternal body mass index before pregnancy	21.2 (20.3-23.2)	21.8 (19.7-23.1)	20.6 (19.5-22.2)	20.8 (19.1-23.4)	.66
Maternal weight gain during pregnancy	10.6 (6.3-11.6)	10.3 (8.0-11.6)	10.5 (9.3-12.2)	9.7 (7.6-12.3)	.48
Maternal atopic diseases*	8 (47.1)	8 (30.8)	27 (39.1)	131 (41.1)	.70
Maternal smoking	0 (0)	0 (0)	2 (2.9)	12 (3.8)	.94
Paternal age	35 (30-38)	33 (31-39)	33 (30-36)	33 (28-37)	.35
Paternal atopic diseases*	11 (64.7)	10 (38.5)	26 (37.7)	147 (46.1)	.20
Paternal smoking	7 (41.2)	7 (26.9)	18 (26.1)	118 (37.0)	.27
Domestic dog exposure at birth	3 (17.6)	3 (11.5)	9 (13.0)	47 (14.7)	.94
Domestic cat exposure at birth	1 (5.9)	0 (0)	5 (7.2)	22 (6.9)	.65

Continuous group, Continued CMF ingestion up to age 6 mo; *DISC <1-month group*, discontinued CMF ingestion before age 1 mo; *DISC 1-2−month group*, discontinued CMF ingestion between age 1 and 2 mo; *DISC 3-5−month group*, discontinued CMF ingestion between age 3 and 5 mo.
Values are presented as number (percentage) or median (interquartile range). *P* values were calculated using Fisher exact test for categorical variables and the Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables, where appropriate.
*Atopic diseases include food allergy, bronchial asthma, atopic dermatitis, and allergic rhinitis.

CMF ingestion (regardless of daily or nondaily consumption) until age 6 months.

Outcome measures

The primary outcome measure was the proportion of participants who developed CMA at age 6 months. The secondary outcome measures were the median differences in (a) the total number of CMF ingestion days before discontinuation and (b) the mean CMF ingestion quantity per day before discontinuation between participants with and without CMA. In addition, we explored the associations between the reasons for CMF discontinuation and CMA development.

TABLE II. Characteristics and allergen sensitization at age 6 mo

	DISC <1-month group (n = 17)				DISC 1-2−month group (n = 26)				DISC 3-5−month group (n = 69)				Continuous group (n = 319)
Characteristic	**Value**	**RR**	**95% CI**	***P* value**	**Value**	**RR**	**95% CI**	***P* value**	**Value**	**RR**	**95% CI**	***P* value**	**Value**
Body weight at age 6 mo (g)	7340 (6680-7880)	NaN	NaN	.12	7295 (6890-8245)	NaN	NaN	.26	7385 (6909-8171)	NaN	NaN	.20	7560 (7140-8190)
Eczema before age 3 mo	12 (70.6)	1.40	1.01-1.94	.14	7 (26.9)	0.53	0.28-1.01	.02	37 (53.6)	1.06	0.83-1.36	.69	161 (50.5)
Eczema between age 3 and 5 mo	7 (41.2)	1.33	0.74-2.40	.43	6 (23.1)	0.74	0.36-1.53	.51	22 (31.9)	1.03	0.70-1.51	.89	99 (31.0)
Positive SPT response to egg white	8 (47.1)	1.85	1.08-3.17	.09	7 (26.9)	1.06	0.55-2.05	.82	22 (31.9)	1.26	0.85-1.86	.29	81 (25.4)
Positive SPT response to cow's milk	8 (47.1)	7.15	3.72-13.7	<.001	7 (26.9)	4.09	1.92-8.71	.002	13 (18.8)	2.86	1.51-5.43	.003	21 (6.6)

Continuous group, Continued CMF ingestion up to age 6 mo; *DISC <1-month group*, discontinued CMF ingestion before age 1 mo; *DISC 1-2−month group*, discontinued CMF ingestion between age 1 and 2 mo; *DISC 3-5−month group*, discontinued CMF ingestion between age 3 and 5 mo; *NaN*, not a number.

Values are presented as number (percentage) or median (interquartile range). *P* values were calculated using Fisher exact test for categorical variables and the Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables, where appropriate. The Bonferroni correction (significance level: .05/3 = .016) was applied, as appropriate, for multiple comparisons that compared each of the 3 discontinued groups to the continuous group.

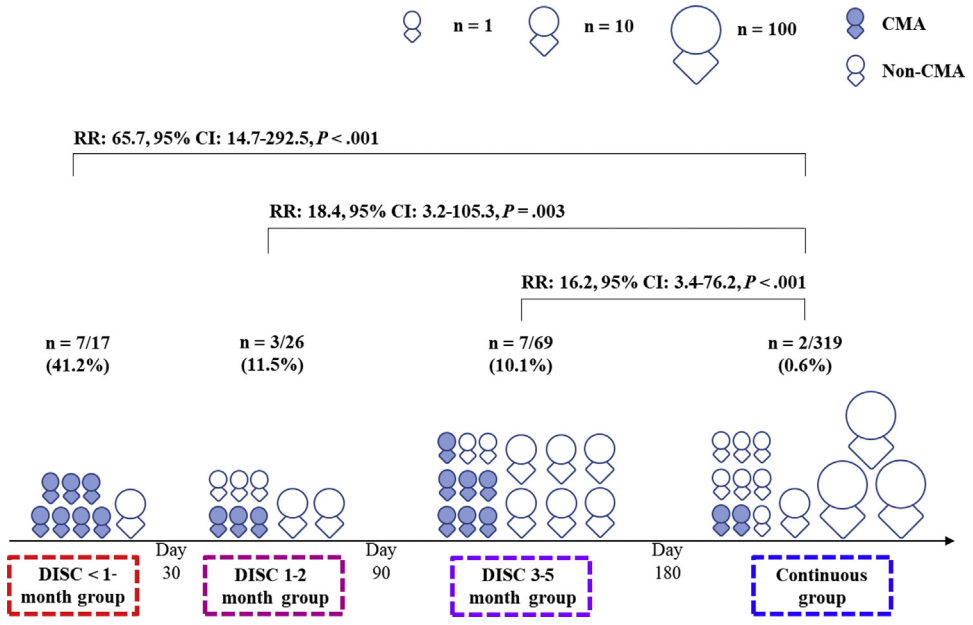

FIGURE 2. Proportion of participants with CMA at age 6 months among infants who had ingested CMF in the first 3 days of life. The RRs and 95% CIs for CMA development were calculated. The Bonferroni correction (significance level: .05/3 = .016) was applied for multiple comparisons that compared each of the 3 discontinued groups to the continuous group. *Continuous group*, Continued CMF ingestion up to age 6 months; *DISC <1-month group*, discontinued CMF ingestion before age 1 month; *DISC 1-2—month group*: discontinued CMF ingestion between age 1 and 2 months; *DISC 3-5—month group*, discontinued CMF ingestion between age 3 and 5 months.

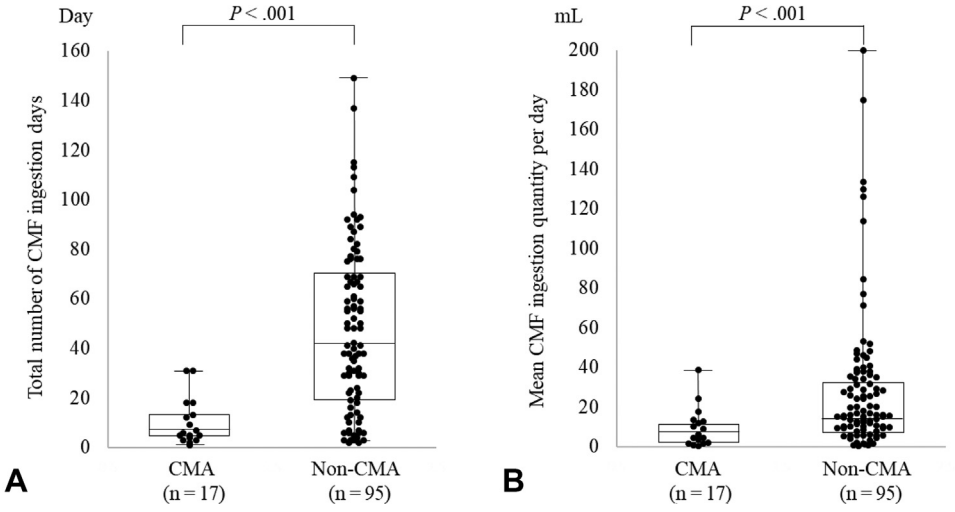

FIGURE 3. Total number of CMF ingestion days and mean CMF ingestion quantity per day before discontinuation. (**A**) Total number of CMF ingestion days before CMF discontinuation. (**B**) Mean CMF ingestion quantity per day before CMF discontinuation. *P* values were calculated using the Mann-Whitney *U* test (significance level: .05).

Statistical analysis

The groups were compared using Fisher exact test for categorical variables and the Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables, as appropriate. Statistical significance was set at *P* less than .05 (2-tailed). We calculated the risk ratios (RRs) and 95% CIs for the primary outcome measure. The Bonferroni correction (significance level: .05/3 = .016) was applied for multiple comparisons that compared each of the 3 discontinued groups to the continuous group. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[12] All study participants provided informed consent on enrollment in the SPADE study, and the study was approved by the institutional ethics committee of each participating hospital. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

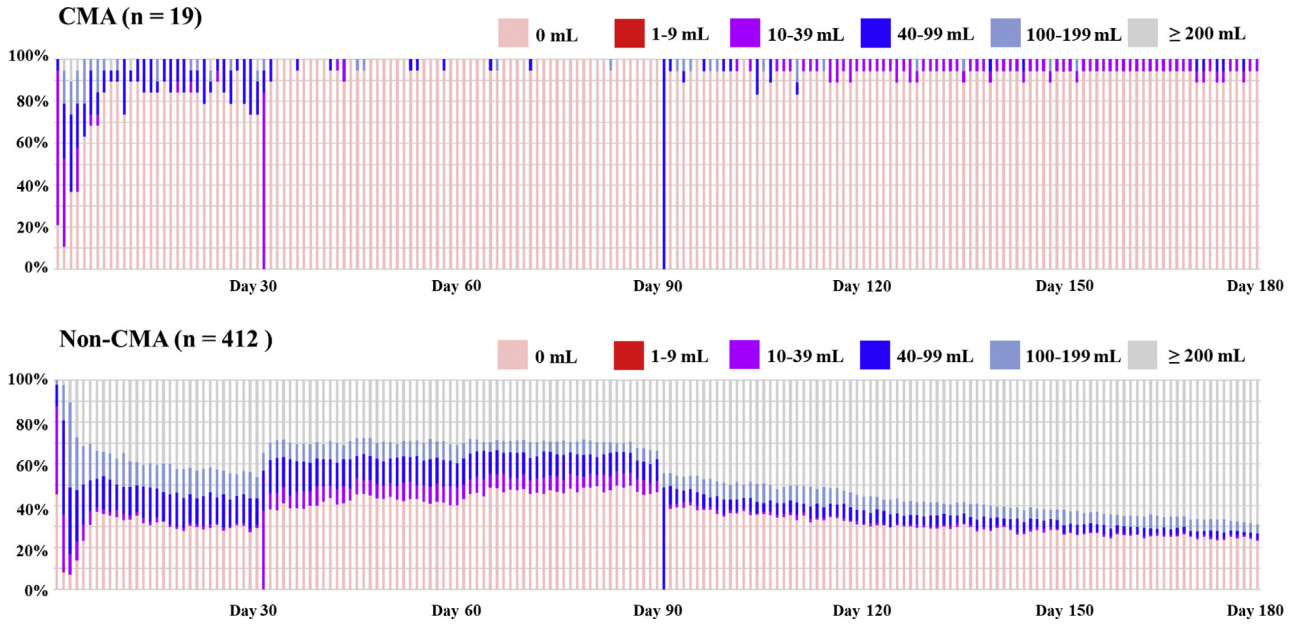

FIGURE 4. Proportions of daily CMF ingestion quantities. The figure shows the proportions of daily CMF ingestion quantities throughout the study period. The ingestion quantities were classified into 6 groups: 0 mL, 1 to 9 mL, 10 to 39 mL, 40 to 99 mL, 100 to 199 mL, and greater than or equal to 200 mL.

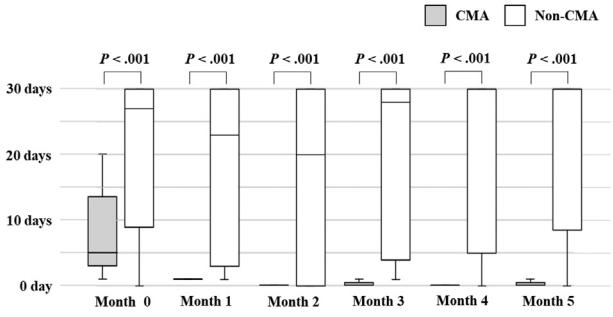

FIGURE 5. Total number of CMF ingestion days in each month of age. *P* values were calculated using the Mann-Whitney *U* test (significance level: .05).

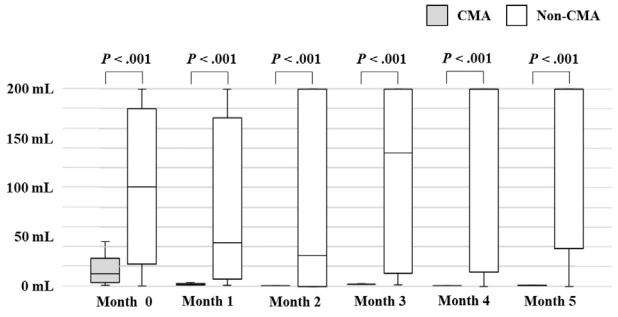

FIGURE 6. Mean CMF ingestion quantity per day in each month of age. *P* values were calculated using the Mann-Whitney *U* test (significance level: .05).

RESULTS

Study population

Enrollment for the SPADE study was conducted from January 1, 2017, to August 31, 2019.[8] A total of 518 infants were initially enrolled, of which 504 underwent randomized allocation and 462 completed the SPTs and OFCs at age 6 months. Among the 462 candidate participants, 31 did not ingest CMF in the first 3 days of life. The remaining 431 participants who had ingested CMF in the first 3 days of life were included in this study and categorized into the following groups: DISC <1-month group (n = 17; 1 from the ingestion group and 16 from the avoidance group), DISC 1-2−month group (n = 26; 8 from the ingestion group and 18 from the avoidance group), DISC 3-5−month group (n = 69; 39 from the ingestion group and 30 from the avoidance group), and continuous group (n = 319; 160 from the ingestion group and 159 from the avoidance group) (Figure 1). The 9 participants from the ingestion group who discontinued CMF before age 1 month and between age 1 and 2 months were not included in the per-protocol analysis of the SPADE study.

Baseline characteristics

The baseline characteristics of the 4 groups are presented in Table I. There were no significant intergroup differences in all characteristics except sex. The characteristics and allergen sensitization results at age 6 months are summarized in Table II. There were no significant intergroup differences in median body weight at age 6 months, proportions of cases with clinician-diagnosed eczema (including mild eczema not considered to be atopic dermatitis), and sensitization to egg white. However, the analysis detected significant intergroup differences in sensitization to cow's milk.

Primary outcome measure

Figure 2 shows the results of the primary outcome measure. The proportions of participants with CMA were higher in the DISC <1-month group (n = 7 of 17, 41.2%; RR, 65.7; 95% CI, 14.7-292.5; $P < .001$), DISC 1-2−month group (n = 3 of 26, 11.5%; RR, 18.4; 95% CI, 3.2-105.3; $P = .003$), and DISC 3-5−month group (n = 7 of 69, 10.1%; RR, 16.2; 95% CI, 3.4-76.2; $P < .001$) when compared with the continuous group (n = 2 of 319; 0.6%). The proportions of participants with CMA were higher in all of the 3 discontinued groups (n = 17 of 112, 15.2%; RR, 24.2; 95% CI, 5.7-103.1; $P < .001$) than the continuous group.

Secondary outcome measures

Among the 112 participants who discontinued CMF ingestion, 17 (15.2%) developed CMA by age 6 months. The median total number of CMF ingestion days before discontinuation was 6 days (interquartile range, 4-13 days) in the CMA participants and 41 days (19.5-69 days) in the non-CMA participants ($P < .001$). The median of the mean CMF ingestion quantity per day before discontinuation was 6.2 mL (interquartile range, 1.9-12.8 mL) in the CMA participants and 16.9 mL (9.9-36.8 mL) in the non-CMA participants ($P < .001$) (Figure 3).

The 112 participants who discontinued CMF ingestion comprised 48 ingestion group participants (including 2 with CMA) and 64 avoidance group participants (including 15 with CMA). Among the ingestion group participants, the reasons for discontinuing CMF ingestion were infant's refusal (n = 14), mother's desire to resume exclusive breast-feeding (n = 1, which had CMA), end of the designated ingestion period (n = 28, including 1 with CMA), and constipation (n = 5). Among the avoidance group participants, the reasons for discontinuing CMF ingestion were infant's refusal (n = 16, including 2 with CMA), mother's desire to resume exclusive breast-feeding (n = 12, including 5 with CMA), start of the designated avoidance period (n = 13, including 5 with CMA), no perceived need to use CMF after the avoidance period (n = 19, including 3 with CMA), and unknown (n = 4). Two (6.7%) of the 30 participants (14 from the ingestion group and 16 from the avoidance group) who discontinued CMF ingestion because of infants' refusal developed CMA. In contrast, 15 (19.2%) of the 78 participants who discontinued CMF ingestion for other reasons developed CMA. None of the participants discontinued CMF ingestion because of suspected CMA symptoms.

Additional analysis

Thirty-one participants did not ingest CMF in the first 3 days of life in the SPADE study. Among these, 19 started CMF ingestion during the first month of life, 9 started CMF ingestion during age 1 to 2 months due to group allocation, 2 started CMF ingestion during age 3 to 5 months, and 1 did not ingest CMF up to age 6 months. We performed an additional analysis with all of the SPADE study participants, including the 30 who did not ingest CMF in the first 3 days of life (the participant who completely avoided CMF during the first 6 months of age was excluded). Among these, 4 were allocated to the revised DISC <1-month group, 5 were allocated to the revised DISC 1-2−month group, 9 were allocated to the revised DISC 3-5−month group, and 12 were allocated to the revised continuous group. The proportions of participants with CMA were higher in the revised DISC <1-month group (n = 7 of 21, 33.3%; RR, 55.2; 95% CI, 12.2-249.3; $P < .001$), DISC 1-2−month group (n = 3 of 31, 9.6%; RR, 16.0; 95% CI, 2.8-92.3; $P = .005$), and DISC 3-5−month group (n = 7 of 78, 9.0%; RR, 14.9; 95% CI, 3.1-70.1; $P < .001$) when compared with the continuous group (n = 2 of 331, 0.6%). These results were similar to those of the main analysis.

Figure 4 shows the proportions of the daily CMF ingestion quantities (including CMF ingestion at the screening and first OFCs) throughout the study period. To evaluate the influence of the timing, volume, and frequency of CMF exposure on CMA development, we compared the total number of CMF ingestion days (Figure 5) and the mean CMF ingestion quantity per day (Figure 6) in each month of age between the CMA and non-CMA participants. In all months of age, CMA participants had a lower frequency and smaller volume of CMF ingestion than non-CMA participants ($P < .001$).

DISCUSSION

This subgroup analysis of the SPADE study examined the association between the timing of CMF discontinuation and CMA development in infants who had ingested CMF in the first 3 days of life. Our results indicated that early discontinuation of CMF ingestion at home, particularly in the first month of life, increased the risk of developing CMA at age 6 months. Although previous studies have reported that early supplementation with CMF can increase the risk of CMA in breast-fed infants,[5,6] the subsequent continuation of CMF ingestion may help to reduce this risk.[7] It has also been reported that the prolonged elimination of cow's milk can induce IgE-mediated CMA in children without previous problems from cow's milk intake.[13,14] Earlier discontinuations result in longer elimination periods, which may have contributed to the development of CMA in our participants.

A lower total number of CMF ingestion days and smaller daily CMF ingestion quantities before discontinuation were identified as risk factors for CMA development. In our study, no participant who had ingested CMF for over 32 days in total developed CMA. This suggests that continuous CMF ingestion over the first month of life may be associated with a reduced risk of CMA development. Furthermore, the main analysis of the SPADE study demonstrated that daily ingestion of CMF between age 1 and 2 months prevented CMA development.[8] Even if an infant cannot ingest CMF during that period for some reason, the risk of CMA may be reduced by the continuous ingestion of CMF during the first month of life and after age 3 months. Our results suggest that the reduction of CMA risk is associated with the timing of CMF discontinuation, the total number of CMF ingestion days, and the daily CMF ingestion quantity. However, further analyses are needed to verify these findings.

Study strengths and limitations

The main strength of this study was the elimination of recall bias because the information on CMF ingestion patterns was gathered prospectively. In addition, CMA was determined by OFC in all participants, including infants who disliked CMF. This ensured the accuracy of CMA incidence at age 6 months. However, the study was limited because we did not perform a double-blind, placebo-controlled OFC to confirm CMA. To compensate for this limitation, objective physical findings were used to identify CMA symptoms, with each evaluation performed by 2 or more investigators. Next, the study was also

limited by the use of relatively small subgroup numbers. In addition, exposure to the screening and first OFCs meant that the participants did not completely discontinue CMF at any point before age 3 months. It is therefore possible that variable exposure over the first 6 months of age, rather than the early discontinuation of CMF, was the driving factor for CMA development. However, none of the participants who did not ingest CMF in the first 3 days of life developed CMA regardless of subsequent variable exposure with the OFCs. This suggests that variable exposure had a limited effect on CMA development, but further interventional trials are needed to clarify this issue. Finally, although CMF refusal may be an indication of CMA, our results suggest that the infants' refusal was not necessarily associated with an elevated risk of CMA development. However, our data on the reasons for CMF discontinuation were observational, and the participants were not randomly assigned to the discontinued groups. Further randomized controlled trials are therefore needed to determine whether CMF refusal is an early sign of allergic reactivity.

CONCLUSIONS

In addition to ascertaining the appropriate timing of CMF introduction, it may be important to avoid the early discontinuation of CMF ingestion, particularly in the first month of life, to prevent CMA development in infants. If an infant is supplemented with CMF in the first 3 days of life, continuous CMF ingestion, even in small quantities, may be effective in reducing the risk of CMA development.

Acknowledgments

We are grateful to the members of the SPADE study team, and thank the participants and their families for their cooperation with the trial.

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