

Original Article

Effects of delivery mode and labor duration on the development of food sensitization in infancy



Tetsuhiro Sakihara, MD^{*}; Daichi Yasuki, MD^{*}; Kenta Otsuji, MD[†]; Yohei Arakaki, MD[‡]; Kazuya Hamada, MD[§]; Shiro Sugiura, MD, MPH, PhD^{||}; Komei Ito, MD, PhD^{||}

^{*} Department of Pediatrics, Heartlife Hospital, Okinawa, Japan

[†] Department of Pediatrics, Okinawa Kyodo Hospital, Okinawa, Japan

[‡] Department of Pediatrics, Naha City Hospital, Okinawa, Japan

[§] Department of Child Health and Welfare (Pediatrics), Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

^{||} Department of Allergy, Aichi Children's Health and Medical Center, Aichi, Japan

ARTICLE INFO

Article history:

Received for publication February 7, 2022.

Received in revised form March 24, 2022.

Accepted for publication April 7, 2022.

ABSTRACT

Background: The effects of delivery mode and labor duration on the development of food sensitization (FS) in infancy remain unclear.

Objective: To elucidate the potential effects of delivery mode and labor duration on FS development by 6 months of age.

Methods: Using data from a randomized controlled trial of a birth cohort from 4 Japanese hospitals that assessed cow's milk allergy development by 6 months of age, we performed a nested case-control trial of 462 participants who had undergone the final assessment at 6 months of age. FS was defined as positive skin prick test reactions to hen's egg, cow's milk, wheat, or soy. For the primary outcome, we calculated the adjusted odds ratio of vaginal delivery (VD) relative to cesarean delivery for FS development by 6 months of age using a multivariable logistic regression analysis. For the secondary outcome, we compared labor durations between participants with and without FS using the Mann-Whitney *U* test.

Results: The adjusted odds ratio of VD for FS development was 2.54 (95% confidence interval, 1.32–4.87; *P* = .005). The median labor duration was significantly longer in participants with FS (5.7 hours, interquartile range, 2.7–10.1) than in participants without FS (4.5 hours, 1.1–8.2) (*P* = .01).

Conclusion: VD was considerably associated with an increased risk of FS in infancy, and longer labor durations may promote FS development.

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Food allergies (FAs) are increasingly prevalent throughout the world. To facilitate the primary prevention of FAs, there is a need to first elucidate the factors that could lead to the development of food sensitization (FS) in infancy.^{1,2}

Previous studies have reported FS and FA to be associated with sex,^{2,3} season of birth,^{1,4} gestational age,^{5,6} birth weight,⁷ presence of siblings,^{1,8,9} maternal age,¹⁰ weight gain during pregnancy,¹¹ parental atopic diseases,^{1,3,5,9} pet ownership,¹² maternal or neonatal antibiotic use,^{13–16} breastfeeding,^{13,17} eczema in early infancy,^{1,18} ingestion of cow's milk formula (CMF) in the first few days after

birth,¹⁹ and the age at which complementary foods are introduced.^{9,20}

However, the potential effect of delivery mode on the risk of childhood allergic disease development remains unclear, and the current evidence is conflicting. Several reports have indicated that cesarean delivery (CD) can elevate the risk of FS and FA when compared with vaginal delivery (VD),^{5,6,13,21} whereas other studies have found no such associations.^{12,18,22,23} Furthermore, maternal and infant stress during labor may affect prenatal immune development by reducing naive regulatory T cell numbers,²⁴ but little is known about the relationship between labor duration (which can be indicative of stress exposure) and the risk of FS. In general, labor duration tends to be longer for the first child, and studies have reported that the first child has an increased risk of developing FS and FA.^{1,8,9} However, whether this relationship is owing to longer labor duration, remains unclear.

Reprints: Tetsuhiro Sakihara, MD, Department of Pediatrics, Heartlife Hospital, 208 Iju, Nakagusuku-son, Nakagami-gun, Okinawa 901-2492, Japan. E-mail: odekori2000@yahoo.co.jp.

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2022.04.008>

1081-1206/© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

To bridge these gaps in the literature, this study was conducted to assess whether delivery mode and labor duration affect the risk of developing FS in infancy.

Methods

To assess whether delivery mode (VD vs CD) and labor duration affect the risk of developing FS (hen's egg, cow's milk, wheat, and soy) in infancy, we conducted a nested case-control trial on infants who had participated in the Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study.²⁵ The SPADE study was originally designed to assess the impact of early CMF introduction on cow's milk allergy (CMA) development in Japanese newborns until 6 months of age. For the present study, we identified FS using skin prick tests (SPTs) at 3 and 6 months of age.

Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) Study Design

The SPADE study was a multicenter, open-label randomized controlled trial of newborns recruited from 4 hospitals in Okinawa, Japan. Recruitment was conducted from January 1, 2017, to August 31, 2019.²⁵ The study population included newborns (≤ 5 days of birth) with a gestational age of more than or equal to 35 weeks and a birth weight of more than or equal to 2000 g and excluded those with complications from any severe underlying disease. Participants ingested CMF on an as-needed basis to supplement breastfeeding before 1 month of age. To acquire baseline information on demographics and other characteristics, the participating families answered a standardized questionnaire after recruitment. The questionnaire included items on the presence of siblings, the mother's elimination diet during pregnancy, parental smoking habits, pet (dogs or cats) ownership, and parental history of atopy (FA, bronchial asthma, atopic dermatitis, and allergic rhinitis).

The SPADE study randomly assigned the participants to a CMF ingestion group (≥ 10 mL daily) or an avoidance group between 1 and 2 months of age. A screening oral food challenge (OFC) (20 mL CMF) at 1 month of age and follow-up OFCs at 3 (50 mL CMF) and 6 (100 mL CMF) months of age were performed to evaluate CMA development.

By reviewing medical records from each participant's delivery hospitalization, the investigators acquired information on perinatal characteristics (including gestational age, birth weight, maternal age, maternal body mass index before pregnancy, maternal weight gain during pregnancy, delivery mode, vacuum extraction or emergency CD delivery, labor duration, Apgar score, umbilical artery pH, and neonatal respiratory distress) and the daily quantity of CMF consumed during hospitalization. After hospital discharge, parents recorded adverse events, daily CMF consumption quantities, and breastfeeding status in event diaries. These diaries were checked by physicians every month until the participants reached 6 months of age.

Skin Prick Tests

During the SPADE study, SPTs were administered at 3 and 6 months of age to assess FS to hen's egg, cow's milk, wheat, and soy using commercial allergen extracts (Torii Pharmaceutical Co, Ltd, Tokyo, Japan). Histamine dihydrochloride (10 mg/mL) and 50% glycerol solution were used as positive and negative controls, respectively. We used bifurcated needles (Allergy Laboratories of Ohio, Inc, Ohio) as the puncture device, and the SPT reaction was evaluated 15 minutes after puncture. SPTs were not performed in duplicate. A positive SPT reaction was defined as a wheal diameter larger than half of

the positive control or more than or equal to 3 mm larger than the negative control.²⁶ In this study, FS refers to more than or equal to 1 positive SPT reactions (hen's egg, cow's milk, wheat, or soy) experienced by a participant by 6 months of age.

Eczema Control

During the study period, all episodes of eczema were controlled and treated. Corticosteroids were used to treat cases of moderate-to-severe eczema and were subsequently administered intermittently to maintain remission. Participants were assessed every month to monitor their growth parameters and the occurrence of atopic eczema, which was identified according to the Japanese Guidelines for Atopic Dermatitis 2017.²⁷

Outcome Measures

The primary outcome measure was the adjusted odds ratio (aOR) of VD-born infants for FS development by 6 months of age relative to CD-born infants. The secondary outcome measure was the statistical relationship between labor duration (in hours) and the development of FS by 6 months of age.

Statistical Analysis

Categorical variables were analyzed using Fisher's exact test, and continuous variables were analyzed using the Mann-Whitney *U* test. For the primary outcome measure, multivariable logistic regression analysis was conducted on the primary outcome population (ie, all participants who had been assessed with SPTs at 6 months of age) to determine the possible effects of VD on FS development. There were 2 different models used to analyze these effects. Model 1 included the following independent variables: sex, season of birth, gestational age, birth weight, mode of delivery, vacuum extraction or emergency CD delivery, neonatal asphyxia, umbilical artery pH, neonatal respiratory distress, no siblings (first child), maternal age, maternal body mass index before pregnancy, maternal weight gain during pregnancy, maternal atopic diseases, maternal smoking, paternal age, paternal atopic diseases, paternal smoking, domestic dog exposure at birth, domestic cat exposure at birth, maternal antibiotic use, neonatal antibiotic use, no CMF ingestion in the first 3 days of life, eczema occurrence within the first 6 months of age, and continuous breastfeeding up to 6 months of age. Model 2 included the same independent variables as model 1 and allocation to the CMF ingestion group in the SPADE study. The aORs and 95% confidence intervals (CIs) were calculated using these models.

For the secondary outcome measure, labor durations between participants with and without FS were compared using the Mann-Whitney *U* test in the secondary outcome population (ie, primary outcome population excluding participants with inadequate information on labor duration). Next, labor duration was categorized into quartiles and analyzed using the Cochran-Armitage test.

In addition to the main analysis of FS, we conducted subgroup analyses focused on hen's egg sensitization (ES) and cow's milk sensitization (CMS). We also investigated the statistical relationship between labor duration and the development of FS among participants stratified according to the presence or absence of siblings and among the VD-born participants.

P values (2-tailed) below .05 were considered statistically significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).²⁸ All study participants provided informed consent on enrollment in the SPADE study, and the study was approved by the institutional review boards of the participating hospitals.

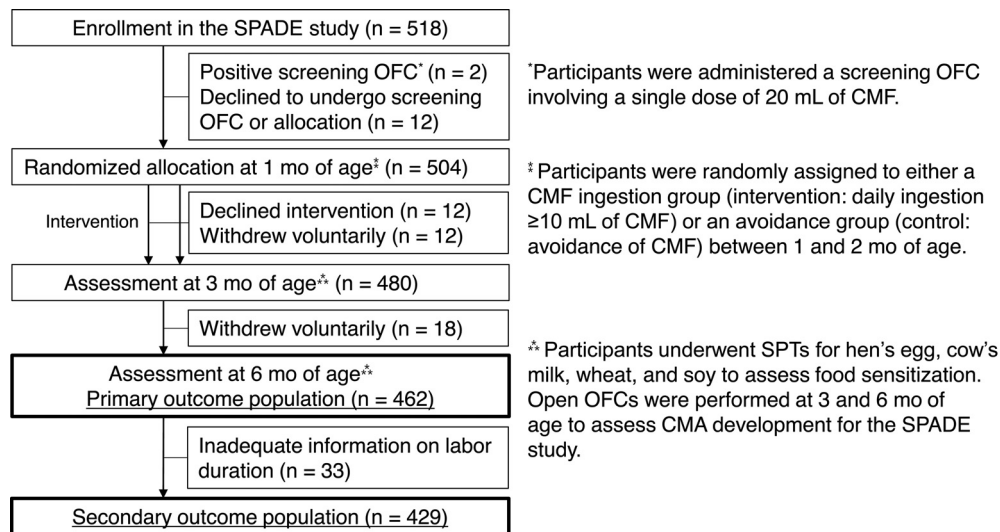


Figure 1. Study design. CMA, cow's milk allergy; CMF, cow's milk formula; OFC, oral food challenge; SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy; SPT, skin prick test.

Results

Study Population

The study design is presented in Figure 1. Of the 518 infants initially enrolled in the SPADE study, 504 underwent randomized allocation and 462 completed the assessments at 6 months of age. These 462 participants (VD, 353; CD, 109) comprised the primary outcome population for the present study. Table 1 and eTable 1 present the baseline characteristics of the primary outcome population and nonanalyzed population (ie, SPADE study enrollees who were not assessed at 6 months of age). There were no significant intergroup differences in baseline characteristics except for the proportion of participants with no siblings (first child) ($P = .03$). After excluding 33 participants with inadequate information on labor duration, the secondary outcome population comprised 429 participants (VD, 325; CD, 104). None of the participants had been introduced to hydrolyzed formula, hen's egg, wheat, or soy protein before 6 months of age.

Demographic and Other Characteristics

Table 2 and eTable 2 summarize the demographic and other characteristics of the participants in the primary outcome population according to delivery mode. When compared with the CD-born group, the VD-born group tended to have a higher gestational age at birth, higher proportion of infants with no CMF ingestion in

the first 3 days of life, lower parental age at delivery, and lower maternal body mass index before pregnancy. The proportion of vacuum extraction cases among all VD-born participants (13.0%) was lower than the proportion of emergency CD cases among all CD-born participants (32.1%). There were no forceps delivery cases. Although there were significant intergroup differences in the proportions of maternal antibiotic use ($P < .001$), there was no significant difference in the proportion of neonatal antibiotic use ($P = .79$). There were also no important differences in the other parental and perinatal factors, proportions of clinician-diagnosed eczema (including mild eczema not considered to be atopic dermatitis) within the first 6 months of age, and proportions of participants who had been continuously breastfed (including exclusive breastfeeding and mixed feeding) up to 6 months of age. None of the mothers had eliminated hen's egg, cow's milk, wheat, or soy from their diet during pregnancy or lactation.

Incidences of Food Sensitization and Cow's Milk Allergy

The incidences of FS by 3 and 6 months of age are found in Figure 2. The incidences of FS (referring to ≥ 1 positive SPT reactions to hen's egg, cow's milk, wheat, or soy) and ES at 6 months of age were significantly higher in the VD-born participants than in the CD-born participants ($P = .01$, $P = .01$, respectively). However, there were no significant differences in the incidences of sensitization to cow's

Table 1
Baseline Characteristics

Characteristics	SPADE study enrollees (n = 518)	Primary outcome population (n = 462)	Nonanalyzed population (n = 56)	P value
Male	279 (53.9)	253 (54.8)	26 (46.3)	.26
Gestational age (wk)	39 (38–40)	39 (38–40)	39 (38–39)	.52
Birth weight (g)	3011 (2798–3240)	3011 (2791–3243)	3012 (2850–3206)	.63
Vaginal delivery	396 (76.5)	353 (76.4)	43 (76.8)	>.99
No siblings (first child)	199 (38.4)	185 (40.0)	14 (25.0)	.03
Maternal age	32 (28–36)	32 (28–36)	33 (29–35)	.89
Maternal atopic diseases ^a	218 (42.1)	193 (41.8)	25 (44.6)	.56
Paternal age	33 (29–33)	33 (29–37)	33 (29–36)	.96
Paternal atopic diseases ^a	231 (44.6)	209 (45.2)	22 (39.3)	.56

Abbreviation: SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy

NOTE. Values are presented as number (percentage) or median (interquartile range). P values were calculated using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

^aAtopic diseases include food allergy, bronchial asthma, atopic dermatitis, and allergic rhinitis.

Table 2
Demographic and Other Characteristics of the Participants According to Delivery Mode

Characteristics	Total (n = 462)	Vaginal delivery (n = 353)	Cesarean delivery (n = 109)	P value
Male	253 (54.8)	194 (55.0)	59 (54.1)	.91
Gestational age (wk)	39 (38–40)	39 (38–40)	38 (38–39)	<.001
Birth weight (g)	3011 (2791–3243)	3014 (2815–3244)	2994 (2655–3200)	.26
Vacuum extraction or emergency cesarean delivery	81 (17.5)	46 (13.0)	35 (32.1)	<.001
No siblings (first child)	185 (40.0)	148 (41.9)	37 (33.9)	.15
Maternal age	32 (28–36)	32 (38–35)	34 (30–37)	<.001
Maternal body mass index before pregnancy	20.8 (19.3–23.2)	20.6 (19.1–22.8)	22.2 (20.5–25.2)	<.001
Maternal atopic diseases ^a	193 (41.8)	150 (42.5)	43 (39.5)	.66
Paternal age	33 (29–37)	32 (29–36)	35 (30–38)	.009
Paternal atopic diseases ^a	209 (45.2)	153 (43.3)	56 (51.4)	.15
Maternal antibiotic use for treatment of chorioamnionitis or prevention of GBS infection ^b	67 (14.5)	63 (17.9)	4 (3.7)	<.001
Neonatal antibiotic use ^c	19 (4.1)	14 (4.0)	5 (4.6)	.79
No CMF ingestion in the first 3 d of life	31 (6.7)	29 (8.2)	2 (1.8)	.01
Eczema occurrence within the first 6 mo of life	290 (62.8)	221 (62.6)	69 (63.3)	>.99
Continuous breastfeeding up to 6 mo of age	323 (69.9)	245 (69.4)	78 (71.6)	.72

Abbreviations: CMF, cow's milk formula; GBS, group B *Streptococcus*.

NOTE. Values are presented as number (percentage) or median (interquartile range). P values were calculated using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

^aAtopic diseases include food allergy, bronchial asthma, atopic dermatitis, and allergic rhinitis.

^bIntrapartum antibiotic treatment for chorioamnionitis or intrapartum antibiotic prophylaxis to prevent the vertical transmission of GBS.

^cAntibiotic use in newborns within the first 7 days of life.

milk, wheat, or soy ($P = .70$, $P = .24$, $P > .99$, respectively). To assess the robustness of these results, we reperformed the analyses using different definitions for a positive SPT reaction. When the positive SPT reaction was defined as a wheal diameter more than or equal to 4 mm larger than the negative control, the incidence of ES was significantly higher in the VD-born participants than the CD-born participants ($P = .02$) (eFig 1). However, when the positive SPT reaction was defined as a wheal diameter more than or equal to 6 mm larger than the negative control, there were no differences in FS or sensitization to the specific foods (eFig 2). eTable 3 presents the results of the univariate

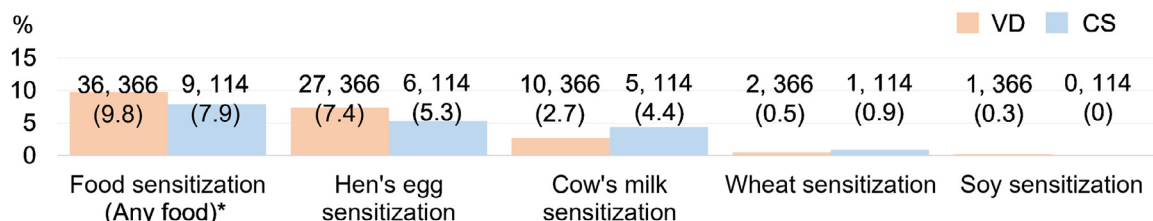
analyses to assess the risk factors for FS development by 6 months of age.

The proportion of CMA development by 3 months of age was 1.5% (7 of 480) (VD, 1.1% [4 of 366]; CD, 2.6% [3 of 114], $P = .36$), and the proportion of CMA development by 6 months of age was 4.1% (19 of 462) (VD, 4.2% [15 of 353]; CD, 3.7% [4 of 109], $P > .99$).

Primary Outcome Measure

The results of the multivariable logistic regression analyses are presented in Figure 3 and Table 3. Model 1 and model 2 calculated

3 months of age (n = 480)



6 months of age (n = 462)

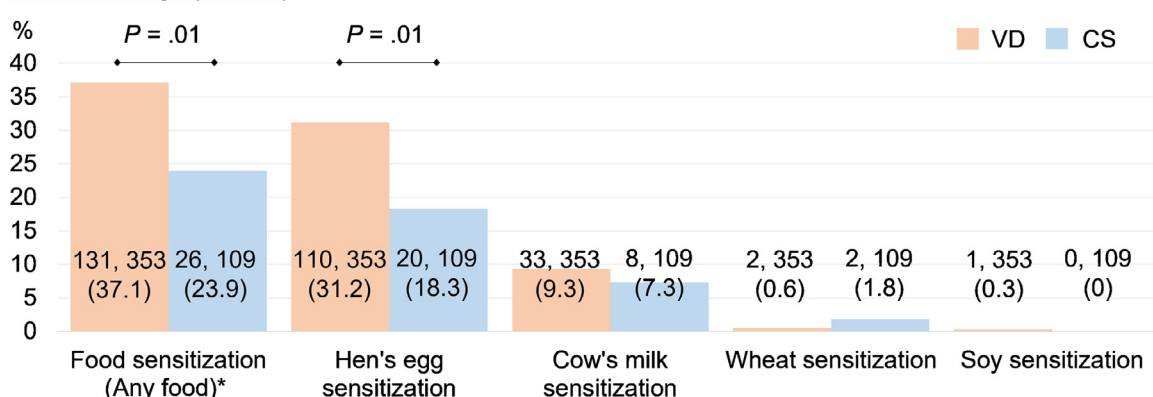


Figure 2. Incidences of food sensitization by 3 and 6 months of age according to delivery mode. Values are presented as number of participants with food sensitization and number of participants in the corresponding delivery mode group (percentage). P values were calculated using Fisher's exact test. ^aAny food refers to more than or equal to 1 of the 4 target foods (hen's egg, cow's milk, wheat, and soy). CD, cesarean delivery; VD, vaginal delivery

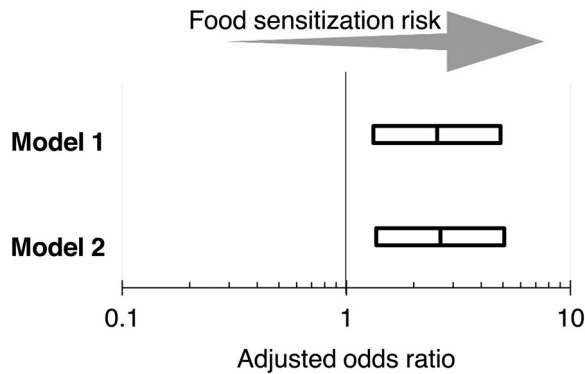


Figure 3. Adjusted odds ratios of vaginal delivery for the development of food sensitization by 6 months of age. The odds ratios were calculated using multivariable logistic regression models. Model 1 calculated the adjusted odds ratio of vaginal delivery for the development of food sensitization while adjusting for a variety of parental, perinatal, and environmental factors. Model 2 adjusted for the same independent variables included in model 1 and allocation group during the SPADE study. SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy.

the aORs of VD for FS development to be 2.54 (95% CI, 1.32–4.87; $P = .005$) and 2.63 (95% CI, 1.36–5.06; $P = .004$), respectively.

Secondary Outcome Measure

Figure 4 illustrates the relationship between labor duration and the development of FS by 6 months of age. The median labor duration was significantly longer in participants with FS (5.7 hours, interquartile

range, 2.7–10.1) than in participants without FS (4.5 hours, 1.1–8.2) ($P = .01$). Furthermore, longer labor durations were significantly associated with a higher proportion of participants with FS ($P = .008$) (Fig 5).

Subgroup Analyses

Using the same multivariable logistic regression model (model 1) as the main analysis, the aORs of VD for the development of ES and CMS were calculated to be 2.75 (95% CI, 1.34–5.64) and 1.98 (0.72–5.46), respectively.

The statistical relationships between labor duration and the development of ES and CMS were assessed using the Mann-Whitney U test. The median labor duration was significantly longer in participants with ES (5.7 hours, interquartile range, 3.4–10.5) than in participants without ES (4.5 hours, 1.1–8.2) ($P = .005$). However, there was no significant difference in the median labor duration between participants with CMS (4.5 hours, 2.3–10.5) and participants without CMS (4.7 hours, 1.9–9.0) ($P = .53$).

Next, we evaluated the statistical relationship between labor duration and the development of FS among participants stratified according to the presence or absence of siblings using the Mann-Whitney U test. There was no significant difference in the median labor duration between participants with FS (9.1 hours, interquartile range, 4.9–14.3) and participants without FS (9.1 hours, 4.7–16.1) among the 169 participants without any siblings ($P = .77$). However, the median labor duration was significantly longer in participants with FS (4.2 hours, 2.4–6.1) than in participants without FS (3.1 hours, 0–5.3) among the 260 participants with more than or equal to 1 sibling ($P = .02$).

Table 3
Multivariable Analyses of the Risk Factors for Food Sensitization Development by 6 Mo of Age

Variables	Model 1 Adjusted odds ratio	95% CI	P value	Model 2 Adjusted odds ratio	95% CI	P value
Male	0.83	0.52–1.32	.42	0.81	0.51–1.30	.39
Season of birth: spring or summer	1.01	0.61–1.65	.97	1.00	0.61–1.65	.99
Gestational age: ≥ 39 wk ^a	0.91	0.54–1.54	.73	0.91	0.54–1.55	.73
Birth weight: ≥ 3000 g ^a	1.70	1.04–2.77	.03	1.73	1.06–2.82	.03
Vaginal delivery	2.54	1.32–4.87	.005	2.63	1.36–5.06	.004
Vacuum extraction or emergency cesarean delivery	0.90	0.45–1.81	.77	0.90	0.44–1.81	.76
Neonatal asphyxia ^b	1.25	0.31–5.05	.75	1.36	0.34–5.44	.66
Umbilical artery pH: ≥ 7.30 ^a	1.13	0.70–1.83	.63	1.09	0.67–1.77	.73
Neonatal respiratory distress	0.39	0.14–1.09	.07	0.37	0.13–1.03	.06
No siblings (first child)	1.96	1.17–3.27	.01	1.93	1.15–3.24	.01
Maternal age: ≥ 32 y ^a	1.05	0.56–1.97	.87	1.00	0.53–1.89	.99
Maternal body mass index before pregnancy: ≥ 21 ^a	1.23	0.76–2.00	.40	1.19	0.73–1.94	.48
Maternal weight gain during pregnancy: ≥ 10 kg ^a	0.81	0.50–1.29	.36	0.82	0.51–1.31	.40
Maternal atopic diseases ^c	1.15	0.73–1.83	.55	1.17	0.73–1.86	.52
Maternal smoking	1.47	0.36–6.00	.59	1.64	0.40–6.73	.50
Paternal age: ≥ 33 y ^a	1.09	0.59–1.99	.79	1.13	0.61–2.09	.69
Paternal atopic diseases ^c	1.73	1.09–2.74	.02	1.78	1.12–2.83	.02
Paternal smoking	1.09	0.66–1.80	.74	1.07	0.64–1.78	.79
Domestic dog exposure at birth	0.74	0.38–1.46	.39	0.78	0.39–1.53	.46
Domestic cat exposure at birth	2.20	0.87–5.58	.10	2.20	0.86–5.62	.10
Maternal antibiotic use for treatment of chorioamnionitis or prevention of GBS infection ^d	0.75	0.39–1.46	.40	0.77	0.40–1.50	.44
Neonatal antibiotic use ^e	2.45	0.78–7.70	.13	2.63	0.84–8.23	.10
No CMF ingestion in the first 3 d of life	0.75	0.24–2.32	.62	0.78	0.25–2.43	.66
Allocation to the SPADE study's CMF ingestion group at 1 mo of age				0.65	0.41–1.04	.07
Eczema occurrence within the first 6 mo of life	4.66	2.74–7.93	<.001	4.56	2.68–7.76	<.001
Continuous breastfeeding up to 6 mo of age	2.64	1.52–4.59	<.001	2.72	1.56–4.74	<.001

Abbreviations: CI, confidence interval; CMF, cow's milk formula; GBS, group B *Streptococcus*; SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy.

NOTE. P values were calculated using multivariable logistic regression models.

^aConverted to a binary variable with the median as the cutoff.

^bNeonatal asphyxia refers to an Apgar score less than 7 points at 1 and/or 5 min after birth.

^cAtopic diseases include food allergy, bronchial asthma, atopic dermatitis, and allergic rhinitis.

^dIntrapartum antibiotic treatment for chorioamnionitis or intrapartum antibiotic prophylaxis to prevent the vertical transmission of GBS.

^eAntibiotic use in newborns within the first 7 d of life.

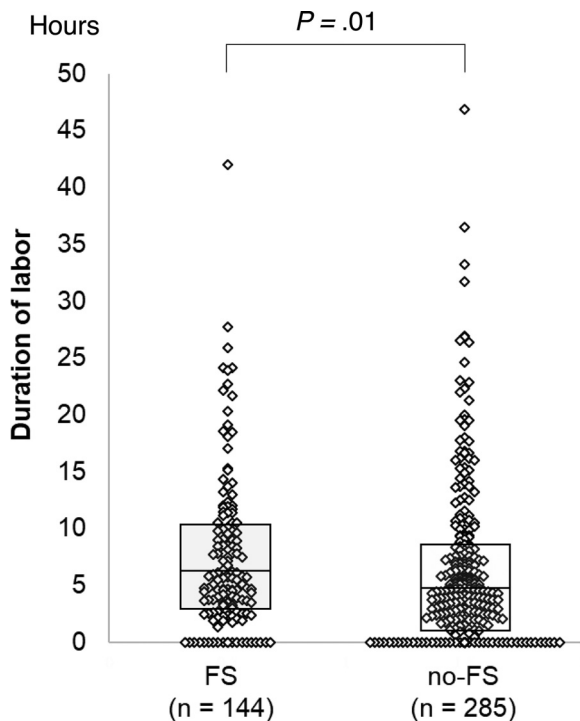


Figure 4. Relationship between labor duration and the development of food sensitization by 6 months of age. *P* value was calculated using the Mann-Whitney *U* test. FS, food sensitization.

Finally, we evaluated the statistical relationship between labor duration and the development of FS among the 325 VD-born participants using the Mann-Whitney *U* test. Although the median labor duration was longer in participants with FS (6.6 hours, interquartile range, 4.2–10.7) than in participants without FS (5.6 hours, 3.5–9.4), this difference was not statistically significant ($P = .06$).

Discussion

In this nested case-control trial of Japanese infants, we demonstrated the effect of VD on FS development in infancy and characterized the relationship between labor duration and FS development.

Effects of Delivery Mode and Labor Duration on Food Sensitization in Infants

In this study, the incidence of FS development by 6 months of age was significantly higher in VD-born infants than in CD-born infants ($P = .01$). This positive association between VD and FS development remained statistically significant even after adjusting for other parental, perinatal, and environmental factors ($P = .005$). Few studies have revealed that CD is a protective factor for the development of allergic diseases. Our findings corroborate those of Sánchez-Valverde et al,²⁹ who reported that CD seemed to protect CMA patients from subsequent allergic march development.

Previous reports have indicated that gut microbiota compositions differ between CD-born infants and VD-born infants,^{30,31} which may account for their differences in the risk of allergic disease development.^{32,33} A review of the association between gut microbiota and atopic disease suggested that the effects of environmental factors (including delivery mode) on FS through microbial changes involve highly complex mechanisms.³⁴ If the mechanism of microbiome seeding can account for associations between delivery mode and allergic disease development, CD births would be expected to be associated with allergies regardless of indication (ie, elective versus emergency). However, previous cohort studies found differences between elective and emergency CD in allergic disease development,^{35,36} suggesting that the relationship between CD and allergic diseases is influenced by its underlying indications. As the proportion of CD births and their medical indications vary among countries,³⁷ it is difficult to consistently reproduce such studies despite the clear differences in infant gut microbiota between delivery modes.³⁸

Our analysis revealed that participants who developed FS had longer labor durations than those without FS. Furthermore, the relationship between labor duration and FS was maintained even in the subgroup analysis of participants with siblings. Previous research has reported that endogenous ouabain (a digitalis-like factor) is secreted from adrenal glands in stressful situations³⁹ and that maternal and fetal ouabain concentrations are elevated in cases of severe preeclampsia.⁴⁰ Ouabain has also been reported to have both pro- and anti-inflammatory properties.⁴¹ For example, this steroid hormone was found to reduce the number of regulatory T cells in the spleen of mice through interleukin-2 suppression.³⁹ Zhang et al⁴² reported that the cord blood of infants who developed FA had a higher proportion of monocytes and a lower proportion of natural regulatory T cells that were associated with longer labor durations. In addition, that study found an increased secretion of

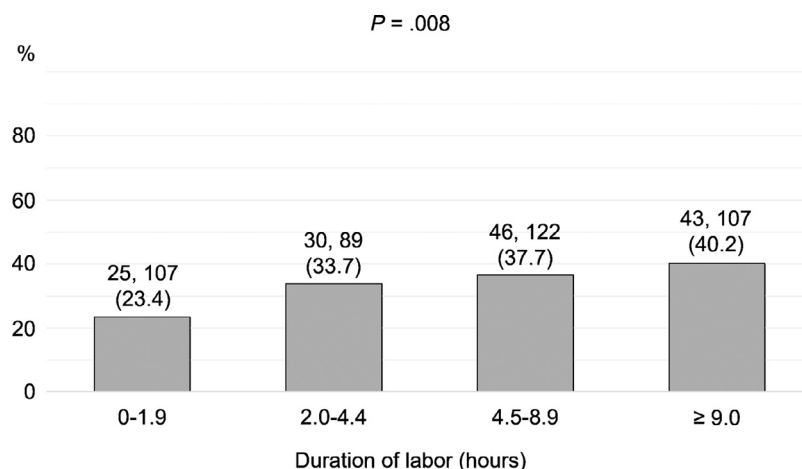


Figure 5. Proportions of participants who developed food sensitization by 6 months of age according to labor duration quartiles. Labor duration was categorized into quartiles. Values are presented as number of participants with food sensitization and number of participants within each quartile (percentage). *P* value was calculated using the Cochran-Armitage test.

inflammatory cytokines by CD14+ monocytes in infants with FA, which lead to the suppression of interleukin-2 expression by CD4+ T cells.⁴² Collier et al.²⁴ reported that infants who were exposed to labor were associated with a transient decrease in naive regulatory T cells when compared with those delivered by pre-labor CD and that this decrease was more pronounced among infants who eventually developed FA. Our findings support their supposition that exposure to labor increases the risk of FS in infancy through the stimulation of inflammatory pathways. However, we found no significant relationship between labor duration and FS in the subgroup analysis of participants without any siblings ($P = .77$). A possible explanation for this observation could be that the first child may already have a higher propensity to develop FS and FA and would be less influenced by labor duration. Further studies are needed to evaluate whether there are differences in stress hormone levels or other factors (eg, changes in uterine environment) according to birth order in infants with the same labor duration.

The development of allergic diseases in infants may be affected not only by exposure to the maternal vaginal microbiome but also by various biological and environmental factors, such as the underlying indications for CD, maternal dietary factors during pregnancy,^{9,43} and maternal gut microbiome during pregnancy.⁴⁴ In addition, the effects of delivery mode on the diversity and colonization of an infant's gut microbiota may be temporary.^{31,45} Gut microbiomes can also be affected by exposure to antibiotics,^{46,47} early skin-to-skin contact,⁴⁸ breastfeeding,^{38,45,49} and the introduction of complementary foods.⁵⁰ Moreover, recent studies have suggested the presence of variations in gut microbiome composition across different human populations.²⁹ These potential confounders were not analyzed in our study and should be considered in future research.

Study Strengths and Limitations

The strengths of our study lie in the prospective collection of perinatal and child health information and the objective assessment of FS through planned SPTs before the introduction of complementary foods.

However, the study had several limitations. First, our analysis was conducted using a relatively small sample size and short follow-up period. Second, we did not investigate the effects of delivery mode and labor duration on FA (except for CMA) development in our study. This was because the SPADE study did not include planned OFCs at 6 months of age for hen's egg, wheat, and soy. However, infants with FS have been found to be at a greater risk of an allergic reaction when exposed to allergenic foods. Additional prospective cohort studies are needed to assess FS and FA development in larger community-based populations over longer follow-up periods. Third, all participants were exposed to the screening and OFC with CMF. It is possible that this variable exposure to CMF over the first 6 months of age was a driving factor for CMS development. However, our main findings were more heavily influenced by ES than by CMS, and the variable exposure to CMF may therefore have a limited effect on our conclusions. Fourth, the mothers in our study population were advised to follow the Japanese Guidelines for Food Allergy 2017, which do not recommend food elimination as an allergy prevention measure during pregnancy and lactation.²⁵ Because maternal protein intake was not restricted, the effects of protein intake by breast milk could not be investigated. Fifth, serum vitamin D concentrations⁴ and gut microbiota were not evaluated in our study. Further randomized controlled trials and meta-analyses are therefore needed to determine whether these factors contribute to allergic disease development in infants.

Conclusions

This nested case-control trial of SPADE study participants demonstrated that VD was associated with an increased risk of FS in infancy. Longer labor durations may have promoted the development of FS through increased stress and inflammatory stimulation.

Acknowledgments

The authors thank the SPADE study team and the participants and their families for their participation in the trial.

Supplementary Data

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2022.04.008>.

References

- Sugiura S, Hiramitsu Y, Futamura M, Kamioka N, Yamaguchi C, Umemura H, et al. Development of a prediction model for infants at high risk of food allergy. *Asia Pac Allergy*. 2021;11(1):e5.
- Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41–58.
- Pyrhonen K, Kulmala P. Atopic diseases of the parents predict the offspring's atopic sensitization and food allergy. *Pediatr Allergy Immunol*. 2021;32(5):859–871.
- Matsui T, Tanaka K, Yamashita H, Saneyasu K, Tanaka H, Takasato Y, et al. Food allergy is linked to season of birth, sun exposure, and vitamin D deficiency. *Allergol Int*. 2019;68(2):172–177.
- Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. *Pediatr Allergy Immunol*. 2016;27(4):419–424.
- Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. Cesarean delivery, preterm birth, and risk of food allergy: nationwide Swedish cohort study of more than 1 million children. *J Allergy Clin Immunol*. 2018;142(5):1510–1514. e2.
- Wooldridge AL, McMillan M, Kaur M, Giles LC, Marshall HS, Gattford KL. Relationship between birth weight or fetal growth rate and postnatal allergy: a systematic review. *J Allergy Clin Immunol*. 2019;144(6):1703–1713.
- Kikkawa T, Yorifuji T, Fujii Y, Yashiro M, Okada A, Ikeda M, et al. Birth order and paediatric allergic disease: a nationwide longitudinal survey. *Clin Exp Allergy*. 2018;48(5):577–585.
- Gao X, Yan Y, Zeng G, Sha T, Liu S, He Q, et al. Influence of prenatal and early-life exposures on food allergy and eczema in infancy: a birth cohort study. *BMC Pediatr*. 2019;19(1):239.
- Dioun AF, Harris SK, Hibberd PL. Is maternal age at delivery related to childhood food allergy? *Pediatr Allergy Immunol*. 2003;14(4):307–311.
- Chen Y, Zhu J, Lyu J, Xia Y, Ying Y, Hu Y, et al. Association of maternal prepregnancy weight and gestational weight gain with children's allergic diseases. *JAMA Netw Open*. 2020;3(9):e2015643.
- Marrs T, Logan K, Craven J, Radulovic S, McLean WHA, Lack G, et al. Dog ownership at three months of age is associated with protection against food allergy. *Allergy*. 2019;74(11):2212–2219.
- Gabryszewski SJ, Dudley J, Grundmeier RW, Hill DA. Early-life environmental exposures associate with individual and cumulative allergic morbidity. *Pediatr Allergy Immunol*. 2021;32(5):1089–1093.
- Metzler S, Frei R, Schmaußer-Hochfellner E, von Mutius E, Pekkanen J, Karvonen AM, et al. Association between antibiotic treatment during pregnancy and infancy and the development of allergic diseases. *Pediatr Allergy Immunol*. 2019;30(4):423–433.
- Ahmadizar F, Vijverberg SJH, Arets HGM, de Boer A, Lang JE, Garssen J, et al. Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: a meta-analysis. *Allergy*. 2018;73(5):971–986.
- Zhong Y, Zhang Y, Wang Y, Huang R. Maternal antibiotic exposure during pregnancy and the risk of allergic diseases in childhood: a meta-analysis. *Pediatr Allergy Immunol*. 2021;32(3):445–456.
- Matsumoto N, Yorifuji T, Nakamura K, Ikeda M, Tsukahara H, Doi H. Breastfeeding and risk of food allergy: a nationwide birth cohort in Japan. *Allergol Int*. 2020;69(1):91–97.
- Shoda T, Futamura M, Yang L, Yamamoto-Hanada K, Narita M, Saito H, et al. Timing of eczema onset and risk of food allergy at 3 years of age: a hospital-based prospective birth cohort study. *J Dermatol Sci*. 2016;84(2):144–148.
- de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, et al. Preventing food allergy in infancy and childhood: systematic review of randomised controlled trials. *Pediatr Allergy Immunol*. 2020;31(7):813–826.
- Burgess JA, Dharmage SC, Allen K, Koplin J, Garcia-Larsen V, Boyle R, et al. Age at introduction to complementary solid food and food allergy and sensitization: a systematic review and meta-analysis. *Clin Exp Allergy*. 2019;49(6):754–769.
- Marrs T, Bruce KD, Logan K, Rivett DW, Perkin MR, Lack G, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol*. 2013;24(4):311–320.e8.

22. Kim HI, Nam S, Park Y, Jung YJ, Kim HY, Kim KW, et al. Cesarean section does not increase the prevalence of allergic disease within 3 years of age in the offsprings. *Obstet Gynecol Sci*. 2019;62(1):11–18.
23. Gorris A, Bustamante G, Mayer KA, Kinaciyan T, Zlabinger GJ. Cesarean section and risk of allergies in Ecuadorian children: a cross-sectional study. *Immun Inflamm Dis*. 2020;8(4):763–773.
24. Collier F, Ponsonby AL, O'Hely M, Tang MLK, Saffery R, Molloy J, et al. Naïve regulatory T cells in infancy: associations with perinatal factors and development of food allergy. *Allergy*. 2019;74(9):1760–1768.
25. Sakihara T, Otsuji K, Arakaki Y, Hamada K, Sugiura S, Ito K. Randomized trial of early infant formula introduction to prevent cow's milk allergy. *J Allergy Clin Immunol*. 2021;147(1):224–232.
26. Ebisawa M, Ito K, Fujisawa T. Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology. Japanese guidelines for food allergy 2017. *Allergol Int*. 2017;66(2):248–264.
27. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, et al. Japanese guidelines for atopic dermatitis 2017. *Allergol Int*. 2017;66(2):230–247.
28. Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452–458.
29. Sánchez-Valverde F, Gil F, Martínez D, Fernández B, Aznal E, Oscoz M, et al. The impact of caesarean delivery and type of feeding on cow's milk allergy in infants and subsequent development of allergic march in childhood. *Allergy*. 2009;64(6):884–889.
30. Sordillo JE, Zhou Y, McGeachie MJ, Ziniti J, Lange N, Laranjo N, et al. Factors influencing the infant gut microbiome at age 3–6 months: findings from the ethnically diverse Vitamin D Antenatal Asthma Reduction Trial (VDAART). *J Allergy Clin Immunol*. 2017;139(2):482–491. e14.
31. Rutayisire E, Huang K, Liu Y, Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol*. 2016;16(1):86.
32. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosch D, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. 2016;22(10):1187–1191.
33. Fazlollahi M, Chun Y, Grishin A, Wood RA, Burks AW, Dawson P, et al. Early-life gut microbiome and egg allergy. *Allergy*. 2018;73(7):1515–1524.
34. Plunkett CH, Nagler CR. The influence of the microbiome on allergic sensitization to food. *J Immunol*. 2017;198(2):581–589.
35. Adeyeye TE, Yeung EH, McLain AC, Lin S, Lawrence DA, Bell EM. Wheeze and food allergies in children born via cesarean delivery: the upstate KIDS study. *Am J Epidemiol*. 2019;188(2):355–362.
36. Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases—a sibling study. *Clin Exp Allergy*. 2012;42(9):1369–1376.
37. Fröhlich M, Koga C, Bühner C, Mori C, Yamamoto M, Sakurai K, et al. Differences in rate and medical indication of caesarean section between Germany and Japan. *Pediatr Int*. 2020;62(9):1086–1093.
38. Kim H, Sitarik AR, Woodcroft K, Johnson CC, Zoratti E. Birth mode, breastfeeding, pet exposure, and antibiotic use: associations with the gut microbiome and sensitization in children. *Curr Allergy Asthma Rep*. 2019;19(4):22.
39. da Silva JMC, das Neves Azevedo A, dos Santos Barbosa RP, Teixeira MP, Vianna TAG, Fittipaldi J, et al. Ouabain decreases regulatory T cell number in mice by reducing IL-2 secretion. *Neuroimmunomodulation*. 2019;26(4):188–197.
40. Buckalew VM. Role of endogenous digitalis-like factors in the clinical manifestations of severe preeclampsia: a systematic review. *Clin Sci (Lond)*. 2018;132(12):1215–1242.
41. Teixeira MP, Rumjanek VM. Ouabain affects the expression of activation markers, cytokine production, and endocytosis of human monocytes. *Mediators Inflamm*. 2014;2014:760368.
42. Zhang Y, Collier F, Naselli G, Saffery R, Tang MLK, Allen KJ, et al. Cord blood monocyte-derived inflammatory cytokines suppress IL-2 and induce nonclassical "T(H)2-type" immunity associated with development of food allergy. *Sci Transl Med*. 2016;8(321):321ra8.
43. Kim YH, Kim KW, Lee SY, KO Koo, Kwon SO, Seo JH, et al. Maternal perinatal dietary patterns affect food allergy development in susceptible infants. *J Allergy Clin Immunol Pract*. 2019;7(7):2337–2347. e7.
44. Gao Y, Nanan R, Macia L, Tan J, Sominsky L, Quinn TP, et al. The maternal gut microbiome during pregnancy and offspring allergy and asthma. *J Allergy Clin Immunol*. 2021;148(3):669–678.
45. Stokholm J, Thorsen J, Chawes BL, Schjørring S, Krogfelt KA, Bønnelykke K, et al. Cesarean section changes neonatal gut colonization. *J Allergy Clin Immunol*. 2016;138(3):881–889. e2.
46. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med*. 2016;8(343):343ra82.
47. Yassour M, Vatanen T, Siljander H, Hämäläinen AM, Härkönen T, Ryhänen SJ, et al. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med*. 2016;8(343):343ra81.
48. Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, Walker WA. The very low birth weight infant microbiome and childhood health. *Birth Defects Res C Embryo Today*. 2015;105(4):252–264.
49. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018;562(7728):583–588.
50. Marrs T, Jo JH, Perkin MR, Rivett DW, Whitney AA, Bruce KD, et al. Gut microbiota development during infancy: impact of introducing allergenic foods. *J Allergy Clin Immunol*. 2021;147(2):613–621. e9.

Supplementary Data

eTable 1

Additional Baseline Characteristics

Characteristics	SPADE study enrollees (n = 518)	Primary outcome population (n = 462)	Nonanalyzed population (n = 56)	P value
Season of birth: spring or summer	339 (65.4)	299 (64.7)	40 (71.4)	.37
Maternal body mass index before pregnancy	20.9 (19.4–23.3)	20.8 (19.3–23.2)	21.7 (20.1–23.7)	.07
Maternal weight gain during pregnancy	10 (7.5–12.2)	10 (7.7–12.2)	9.6 (6.9–12.2)	.42
Maternal smoking	17 (3.3)	15 (3.3)	2 (3.6)	.70
Paternal smoking	170 (32.8)	152 (32.9)	18 (32.1)	>.99
Domestic dog exposure at birth	69 (13.3)	64 (13.9)	5 (8.9)	.53
Domestic cat exposure at birth	35 (6.8)	30 (6.5)	5 (8.9)	.40
Maternal antibiotic use, including preoperative antibiotic prophylaxis	195 (37.6)	172 (37.2)	23 (41.1)	.66
Maternal antibiotic use for treatment of chorioamnionitis or prevention of GBS infection ^a	77 (14.9)	67 (14.5)	10 (17.9)	.55
Neonatal antibiotic use ^b	19 (3.7)	19 (4.1)	0 (0)	.25
No CMF ingestion in the first 3 d of life	32 (6.2)	31 (6.7)	1 (1.8)	.24

Abbreviations: CMF, cow's milk formula; GBS, group B *Streptococcus*.

NOTE. Values are presented as number (percentage) or median (interquartile range). P values were calculated using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

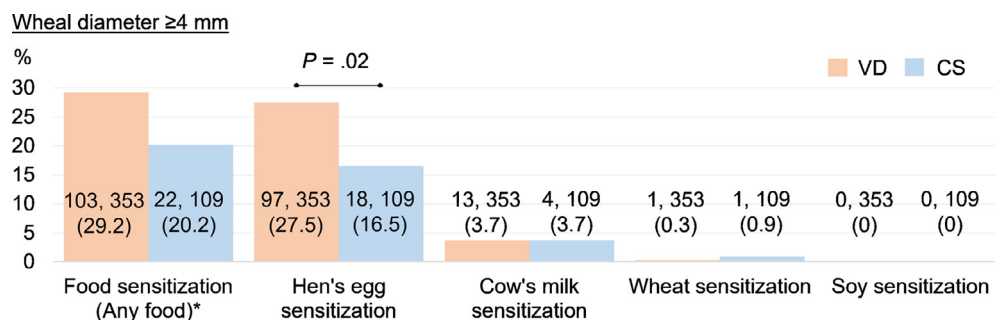
^aIntrapartum antibiotic treatment for chorioamnionitis or intrapartum antibiotic prophylaxis to prevent the vertical transmission of GBS.^bAntibiotic use in newborns within the first 7 d of life.**eTable 2**

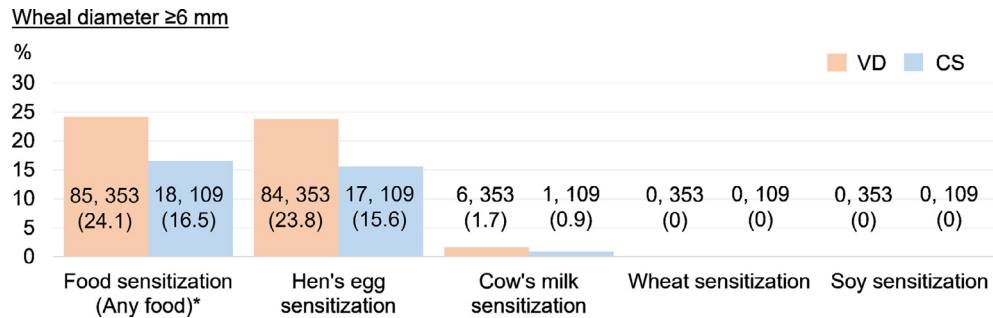
Additional Demographic and Other Characteristics of the Participants According to Delivery Mode

Characteristics	Total (n = 462)	Vaginal delivery (n = 353)	Cesarean delivery (n = 109)	P value
Season of birth: spring or summer	299 (64.7)	227 (64.3)	72 (66.1)	.82
Neonatal asphyxia	15 (3.3)	12 (3.4)	3 (2.8)	>.99
Umbilical artery pH	7.29 (7.25–7.32)	7.29 (7.25–7.32)	7.29 (7.26–7.31)	.25
Neonatal respiratory distress	36 (7.8)	25 (7.1)	11 (10.1)	.42
Maternal weight gain during pregnancy	10 (7.7–12.2)	9.9 (7.7–12.2)	10.3 (7.6–12.5)	.64
Maternal smoking	15 (3.3)	10 (2.8)	5 (4.6)	.36
Paternal smoking	152 (32.9)	120 (34.0)	32 (29.4)	.42
Domestic dog exposure at birth	64 (13.9)	44 (12.5)	20 (18.4)	.15
Domestic cat exposure at birth	30 (6.5)	20 (5.7)	10 (9.2)	.19
Maternal antibiotic use, including preoperative antibiotic prophylaxis	172 (37.2)	63 (17.9)	109 (100)	<.001
Allocation to the SPADE study's CMF ingestion group at 1 mo of age	226 (48.9)	177 (50.1)	49 (45.0)	.38

Abbreviations: CMF, cow's milk formula; SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy.

NOTE. Values are presented as number (percentage) or median (interquartile range). P values were calculated using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

^aNeonatal asphyxia refers to an Apgar score less than 7 points at 1 or 5 min after birth.**eFigure 1.** Incidences of food sensitization by 6 mo of age according to delivery mode: positive skin prick tests refer to wheal diameters more than or equal to 4 mm larger than the negative control. Values are presented as number of participants with food sensitization and number of participants in the corresponding delivery mode group (percentage). P values were calculated using Fisher's exact test. *Any food refers to more than or equal to 1 of the 4 target foods (hen's egg, cow's milk, wheat, and soy). CD, cesarean delivery; VD, vaginal delivery.



eFigure 2. Incidences of food sensitization by 6 mo of age according to delivery mode: positive skin prick tests refer to wheal diameters more than or equal to 6 mm larger than the negative control. Values are presented as number of participants with food sensitization and number of participants in the corresponding delivery mode group (percentage). *P* values were calculated using Fisher's exact test. *Any food refers to more than or equal to 1 of the 4 target foods (hen's egg, cow's milk, wheat, and soy). CD, cesarean delivery; VD, vaginal delivery.

eTable 3

Univariate Analyses of the Risk Factors for Food Sensitization Development by 6 Mo of Age

Variables	Food sensitization (n = 157)	No food sensitization (n = 305)	Odds ratio	95% CI	<i>P</i> value
Male	85 (54.1)	168 (55.1)	0.96	0.64-1.44	.92
Season of birth: spring or summer	100 (63.7)	199 (65.3)	0.93	0.61-1.43	.76
Gestational age: ≥ 39 wk ^a	97 (61.8)	168 (55.1)	1.32	0.87-1.99	.20
Birth weight: ≥ 3000 g ^a	92 (58.6)	148 (48.5)	1.50	1.00-2.26	.049
Vaginal delivery	131 (83.4)	222 (72.8)	1.88	1.13-3.21	.01
Vacuum extraction or emergency cesarean delivery	23 (14.7)	58 (19.0)	0.74	0.41-1.28	.30
Neonatal asphyxia ^b	6 (3.8)	9 (3.0)	1.32	0.38-4.24	.59
Umbilical artery pH: ≥ 7.30 ^a	68 (43.3)	142 (46.6)	0.90	0.59-1.36	.61
Neonatal respiratory distress	8 (5.1)	28 (9.2)	0.53	0.20-1.25	.14
No siblings (first child)	71 (45.2)	114 (37.4)	1.38	0.92-2.08	.11
Maternal age: ≥ 32 y ^a	86 (54.8)	166 (54.4)	1.01	0.68-1.52	>.99
Maternal body mass index before pregnancy: ≥ 21 ^a	75 (47.8)	144 (47.2)	0.99	0.66-1.49	>.99
Maternal weight gain during pregnancy: ≥ 10 kg ^a	78 (49.7)	153 (50.2)	0.95	0.63-1.42	.84
Maternal atopic diseases ^c	73 (46.5)	120 (39.3)	1.34	0.89-2.01	.16
Maternal smoking	5 (3.2)	10 (3.3)	0.97	0.26-3.18	>.99
Paternal age: ≥ 33 y ^a	88 (56.1)	157 (51.5)	1.19	0.79-1.78	.43
Paternal atopic diseases ^c	82 (52.2)	127 (41.6)	1.51	1.01-2.27	.04
Paternal smoking	53 (33.8)	99 (32.5)	1.05	0.68-1.61	.83
Domestic dog exposure at birth	19 (12.1)	45 (14.8)	0.80	0.42-1.45	.48
Domestic cat exposure at birth	14 (8.9)	16 (5.3)	1.77	0.77-3.98	.16
Maternal antibiotic use for treatment of chorioamnionitis or prevention of GBS infection ^d	23 (14.7)	44 (14.4)	1.02	0.56-1.81	>.99
Neonatal antibiotic use ^e	9 (5.7)	10 (3.3)	1.80	0.63-5.04	.22
No CMF ingestion in the first 3 d of life	13 (8.3)	18 (5.9)	1.46	0.64-3.25	.33
Allocation to the SPADE study's CMF ingestion group at 1 mo of age	71 (45.2)	155 (50.8)	0.81	0.54-1.21	.32
Eczema occurrence within the first 6 mo of life	126 (80.3)	164 (53.8)	3.60	2.24-5.91	<.001
Continuous breastfeeding up to 6 mo of age	125 (79.6)	198 (64.9)	2.18	1.35-3.57	<.001

Abbreviations: CI, confidence interval; CMF, cow's milk formula; GBS, group B *Streptococcus*; SPADE, Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy.

NOTE. Values are presented as number (percentage). *P* values were calculated using Fisher's exact test.

^aConverted to a binary variable with the median as the cutoff.

^bNeonatal asphyxia refers to an Apgar score less than 7 points at 1 and/or 5 min after birth.

^cAtopic diseases include food allergy, bronchial asthma, atopic dermatitis, and allergic rhinitis.

^dIntrapartum antibiotic treatment for chorioamnionitis or intrapartum antibiotic prophylaxis to prevent the vertical transmission of GBS.

^eAntibiotic use in newborns within the first 7 d of life.