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Age at First Introduction of Cow Milk Products and Other Food Products in Relation to Infant Atopic Manifestations in the First 2 Years of Life: The KOALA Birth Cohort Study

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What's Known on This Subject

There is only little information about timing of solid-food introduction and its association with the development of atopy. Most studies have focused on the duration of breastfeeding.

What This Study Adds

We were able to establish associations between the timing of the introduction of cow milk products/other (solid) food products and infant atopic manifestations in first 2 years of life in a large prospective birth cohort study.

ABSTRACT

OBJECTIVES. Scientific evidence is scarce about timing of solid-food introduction and its association with the development of atopy. We aimed to evaluate any associations between the introduction of cow milk products/other solid food products and infant atopic manifestations in the second year of life, taking into account reverse causation.

METHODS. Data from 2558 infants in an ongoing prospective birth cohort study in the Netherlands were analyzed. Data on the main determinants (introduction of cow milk products and other food products), outcomes (eczema; atopic dermatitis [United Kingdom Working Party criteria]; recurrent wheeze; any sensitization; sensitization against cow milk, hen egg, peanut, and at least 1 inhalant allergen), and confounders were collected by repeated questionnaires at 34 weeks of gestation and 3, 7, 12, and 24 months postpartum. Information on sensitization was gathered by venous blood collections performed during home visits at age 2. Analyses were performed by multiple logistic regression analyses.

RESULTS. More delay in introduction of cow milk products was associated with a higher risk for eczema. In addition, a delayed introduction of other food products was associated with an increased risk for atopy development at the age of 2 years. Exclusion of infants with early symptoms of eczema and recurrent wheeze (to avoid reverse causation) did not essentially change our results.

DISCUSSION. Delaying the introduction of cow milk or other food products may not be favorable in preventing the development of atopy. *Pediatrics* 2008;122:e115–e122

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Key Words

cow milk, solids, atopy, reverse causation, oral tolerance, infant

Abbreviations

AD—atopic dermatitis
UK-WP—United Kingdom Working Party
cOR—crude odds ratio
IgE—immunoglobulin E
aOR—adjusted odds ratio
CI—confidence interval

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THE PREVALENCE OF atopic manifestations has increased worldwide, especially in children.¹ Symptoms are most common in Western countries: approximately one third of the children in Western societies show symptoms.² Possible approaches to allergy prevention may include a wide variety of measures, including maternal dietary restriction during pregnancy, breastfeeding, dietary restrictions while breastfeeding, the use of hypoallergenic formulas, and delays in the introduction of certain foods into the infant's diet.³ Among these possible approaches, delaying the introduction of solid foods into the infant's diet is 1 of the most commonly recommended.⁴ The age when solid foods are introduced to infants has varied greatly during the past century.⁵ In 2001, the World Health Organization issued a revised global recommendation that mothers exclusively breastfeed until 6 months of age.⁶ The American Academy of Pediatrics suggest that solids be delayed until 6 months of age but cow milk to 1 year; egg to 2 years; and peanuts, tree nuts, and fish to 3 years.⁷ It is not surprising that these guidelines differ in emphasis, because they are based on limited evidence.⁵

Because most studies on dietary habits and atopy development have focused mainly on the duration of breastfeeding, scientific evidence about timing of solid-food introduction is scarce and conflicting. Of interest is a study by Zutavern et al⁸ showing an increased risk for eczema in relation to late introduction to egg and milk. This study

challenges the widely held belief that delayed introduction of solids reduces the risk for allergy. Tarini et al⁵ conducted a systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. Thirteen studies that met the inclusion criteria were critically evaluated, concluding that the available evidence suggests that early solid feeding may increase the risk for eczema, but there is only a few data supporting an association between early solid feeding and other allergic conditions.⁵

Previously, we reported on the relationship between breastfeeding duration and infant eczema in which we also explored the possible influence of reverse causation.⁹ In this large prospective birth cohort study, we had data available on the age of first introduction of cow milk and other food products. Because only a few studies have added new evidence in this conflicting research area, we aimed to establish any associations between the timing of the introduction of cow milk products/other (solid) food products and infant atopic manifestations in first 2 years of life.

METHODS

Study Population

Study subjects were mother–infant pairs who were previously enrolled in the ongoing KOALA Birth Cohort Study, that was set up mainly to study the cause of allergic diseases.¹⁰ KOALA is (in Dutch) an acronym for Child, Parent and health: lifestyle and genetic constitution. At 34 weeks of gestation, we recruited participants with diverse lifestyles (conventional and alternative). Pregnant women with a conventional lifestyle ($n = 2343$) were recruited from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain in the Netherlands. In addition, pregnant women with an alternative lifestyle ($n = 491$) were recruited through several “alternative” channels: organic food shops, anthroposophic doctors and midwives, Steiner Schools, and magazines. The alternative group had more intention to breastfeed (93%) and were less likely to smoke during pregnancy.¹⁰ The study was approved by the medical ethics committee of Maastricht University.

Data Collection

During pregnancy and during the first 2 years postpartum, information on infant feeding patterns (age of first introduction of cow milk products or other food products and/or breastfeeding), other determinants and allergic outcome were collected for all members of the cohort by repeated questionnaires at 34 weeks of gestation and at 3, 7, 12, and 24 months. All infant's of participants ($n = 2834$) with a completed informed consent and the presence of the first questionnaire (34 weeks of gestation) were included. We excluded infants with Down syndrome and those with missing information on the introduction of cow milk products and/or other food products.

Exposures

The age of introduction of cow milk products was defined as artificial formulas (including hypoallergenic for-

mulas), raw/pasteurized milk, porridge, dairy products, and yogurts and categorized as the age of first introduction: 0 to 3 months, 4 to 6 months, 7 to 9 months, > 9 months. The age of introduction of other food products (eg, fruit mash) was categorized as the age of first introduction: 3 months, 4 to 6 months, or after 7 months of age.

Adjustments were made for the following potential confounders: duration of breastfeeding (never, 0–3 months, 4–6 months, 7–9 months, or >9 months), gender of infant (boys or girls), recruitment group (conventional or alternative lifestyle), maternal smoking during pregnancy (yes or no), infant's exposure to environmental tobacco smoke (yes or no), maternal age at delivery (in years), maternal education (primary school, preparatory vocational, or lower general secondary education [low]; vocational education, higher general secondary, or preuniversity education [middle]; or higher vocational or academic education [high]), presence of parental allergic disease (both parents nonallergic, only father allergic, only mother allergic, or both parents allergic), siblings' atopic history (parent-reported doctor's diagnosed food allergy, eczema, hay fever, asthma, pet, and/or house dust mite allergy: no siblings; ≥ 1 sibling, all nonatopic; or ≥ 1 sibling, at least 1 atopic).

Infant Outcomes (Atopic Manifestations)

Eczema (According to Parental Questionnaires)

In the 7-, 12-, and 24-months' postpartum questionnaires, parents were asked, “Has your child ever had an itchy rash that was coming and going in the past months?” When this question was answered affirmatively, infants were defined as having developed eczema in the first 2 years of life. Cases of only diaper rash, rash around the eyes, and/or scalp scaling were excluded.

Atopic Dermatitis According to United Kingdom Working Party Criteria

To specify eczema reported by parents as described previously, we defined atopic dermatitis (AD) according to United Kingdom Working Party (UK-WP) criteria¹¹ for all infants who were visited at home at 2 years of age. The probability of the presence of AD was derived from 4 clinical symptoms: (1) presence of itchy rash (coded as 0 = absent, 1 = present), (2) history of flexural dermatitis (0 = absent, 1 = present), (3) presence of visible flexural dermatitis (0 = absent, 1 = present), and (4) onset before age of 2 years (0 = absent, 1 = present). The UK-WP probability score of AD was then computed as $\text{odds (AD)} / [\text{odds (AD)} + 1]$, where $\text{odds (AD)} = \exp[-4.36 + 1.84 (\text{history of flexural dermatitis}) + 3.46 (\text{onset before 2 years}) + 2.09 (\text{visible flexural dermatitis}) + 1.71 (\text{presence of itchy rash})]$.¹¹ In this study, infants with a UK-WP probability score of AD > 0.9 were regarded as infants with “probable presence of AD.” Recurrent wheezing in the second year of life was defined as reported presence of wheezing with at least 4 attacks between 0 and 7 months, mentioned in the 7 months' postpartum questionnaire, and/or between 7 and 12 months of life, mentioned in the 12 months'

postpartum questionnaire, and/or between 13 and 24 months, mentioned in the 24 months' postpartum questionnaire.

Measurements and Definitions of Infant Allergic Sensitization
Infants' venous blood samples were obtained during a home visit at 2 years' postpartum. All blood samples were analyzed for specific immunoglobulin E (IgE) against hen eggs, cow milk, peanuts, birch, grass pollen, cat, dog, and house dust mite using Radio Allergen Sorbent Test as described previously.¹² The detection limit for specific IgE was 0.10 IU/mL. Any sensitization was regarded as positive when specific serum IgE levels were >0.3 IU/mL against ≥1 of the tested food or inhalant allergens. Sensitization against 1 of the food allergens (hen egg, cow milk, or peanut) was positive when specific serum IgE levels were >0.3 IU/mL against the corresponding food allergens. Sensitization against inhalant allergens was regarded as positive when specific serum IgE levels were >0.3 IU/mL against at least 1 of the tested inhalant allergens (birch, grass pollen, cat, dog, or house dust mite).

Statistical Analysis

Relationships between the age of introduction of cow milk products/other food products and (atopic) outcome measures (eczema; AD according UK-WP criteria; recurrent wheeze; and (any) sensitization against cow milk, hen egg, peanut, at least 1 inhalant allergen) were analyzed. The relationships were analyzed using logistic regression, and results are presented as crude odds ratios (cORs) and adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs). All potential confounders were put in the logistic regression model simultaneously. For all trend analysis, we considered all categorical variables as a continuous variable to test linearity.

Reverse causation was addressed by means of a risk-period-specific analysis as described previously.¹⁰ Briefly, we excluded in the analyses infants with early symptoms of eczema or wheeze to disentangle the exposure from the onset of symptoms. In other words, no overlap occurs between exposure immediately after birth and onset of disease. This analysis has the advantage that it keeps track of infants with early symptoms.

Separate analyses of the conventional versus the alternative cohort showed that the key findings were similar between these groups. Hence, we have combined all infants in the final analyses, adjusting for "recruitment group."

RESULTS

Of the 2834 infants enrolled at birth, we included 2558 infants in this study (after excluding infants with Down syndrome [$n = 3$]) and participants with missing information of the main determinants (age of introduction of cow milk products and/or other food products [$n = 273$]). The response rate of the questionnaire at age 2 years was high ($n = 2434$ of 2558 [95%]). Mothers in the alternative cohort showed more delay in the age of

TABLE 1 Baseline Characteristics in Both Recruitment Groups

Characteristic	Conventional ($n = 2110$)	Alternative ($n = 448$)	Total ($N = 2558$)
Age of introduction cow milk products, n (%)			
0–3 mo	946 (45)	49 (11)	995 (39)
4–6 mo	687 (33)	138 (31)	825 (32)
7–9 mo	434 (21)	234 (52)	668 (26)
>9 mo	43 (2%)	27 (6)	70 (3)
Age of introduction other foods products, n (%)			
3 mo	183 (9)	22 (5)	205 (8)
4–6 mo	1880 (90)	397 (89)	2277 (89)
>7 mo	47 (2)	29 (7)	76 (3)
Use of hypoallergenic formulas, n (%)			
Yes	150 (7)	22 (5)	172 (7)
Breastfeeding, n (%)			
Never	377 (18)	11 (3)	388 (15)
0–3 mo	797 (38)	56 (13)	853 (33)
4–6 mo	357 (17)	70 (16)	427 (17)
7–9 mo	280 (13)	111 (25)	391 (15)
>9 mo	250 (12)	196 (44)	446 (17)
Unknown	49 (2%)	4 (1)	53 (2)
Gender of infants (boys) n (%)	1083 (51)	230 (51)	1313 (51)
Maternal age, mean (SD), y	32 (4)	34 (4)	32 (4)
Maternal smoking during pregnancy, n (%)	174 (8)	2 (<1)	176 (7)
Environmental tobacco smoke exposure, n (%)	107 (5)	2 (<1)	109 (4)
Maternal education, n (%)			
Low	239 (11)	17 (4)	256 (10)
Middle	814 (39)	79 (18)	79 (35)
High	943 (45)	341 (76)	341 (50)
Unknown	114 (5)	11 (3)	125 (5)
Parental allergic disease, n (%)			
Both parents nonallergic	842 (40)	173 (39)	1015 (40)
Only father allergic	450 (21)	102 (23)	552 (22)
Only mother allergic	468 (22)	102 (23)	570 (22)
Both parents allergic	284 (14)	65 (15)	349 (14)
Unknown	66 (3)	6 (1)	72 (3)
Sibling history of atopic manifestations, n (%)			
No siblings	1734 (82)	343 (77)	2077 (81)
≥1 sibling(s), all nonatopic	235 (11)	69 (15)	304 (12)
≥1 sibling(s), at least 1 atopic	83 (4)	33 (7)	116 (5)
Unknown	58 (3)	3 (1)	61 (2)
Infants atopic outcome at 2 y of age, n (%)			
Eczema	665 (31)	128 (29)	783 (31)
AD UK-WP ($n = 822$) ^a	85 (14)	24 (11)	109 (13)
Recurrent wheeze	230 (11)	29 (7)	259 (10)
Sensitization (overall) ($n = 782$) ^a	164 (30)	56 (25)	220 (28)
Sensitization against cow milk ($n = 789$) ^a	115 (20)	35 (16)	150 (19)
Sensitization against (hen) egg ($n = 789$) ^a	38 (7)	9 (4)	47 (6)
Sensitization against peanut ($n = 789$) ^a	36 (6)	6 (3)	42 (5)
Sensitization against at least 1 inhalant allergen ($n = 756$) ^a	55 (10)	29 (13)	84 (11)

Numbers may not add up total because of missing values.

^a Available only for infants who had a home visit.

TABLE 2 Associations Between Introduction of Cow Milk/Food Products and the Development of Infants' Eczema and AD by UK-WP at Age 2

Parameter	Eczema (Questionnaires)				AD (UK-WP)			
	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a
Age of introduction of cow milk products, mo ^b								
0–3	976	297 (30)	1.00	1.00	286	36 (13)	1.00	1.00
4–6	800	239 (30)	0.97 (0.79–1.19)	1.13 (0.83–1.56)	249	32 (13)	1.02 (0.62–1.71)	0.65 (0.25–1.67)
7–9	664	219 (33)	1.13 (0.91–1.39)	1.55 (1.03–2.33)	265	35 (13)	1.06 (0.64–1.74)	0.64 (0.22–1.90)
>9	70	28 (40)	1.52 (0.93–2.51)	2.29 (1.21–4.33)	22	6 (27)	2.60 (0.96–7.09)	1.43 (0.33–6.29)
P trend			.12	.01			.35	.93
Age of introduction of other foods products, mo ^b								
3	191	51 (27)	1.00	1.00	55	3 (6)	1.00	1.00
4–6	2245	701 (31)	1.25 (0.90–1.74)	1.28 (0.91–1.81)	743	98 (13)	2.63 (0.81–8.60)	2.67 (0.80–8.97)
>7	74	31 (42)	1.98 (1.13–3.47)	2.10 (1.17–3.76)	24	8 (33)	8.67 (2.05–36.59)	9.46 (2.05–43.61)
P trend			.03	.02			.00	.00
Breastfeeding duration (confounder), mo								
Never	388	112 (29)	1.00	1.00	109	12 (11)	1.00	1.00
0–3	853	263 (31)	1.09 (0.83–1.42)	1.00 (0.75–1.33)	236	28 (12)	1.09 (0.53–2.23)	1.11 (0.51–2.41)
4–6	427	135 (32)	1.11 (0.82–1.50)	0.87 (0.55–1.35)	154	28 (18)	1.80 (0.87–3.71)	2.58 (0.77–8.67)
7–9	391	126 (32)	1.12 (0.82–1.52)	0.74 (0.46–1.20)	159	23 (15)	1.37 (0.65–2.88)	1.58 (0.44–5.66)
>9	446	133 (30)	1.00 (0.74–1.35)	0.66 (0.40–1.09)	158	18 (11)	1.04 (0.48–2.26)	1.30 (0.34–4.95)
P trend			.95	.06			.75	.60

May not add up to total numbers because of missing values.

^a Based on logistic regression analysis, adjusted for duration of breastfeeding, gender of infant, recruitment group (conventional, alternative lifestyle), maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery (in years), maternal education, presence of parental allergic disease, and (older) siblings' atopic history.

^b The age of introduction of cow milk products and the age of introduction of other food products were simultaneously included in the logistic regression analysis, which means that these variable were adjusted for each other.

introduction of cow milk products (Table 1). Also, they had a higher rate and a longer duration of breastfeeding compared with the conventional cohort (Table 1). Other characteristics that differed between both groups were maternal age, maternal smoking during pregnancy, environmental tobacco smoking, and maternal education (Table 1).

More delay in introduction of both cow milk products and other food products was associated with a higher risk for eczema ($P = .01$ and $.02$ for trend, respectively; Table 2). No associations were found between the introduction of cow milk products and AD according to UK-WP criteria; however, more delay in other food products was associated with a higher risk for AD according to UK-WP criteria ($P = .00$ trend; Table 2).

A delayed introduction of other food products showed a higher risk for recurrent wheeze ($P = .01$ for trend; Table 3), whereas this was not found for a delayed introduction of cow milk products (after adjustment for confounding factors). The results for breastfeeding duration (confounder) between 7 and 9 months showed a reduced risk for recurrent wheeze (aOR: 0.31 [95% CI: 0.14–0.70]).

Delaying the introduction of cow milk products tended to be associated with a lower risk for atopic sensitization but did not reach statistical significance ($P = .26$ for trend; Table 3). Unexpected, a delayed introduction of other food products was positively associated with atopic sensitization at 2 years ($P = .01$ for trend; Table 3).

In addition, besides “any sensitization,” we assessed whether the introduction of cow milk or other food products was associated with sensitization against the introduction of separate food allergens (cow milk, hen

egg, peanut). A delay in introduction of cow milk products tended to be associated with a lower risk for sensitization against cow milk, but this trend was not statistically significant ($P = .10$ for trend; Table 4). Also, we studied the associations for sensitization against ≥ 1 inhalant allergens (birch, grass pollen, cat, dog, or house dust mite), showing that delayed introduction of other food products led to a higher risk for inhalant allergen sensitization ($P = .00$ for trend; Table 4). To control for reverse causation (early symptoms urging the parents to delay the introduction of foods in the hope of diminishing the symptoms), we excluded infants with early symptoms in several so-called risk-period-specific analyses.

Exclusion of Early Symptoms of Eczema

First, we excluded infants with early symptoms of eczema (ie, between 0 and 7 months). In this respect, only the introduction of cow milk between 4 and 6 months (in comparison with 0–3 months) can be studied, because no overlap occurs with the onset of symptoms after 7 months. The magnitude of the association for introducing cow milk products between 4 and 6 months slightly changed (aOR: 1.21). The OR for introducing other food products between 4 and 6 months turned away from 1 and reached statistical significance (aOR 1.72 [95% CI: 1.00–2.96]). Second, we excluded infants with symptoms of eczema in the first year of life (ie, between 0 and 12 months). The results of introducing cow milk products between 4 and 6 months (aOR: 1.20) and 7 and 9 months (aOR: 1.85) tended toward the same direction (compared with the results presented in Table 2), but both 95% CIs of these risk-period-specific analyses became wider.

TABLE 3 Associations Between Introduction of Cow Milk/Food Products and the Development of Infants' Recurrent Wheeze and Overall Sensitization at Age 2

Parameter	Recurrent Wheeze				Any Sensitization			
	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a	N	n (%)	cOR (95% CI) ^a	aOR (95% CI)
Age of introduction of cow milk products, mo ^b								
0–3	730	127 (17)	1.00	1.00	270	72 (27)	1.00	1.00
4–6	589	83 (14)	0.78 (0.58–1.05)	1.07 (0.66–1.75)	235	72 (31)	1.22 (0.83–1.79)	0.73 (0.36–1.46)
7–9	519	44 (9)	0.44 (0.31–0.63)	0.89 (0.45–1.77)	255	69 (27)	1.02 (0.69–1.50)	0.57 (0.25–1.29)
>9	56	5 (9)	0.47 (0.18–1.19)	0.96 (0.30–3.07)	22	7 (32)	1.28 (0.50–3.28)	0.71 (0.21–2.41)
P trend			.00	.77			.80	.26
Age of introduction of other foods products, mo ^b								
3	153	17 (11)	1.00	1.00	50	5 (10)	1.00	1.00
4–6	1685	232 (14)	1.28 (0.76–2.16)	1.71 (1.00–2.95)	709	208 (29)	3.74 (1.46–9.55)	3.69 (1.42–9.62)
>7	56	10 (18)	1.74 (0.74–4.07)	3.52 (1.42–8.73)	23	7 (30)	3.94 (1.09–14.19)	4.31 (1.14–16.22)
P trend			.20	.01			.01	.01
Breastfeeding duration (confounder), mo								
Never	388	53 (14)	1.00	1.00	102	24 (24)	1.00	1.00
0–3	853	101 (12)	0.86 (0.59–1.24)	0.87 (0.58–1.32)	220	59 (27)	1.19 (0.69–2.06)	1.33 (0.74–2.40)
4–6	427	46 (11)	0.73 (0.47–1.12)	0.74 (0.38–1.45)	148	49 (33)	1.61 (0.91–2.85)	2.42 (0.97–6.03)
7–9	391	21 (5.4)	0.31 (0.18–0.53)	0.31 (0.14–0.70)	153	47 (31)	1.44 (0.81–2.55)	2.22 (0.85–5.76)
>9	446	33 (7.4)	0.42 (0.27–0.68)	0.46 (0.21–1.02)	153	39 (26)	1.11 (0.62–2.00)	1.89 (0.70–5.12)
P trend			.00	.02			.63	.57

May not add up to total numbers because of missing values.

^a Based on logistic regression analysis, adjusted for duration of breastfeeding, gender of infant, recruitment group (conventional, alternative lifestyle), maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery (in years), maternal education, presence of parental allergic disease, and (older) siblings' atopic history.

^b The age of introduction cow's milk products and the age of introduction other food products were simultaneously included in the logistic regression analysis, which means that these variable were adjusted for each other.

Exclusion of Early Symptoms of Recurrent Wheeze

In the same manner as described in the previous section, we first excluded infants with symptoms of recurrent wheeze between 0 and 7 months. The OR for introducing cow milk products between 4 and 6 months (vs 0 and 3 months) changed (aOR: 0.85), and the CIs became wider. The OR for introducing other food products between 4 and 6 months attenuated (aOR: 1.35) and was no more statistically significant. After exclusion of infants who developed symptoms of wheeze in the first year of life, the ORs for introducing cow milk between 4 and 6 months and between 7 and 9 months were 1.19 and 1.48, respectively (the corresponding CIs became clearly wider). The OR for introducing other food products between 4 and 6 months and the risk for recurrent wheeze was comparable with the overall results presented in Table 3 (aOR 1.71, vs 1.50 in the risk-period-specific analysis).

Exclusion of Hypoallergenic Formulas

We found that infants who received hypoallergenic formulas between birth and 3 months ($n = 127$) showed a higher risk for eczema versus infants who were given nonhypoallergenic formula feeding (cOR: 1.78 [95% CI: 1.28–2.47]) even after adjustment for potential confounders (aOR: 1.62 [95% CI: 1.08–2.43]). In addition, hypoallergenic formulas were associated with a higher risk for recurrent wheeze (cOR: 3.86 [95% CI: 2.45–6.09]), also after adjustment for other confounders (aOR: 2.42 [95% CI: 1.33–4.43]). Because these results may suggest the presence of reverse causation (ie, hypoallergenic formulas were introduced after the development of eczema or recurrent wheeze), we repeated all

analyses in which we excluded participants who were introduced to hypoallergenic formulas (0–3 months). The ORs that are presented in Tables 2, 3, and 4 only slightly changed, and the magnitude of the *P* values for trend analyses remained the same; therefore we do not present the results after exclusion of hypoallergenic formulas.

DISCUSSION

In this study, a delayed introduction of cow milk products was associated with an increased risk for eczema and recurrent wheeze. Also, our data demonstrated that a delayed introduction of other food products was associated with an increased risk for eczema, similar to our findings with AD according to UK-WP criteria. Furthermore, a delayed introduction of other food products was associated with an increased risk for recurrent wheeze, atopic sensitization, and, in particular, inhalant allergen sensitization. We also demonstrated that longer breastfeeding duration (7–9 months) showed a reduced risk for recurrent wheeze. The risk for recurrent wheeze for breastfeeding >9 months tended in the same direction. Overall, we found a statistically significant trend toward a reduced risk for recurrent wheeze with longer duration of breastfeeding. Previously, we speculated that these results may be explained by a protection of breastfeeding against respiratory infections.¹³

It has been suggested that early introduction of solid foods may result in allergic sensitization against (food) allergens because the infant's gut-mucosal barrier is immature and early exposure to (food) allergens may trigger an allergic response of the immune system.¹⁴ In a study of children with an immature gastrointestinal tract

TABLE 4 Associations Between Introduction of Cow Milk/Food Products and the Development of Infants' Sensitization Against Egg, Milk, Peanut, and at Least 1 Inhalant Allergen at Age 2

Parameter	Sensitization Against Cow Milk				Sensitization Against Hen Egg			
	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a
Age of introduction of cow milk products, mo ^b								
0–3	270	50 (19)	1.00	1.00	270	16 (6)	1.00	1.00
4–6	235	54 (23)	1.31 (0.85–2.02)	0.87 (0.40–1.87)	235	15 (6)	1.08 (0.52–2.24)	1.10 (0.35–3.51)
7–9	255	44 (17)	0.92 (0.59–1.44)	0.60 (0.24–1.50)	255	12 (5)	0.78 (0.36–1.69)	0.66 (0.16–2.81)
>9	22	2 (9)	0.44 (0.10–1.94)	0.33 (0.06–1.82)	22	4 (18)	3.53 (1.07–11.66)	3.35 (0.56–20.15)
P trend			.44	.10			.70	.86
Age of introduction of other foods products, mo ^b								
3	50	4 (8)	1.00	1.00	50	1 (2)	1.00	1.00
4–6	709	143 (20)	2.91 (1.03–8.20)	2.64 (0.92–7.59)	709	44 (6)	3.24 (0.44–24.03)	3.10 (0.40–24.05)
>7	23	3 (13)	1.73 (0.35–8.43)	1.82 (0.35–9.37)	23	2 (9)	4.67 (0.40–54.31)	5.88 (0.45–76.85)
P trend			.21	.23			.19	.15
Breastfeeding duration (confounder), mo								
Never	104	18 (17)	1.00	1.00	104	4 (4)	1.00	1.00
0–3	223	41 (18)	1.07 (0.58–1.97)	1.17 (0.61–2.26)	223	16 (7)	1.92 (0.63–5.90)	2.08 (0.63–6.93)
4–6	148	33 (22)	1.34 (0.71–2.54)	1.78 (0.65–4.89)	148	7 (5)	1.22 (0.35–4.26)	1.56 (0.27–8.90)
7–9	153	37 (24)	1.49 (0.79–2.79)	2.32 (0.81–6.66)	153	13 (9)	2.28 (0.72–7.19)	2.76 (0.47–16.11)
>9	155	19 (12)	0.66 (0.33–1.33)	1.19 (0.38–3.67)	155	7 (5)	1.18 (0.34–4.12)	1.89 (0.28–12.68)
P trend			.55	.97			.92	.54
Parameter	Sensitization Against Peanut				Sensitization Against at Least 1 Inhalant Allergen			
	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a	N	n (%)	cOR (95% CI)	aOR (95% CI) ^a
Age of introduction of cow milk products, mo ^b								
0–3	271	18 (7)	1.00	1.00	261	21 (8)	1.00	1.00
4–6	235	13 (6)	0.82 (0.39–1.72)	0.86 (0.24–3.08)	228	28 (12)	1.60 (0.88–2.90)	1.06 (0.34–3.29)
7–9	256	10 (4)	0.57 (0.26–1.26)	0.56 (0.12–2.68)	247	31 (13)	1.64 (0.92–2.94)	0.81 (0.23–2.85)
>9	22	1 (5)	0.67 (0.09–5.26)	0.53 (0.40–7.05)	20	4 (20)	2.86 (0.88–9.33)	1.07 (0.19–5.91)
P trend			.18	.42			.05	.67
Age of introduction of other foods products, mo ^b								
3	50	1 (2)	1.00	1.00	50	1 (2)	1.00	1.00
4–6	711	39 (6)	2.84 (0.38–21.14)	2.55 (0.32–20.12)	683	77 (11)	6.23 (0.85–45.73)	6.55 (0.87–49.32)
>7	23	2 (9)	4.67 (0.40–54.31)	7.85 (0.58–106.55)	23	6 (26)	17.29 (1.94–154.17)	20.86 (2.17–200.75)
P trend			.19	.11			.00	.00
Breastfeeding duration (confounder), mo								
Never	104	5 (5)	1.00	1.00	100	9 (9)	1.00	1.00
0–3	223	16 (7)	1.51 (0.54–4.25)	1.68 (0.54–5.30)	210	15 (7)	0.79 (0.33–1.84)	0.68 (0.27–1.74)
4–6	148	7 (5)	0.96 (0.30–3.12)	1.42 (0.24–8.47)	143	21 (15)	1.74 (0.76–3.97)	1.55 (0.37–6.44)
7–9	153	10 (7)	1.36 (0.45–4.09)	2.29 (0.37–14.33)	147	16 (11)	1.24 (0.52–2.92)	0.92 (0.21–4.06)
>9	155	4 (3)	0.52 (0.14–1.97)	1.15 (0.15–9.03)	150	23 (15)	1.83 (0.81–4.14)	1.60 (0.36–7.17)
P trend			.24	.84			.03	.61

May not add up to total numbers because of missing values.

^a Based on logistic regression analysis, adjusted for duration of breastfeeding, gender of infant, recruitment group (conventional, alternative lifestyle), maternal smoking during pregnancy, infant's exposure to environmental tobacco smoke, maternal age at delivery (in years), maternal education, presence of parental allergic disease, and (older) siblings' atopic history.

^b The age of introduction of cow milk products and the age of introduction other food products were simultaneously included in the logistic regression analysis, which means that these variable were adjusted for each other.

or immune response, no increased risk for the development of food allergies was found¹⁵; however, there is only scarce scientific evidence to support this hypothesis. Most studies have focused on the duration of breastfeeding as a preventive measure to avoid the development of asthma and allergy. In 1999, Oddy et al¹⁶ found that it was the later age at which cow milk was introduced rather than the duration of breastfeeding that was more closely associated with lower risk for asthma or atopy at 6 years of age. They found that the introduction of milk other than breast milk was a significant risk factor for asthma, wheeze, and a positive skin prick test reaction against at least 1 common aeroallergen. These results

favor “exclusion mechanisms”; however, it was noted that studies that attempt to separate the effects of breastfeeding duration and the age of introduction of cow milk or food products face problems of high correlation between these variables. Therefore, the possibility that it may be breastfeeding itself that may confer protection cannot be rejected.¹⁶

Several other studies previously focused on the introduction of first exposure of milk or food products. The results of our study tended toward the same direction as several previous studies. Zutavern et al⁹ showed an increased risk for eczema in relation to late introduction of egg and milk in a prospective birth cohort study in the

United Kingdom. Late introduction of egg was furthermore associated with a nonsignificantly increased risk for preschool wheezing. Our results confirm that also wheeze may be implicated as an atopic outcome, because we found that age of introduction of food products other than cow milk products was associated with higher risk not only for eczema but also for wheeze and sensitization for inhalant allergens. Mahrshahi et al¹⁷ showed that breastfeeding for ≥ 6 months (yes versus no) and introduction of solid foods after 3 months (yes versus no) both were associated with an increased risk for atopy (defined as the presence of any allergen wheal ≥ 2 mm and larger than the negative control) at 5 years of age. It is interesting that Poole et al¹⁸ showed that children who were first exposed to cereals after 6 months of age had an increased risk for wheat allergy compared with children who were first exposed to cereals before 6 months of age. In contrast with these studies, Morgan and colleagues¹⁹ showed that the introduction of ≥ 4 solids before 17 weeks' postterm (compared with <4 foods at 17 weeks' postterm) was associated with a higher risk for eczema in infants with and without a family history of allergy, suggesting that a delay of the introduction of solids reduced the development of eczema; however it should be noted that this study was done in preterm infants, which may possibly confound⁸ their results because prematurity has been shown to reduce the long-term risk for atopy.²⁰ Andreasyan et al²¹ showed recently that there was no association between introduction of nonmilk fluids in infancy and childhood atopic disease. The results of a follow-up analysis of a double-blind, placebo-controlled, randomized feeding intervention trial showed that brief neonatal exposure to cow milk (quantity was regarded sufficient to induce sensitization) in breastfed children was not associated with atopic disease or allergic symptoms up to age 5.^{22,23}

Most studies that addressed the relationship between timing of solid introduction and atopy development were prospective birth cohort studies instead of randomized, controlled trials. A major disadvantage of cohort studies has been the phenomenon of reverse causation when interpreting the results.^{8,9} Zutavern et al²⁴ investigated whether a delayed introduction of solids (after 4 or 6 months) is protective against the development of AD and atopic sensitization when taking into account reverse causation in a German prospective birth cohort study. Their results provided evidence (ie, their results changed) for reverse causation between the introduction of solids and early skin or allergic symptoms. In this study, we indeed thought of the idea that parents of infants with early symptoms of eczema or wheeze may delay the introduction of cow milk products or other food products, which would make our results susceptible to reverse causation. We have attempted to avoid reverse causation in our analysis as follows: first, we excluded all infants with reported symptoms of eczema between 0 and 7 months, resulting in cases that were "at risk" for developing eczema between 7 and 24 months. Second, in the same way, we excluded all infants with reported symptoms in the first year of life (0–12 months), resulting in infants who were at risk in the

second year of life (12–24 months). The same was done for the outcome "recurrent wheeze." We noted that the results (ORs and 95% CIs) of our so-called risk-period-specific analysis did slightly change, which suggests that the presence of reverse causation as a potential bias cannot be fully excluded; however, in our opinion, the interpretation of our main findings were minimally affected by reverse causation. Unfortunately, we were not able to assess whether our results of AD according to UK-WP criteria and allergic sensitization were prone to reverse causation, because the data were available only at the age of 2 years; therefore, we could not exclude infants who developed early symptoms.

Another explanation that has been put forward to explain the results of an increased risk for atopy by a delayed introduction of cow milk or food allergens is the induction of "oral tolerance" (ie, the induction of systemic immunologic hyporesponsiveness, a usual response to soluble dietary proteins). Although the biological mechanism of this is largely unexplained, the induction of oral tolerance affects a broad spectrum of immunologic functions, locally and systemically, to a varying degree.²⁵ Previously, it was also put forward that late introduction of food products is associated with allergy, because introducing food products to older infants tends to be in greater amounts.²⁶ Hence, it has been speculated that a larger antigen dosage may result in T-cell activation instead of anergy or tolerance.¹⁸ Indeed, it may be anticipated that our results can be explained by the induction of oral tolerance that will be induced by larger amounts of cow milk and other food products, leading to an increased exposure to (food) antigens in older infants (>7 vs 0–3 months) in this study.

CONCLUSIONS

We have shown that a delayed introduction of cow milk products is associated with a higher risk for eczema. In addition, a delayed introduction of other food products is associated with an increased risk for atopy development in the first 2 years of life (eczema, AD according to UK-WP criteria, recurrent wheeze, any sensitization and inhalant allergen sensitization). Although breastfeeding remains definitely favorable for the infant's health (ie, protection against infections), it may be questioned whether delaying the introduction of cow milk or other food products may have a substantial additional advantage as a possible preventive measure to avoid the development of atopic manifestations. On the basis of the current knowledge, it may be too early to change the current guidelines on the introduction of cow milk (eg, World Health Organization), although these guidelines may be discussed in light of the "induction" of oral tolerance. Future research may focus on separating formula products from "other cow milk products," because the current guidelines suggest that introduction of cow milk products should wait but are not meant to suggest that milk-based formulas cannot be used.

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Age at First Introduction of Cow Milk Products and Other Food Products in Relation to Infant Atopic Manifestations in the First 2 Years of Life: The KOALA Birth Cohort Study

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