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Timing of Solid Food Introduction in Relation to Atopic Dermatitis and Atopic Sensitization: Results From a Prospective Birth Cohort Study

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ABSTRACT

OBJECTIVE. Prophylactic feeding guidelines recommend a delayed introduction of solid foods for the prevention of atopic diseases. Scientific evidence for this is scarce. This study investigates whether a delayed introduction of solids (past 4 months or 6 months) is protective against the development of atopic dermatitis (AD) and atopic sensitization when considering reverse causality.

METHODS. Data from 2612 infants in an ongoing birth cohort study were analyzed at 2 years of age. Information on diet and on symptoms and diagnoses of AD was collected semiannually, and information on specific immunoglobulin E levels was collected at 2 years of age.

RESULTS. Solid food introduction past the first 4 months of life decreased the odds of symptomatic AD but not for doctor-diagnosed AD, combined doctor-diagnosed and symptomatic AD, or atopic sensitization. Postponing the introduction beyond the sixth month of life was not protective in relation to either definition of AD or atopic sensitization. There was also no evidence for a protective effect of a delayed introduction of solids on AD and atopic sensitization in children of atopic parents. There was clear evidence for reverse causality between early skin or allergic symptoms and the introduction of solids.

CONCLUSIONS. This study does not find evidence supporting a delayed introduction of solids beyond the sixth month of life for the prevention of AD and atopic sensitization. We cannot rule out that delaying the introduction of solids for the first 4 months of life might offer some protection. Measures to avoid reverse causality have to be considered in the conduction, analysis, and interpretation of cohort studies on the topic.

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Key Words

eczema, sensitization, dermatitis, cohort, reverse causality, solid food

Abbreviations

AD—atopic dermatitis
LISA—Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood
IgE—immunoglobulin E
aOR—adjusted odds ratio
CI—confidence interval

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PROPHYLACTIC FEEDING GUIDELINES for the prevention of atopic diseases recommend a delayed introduction of solid foods until 4 to 6 months of age.¹⁻⁴ In 2001, the World Health Organization tightened its preceding recommendations of 4 to 6 months of exclusive breastfeeding to 6 months of exclusive breastfeeding with an introduction of solids thereafter.⁴ However, scientific evidence supporting a delayed solid food introduction for the prevention of atopic diseases is scarce, inconsistent, and based on a few studies only.^{5,6}

In the revived discussion, the necessity of new studies avoiding the pitfalls of recall bias and reverse causality (ie, the outcome influencing the exposure) became clear.⁵ Because of high public awareness of a possible association between feeding practices and atopic diseases, reverse causality must be considered in current investigations. Symptoms of atopic dermatitis (AD) may start very early in life, before parents have decided when they should introduce solids into the child's diet. Consequently, children who already are showing first signs of AD (outcome) might be introduced to solid foods (exposure) later, possibly masking a true protective effect or even resulting in false-positive associations between late solid food introduction and AD. This might be enhanced further in children from atopic families. In epidemiologic studies, cohort studies are seen as the design of choice for the investigation of the temporal sequence between exposure and outcome. However, most cohort studies fail to disentangle the temporal relationship between feeding practices and AD, as information on both is often collected simultaneously and retrospectively at age 1 year. To our knowledge, this is the first study to examine the relationship between the introduction of solids and AD considering reverse causality.

We conducted a large, population-based, prospective birth cohort study without any interventional measures. Information on diet, symptoms, and diagnoses of AD was collected semiannually. The aims of this analysis were (1) to assess the role of reverse causality in the associations between solid food introduction and development of AD in a cohort study and (2) to investigate whether a delayed introduction of solids (past 4 months or past 6 months) is protective against the development of AD when reverse causality is taken into account. As an objective parameter in atopic diseases research, we examined further whether a delayed solid food introduction is protective against atopic sensitization. Last, we investigated whether our results hold true for children of atopic parents.

METHODS

Data from the ongoing birth cohort study Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood (LISA) were an-

alyzed for the first 2 years of age. The study design of this population-based, prospective birth cohort study has been described elsewhere.^{7,8} In short, 3097 healthy full-term infants who were delivered between November 1997 and January 1999 at selected maternity hospitals in 4 German cities (Munich, Leipzig, Wesel, and Bad Honnef) were enrolled in the study. Self-completion questionnaires were filled in by the parents at birth and when the children were 6, 12, 18, and 24 months of age. At 2 years of age, children were invited for blood collection and physical examination. The participation in the study ranged between 52% and 58%, depending on the study center.⁸ Informed consent was obtained from the parents of all children. Ethical approval for the study was obtained from the local ethics committees.

Atopic Sensitization

Specific immunoglobulin E (IgE) against common food allergens (egg, cow milk, wheat, peanut, soybean, and cod fish) and common inhalant allergens (house dust mites, cockroach, cat, mixed grasses, birch pollen, and mixed molds) were determined at 2 years of age by standardized methods with CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany). "Any sensitization" was defined as any specific IgE value ≥ 0.35 kU/L. "Food sensitization" was defined as any specific IgE value against food allergens ≥ 0.35 kU/L.

Questionnaires

Questionnaires included semiannual (at infants' age 6, 12, 18, and 24 months) questions on doctor diagnoses and symptoms of AD and other medical conditions. Questions about feeding practices, child characteristics, lifestyle, and environmental factors were also included.

"Doctor-diagnosed AD" was assigned when parents reported a physician's diagnosis of AD in the preceding 6 months in any of the questionnaires. Symptomatic AD was assigned when parents reported an itching eczema within the preceding 6 months that was either recurrent or lasted for >2 weeks and that affected the skin creases, face, neck, extremities, hands, feet, or trunk (not underneath the diaper) in any of the questionnaires. "Early skin or allergic symptoms" was assigned when parents gave an affirmative response to the question, "Has a doctor diagnosed your child with 1 of the following conditions within the first 6 months of life: atopic dermatitis; allergic or atopic eczema; food allergy, hives, urticaria, or allergic edema; milk crust or seborrheic eczema; eczema without further specification?" or when parents reported an increase of eczema as a result of food intolerance within the first 6 months of their child's life.

When the children were 6 months of age, parents were asked about breastfeeding practices and about the timing of solid food introduction into the child's diet. Answer possibilities were first/second month, third/fourth month, fifth/sixth month, and solid food item not

yet introduced. Forty-eight single food items were asked for and classified into the following 8 solid food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and others (eg, soybean, nuts, cacao, chocolate). Summary exposure variables were constructed. "Any solids" defined the timing of first introduction of any of the above-mentioned solid food items. "Solids diversity" was defined at 4 months and at 6 months summing up the number of different food groups that were included in the child's diet by then. The variable "milk or egg" comprises the timing of first introduction of milk or egg. Breastfeeding was categorized into exclusively breastfed, partly breastfed, and exclusively bottle-fed within the first 4 months irrespective of solid food introduction. Parental atopy was considered positive when either parent ever had AD, asthma, or hay fever. Parental education was categorized by the highest number of years of school attendance by either parent (Table 1). Birth weight was categorized into 4 approximately equal size groups.

Statistical Analysis

The statistical analysis was based on the following assumptions:

- Early skin or allergic symptoms might be on the causal pathway to AD and therefore cannot be adjusted for.

- Children with early skin or allergic symptoms might be introduced to solids later because of the early skin or allergic symptoms. This would be seen best in a delayed introduction of milk and egg as public awareness on these nutrients is highest.
- A positive association between a delayed introduction of milk/egg and AD in children with early skin or allergic symptoms only would be interpreted as an indicator of reverse causality.

The analysis was restricted to children with data on early skin or allergic symptoms, solid food, and doctor-diagnosed or symptomatic AD ($N = 2612$).

To explore reverse causality, we first investigated the relationship between early skin or allergic symptoms with AD outcomes in months 6 to 24 and with the timing of first introduction of milk or egg. We then calculated the associations between timing of introduction of milk/egg and AD for children with and children without early skin or allergic symptoms separately. Significance levels in descriptive analyses were determined by χ^2 tests.

Multivariate logistic-regression analyses were performed to investigate the associations between different solid food measures with AD and sensitization outcomes. Solid food measures examined comprised single food groups and the summary exposure variables "any solids" and "solids diversity at 4 and 6 months." All models were

TABLE 1 Characteristics of the Population of All Children and of Children With and Children Without Early Skin or Allergic Symptoms

	All ($N = 2612$), n (%) ^a	No Early Skin or Allergic Symptoms ($N = 1581$), n (%) ^a	Early Skin or Allergic Symptoms ($N = 1031$), n (%) ^a	P^b
AD, food allergy, atopic sensitization				
Doctor-diagnosed AD age 0–2 y ($N = 2537$)	466 (18)	145 (9)	321 (32)	.000
Symptomatic AD age 0–2 y ($N = 2448$)	534 (22)	189 (13)	345 (35)	.000
Any sensitization at age 2 y ($N = 2086$)	258 (12)	133 (11)	125 (15)	.001
Food sensitization at age 2 y ($N = 2094$)	197 (9)	104 (8)	93 (11)	.02
Characteristics				
Center ($N = 2612$)				
Munich	1319 (51)	814 (51)	505 (49)	.01
Leipzig	770 (29)	431 (27)	339 (33)	
Wesel	259 (10)	165 (10)	94 (9)	
Bad Honnef	264 (10)	171 (11)	93 (9)	
Female gender ($N = 2612$)	1251 (48)	767 (49)	484 (47)	.43
Parental atopy ($N = 2606$)	1387 (53)	801 (51)	586 (57)	.002
Number of older siblings ($N = 2606$)				
0	1468 (56)	879 (56)	589 (57)	.58
1	882 (34)	535 (34)	347 (34)	
2–6	256 (10)	162 (10)	94 (9)	
Parental education ($N = 2588$)				
High school graduate	1768 (68)	1069 (68)	699 (68)	.29
≥10 y at school	701 (27)	418 (27)	283 (28)	
<10 y at school	119 (5)	80 (5)	39 (4)	

^a May not add up to the total number because of missing values.

^b P values are from χ^2 test for the comparison of children with and without early skin or allergic symptoms.

adjusted for the a priori defined potential confounding factors study center, parental atopy, child's gender, parental education, birth weight, and breastfeeding type. Multivariate analyses were performed in parallel for the whole cohort for AD from birth to 2 years of age plus for the strata of children with and without early skin or allergic symptoms for AD from month 6 to month 24. Strata of children without early skin or allergic symptoms were considered undistorted by reverse causality. Strata of AD in months 0 to 24 in the whole cohort allowed a comparison of our results with the results of other studies. Sensitization was unlikely to be influenced by reverse causality. Therefore, sensitization models were not stratified by early skin or allergic symptoms. A possible confounding effect of number of older siblings, mother's age at birth of child, and mother's smoking in pregnancy on sensitization outcomes was considered. However, testing in multivariate analyses did not show any confounding effect. Therefore, no adjustment for these variables was made. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CIs). Tests for interaction were performed for parental atopy as an a priori defined effect modifier. All statistical analysis was performed with Stata 8.0 (Stata Corp, College Station, TX).

RESULTS

Study Population

Of the 3097 children who were recruited at birth, 2664 (86%) had completed 2-year questionnaires and 2094 (68%) children had specific IgE results at 2 years of age. Information on solid food, AD outcomes, and early skin or allergic symptoms was available for 2612 (84%) children.

Reverse Causality

In the study population, the prevalence of adverse skin conditions within the first 6 months of life was high, with early skin or allergic symptoms being present in 39% of children (Table 2). In comparison with their asymptomatic peers, children with early skin or allergic symptoms subsequently had significantly more often doctor-diagnosed AD (27% vs 9%) and symptomatic AD (29% vs 12%) in months 6 to 24. They were introduced to milk and egg significantly later (79% vs 74%; Table 2).

Within children who were affected by early skin or allergic symptoms, a later introduction of milk and egg was significantly positively associated with doctor-diagnosed AD in months 6 to 24 ($P < .001$), most likely

TABLE 2 Skin or Allergic Conditions in the First 6 Months in Relation to Doctor-Diagnosed and Symptomatic AD in Months 6 to 24 and in Relation to the Introduction of Milk or Egg

	Total, <i>n</i>	Doctor-Diagnosed AD Months 6–24, <i>n</i> (%) ^a	<i>P</i> ^b	Symptomatic AD Months 6–24, <i>n</i> (%) ^a	<i>P</i> ^b	Introduction of Milk or Egg >6 mo, <i>n</i> (%) ^a	<i>P</i> ^b
All children	2612	414/2524 (16)		458/2444 (19)		1941/2554 (76)	
Skin or allergic conditions in first 6 mo							
Doctor-diagnosed AD							
No	2425	284 (12)	.000	356 (16)	.000	1788 (75)	.01
Yes	174	122 (77)		95 (59)		144 (84)	
Doctor-diagnosed food allergy							
No	2545	379 (15)	.000	423 (18)	.000	1884 (76)	.05
Yes	55	26 (52)		28 (53)		47 (87)	
Doctor-diagnosed urticaria							
No	2600	409 (16)	.38	453 (19)	.50	1931 (76)	.55
Yes	8	2 (29)		2 (29)		6 (86)	
Doctor-diagnosed milk crust or seborrheic eczema							
No	1798	222 (13)	.000	247 (15)	.000	1306 (74)	.002
Yes	808	186 (24)		207 (27)		630 (80)	
Doctor-diagnosed eczema (without specification)							
No	2371	334 (15)	.000	365 (16)	.000	1756 (76)	.75
Yes	223	70 (33)		87 (42)		168 (77)	
Increase of eczema as a result of food intolerance							
No	2330	333 (15)	.000	382 (18)	.000	1735 (76)	.23
Yes	121	51 (44)		47 (41)		98 (81)	
Early skin or allergic symptoms							
No	1581	145 (9)	.000	177 (12)	.000	1147 (74)	.01
Yes	1031	269 (27)		281 (29)		794 (79)	

^a May not add up to the total number because of missing values.

^b *P* values are from χ^2 test.

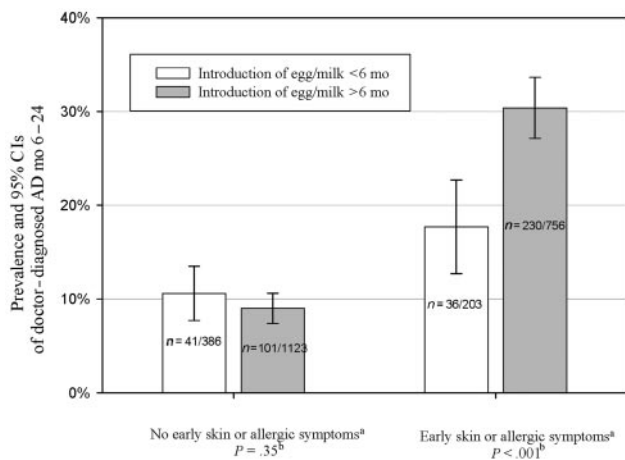


FIGURE 1

Association between the timing of introduction of egg/milk and doctor-diagnosed AD months 6 to 24 stratified by early skin or allergic symptoms. Prevalences with exact 95% CIs are shown. ^a Early skin or allergic symptoms = physician's diagnosis of AD, food allergy, urticaria, milk crust, or any eczema increase of eczema caused by food intolerance within the first 6 months. ^b P value from χ^2 test.

indicating reverse causality. For children who were unaffected by early skin or allergic symptoms, no such association was observed (Fig 1). No significant associations between the timing of introduction of milk or egg with symptomatic AD in months 6 to 24 were seen in either stratum (data not shown).

Population Characteristics

The study population contained slightly more boys than girls. More than half of the children had a positive parental history of atopic diseases. Children with early skin or allergic symptoms were more likely to have atopic parents (57% vs 51%) and to be atopic (15% vs 11% for any sensitization; 11% vs 8% for food sensitization). The parental education level was high (Table 1).

Feeding Practices

At 4 months of age, 34% of children had been introduced to any solids, whereas 18% of children were first introduced to solids when they were older than 6 months (Table 3). Vegetables were introduced first, followed by fruit, cereal, meat products, dairy products, others, egg, and fish in chronological order. Children with early skin or allergic symptoms were introduced to fruit and dairy products somewhat later than children without early skin or allergic symptoms. However, overall, the 2 groups did not differ greatly in relation to their feeding practices.

Doctor-Diagnosed AD

Within the first 2 years, doctor-diagnosed AD was prevalent in 18% of participants (Table 1). Doctor-diagnosed AD between months 6 and 24 was prevalent in 16% of participants, in 9% of children without early skin or

allergic symptoms, and in 27% of children with early skin or allergic symptoms (Table 2).

There was no evidence for a protective effect of a delayed introduction of solids in months 5 to 6 or beyond 6 months on doctor-diagnosed AD (Table 4). This was true for the single food groups as well as for the summary measures "any solids" and "solids diversity at ages 4 and 6 months." Introduction of a high number of different solid food groups by 6 months of age reduced the odds of having a doctor-diagnosed AD within all children (aOR: 0.66; 95% CI: 0.46–0.94) and within children with early skin or allergic symptoms (aOR: 0.47; 95% CI: 0.28–0.77), most likely indicating reverse causality.

Symptomatic AD

Within the first 2 years, symptomatic AD was prevalent in 22% of participants (Table 1). Symptomatic AD between months 6 and 24 was prevalent in 19% of participants, in 12% of children without early skin or allergic symptoms, and in 29% of children with early skin or allergic symptoms (Table 2).

Within all children, there was no evidence for a protective effect of a delayed introduction of solids on symptomatic AD (Table 5). However, in children without early skin or allergic symptoms, a more diverse diet at 4 months of age increased the odds of symptomatic AD (no dose-response relationship), and the introduction of various solid food groups beyond 4 months of age decreased the odds of symptomatic AD, reaching statistical significance for fruit and cereal. There was no additional protective effect when the introduction of solids was postponed to later than 6 months. Within children with early skin or allergic symptoms, late introduction of dairy products was associated with significantly increased odds of symptomatic AD, most likely indicating reverse causality.

Sensitization at 2 Years Of Age

At 2 years of age, any sensitization was present in 12% of children, and sensitization against food allergens was present in 9% of children (Table 1). There was no evidence for a protective effect of a delayed introduction of solids in months 5 to 6 or beyond 6 months on any sensitization or food sensitization (Table 6). Additional adjustment for AD did not change these results. The timing of introduction of milk and egg was not associated with atopic sensitization against the respective items (data not shown).

Additional Analyses

We repeated the analyses for a stricter AD definition that comprised the combination of doctor-diagnosis and symptoms of AD. There was no evidence for a protective effect of a delayed introduction of solids in months 5 to

TABLE 3 Description of Feeding Practices

	All (N = 2612), n (%) ^a	No Early Skin or Allergic Symptoms (N = 1581), n (%) ^a	Early Skin or Allergic Symptoms (N = 1031), n (%) ^a	P ^b
Timing of introduction of solids				
Any solids (N = 2474)				
0–4 mo	840 (34)	525 (35)	315 (32)	.26
5–6 mo	1189 (48)	713 (48)	476 (49)	
>6 mo	445 (18)	258 (17)	187 (19)	
Solids diversity at 4 mo (N = 2410)				
no solid food	1634 (68)	971 (67)	663 (69)	.16
1–2 food groups	420 (17)	252 (17)	168 (18)	
3–8 food groups	356 (15)	231 (16)	125 (13)	
Solids diversity at 6 mo (N = 2407)				
no solid food	445 (18)	258 (18)	187 (20)	.44
1–2 food groups	423 (18)	258 (18)	165 (17)	
3–4 food groups	873 (36)	518 (36)	355 (37)	
5–8 food groups	666 (28)	416 (29)	250 (26)	
Timing of introduction of single solid food groups				
Vegetables (N = 2540)				
0–4 mo	720 (28)	451 (29)	269 (27)	.29
5–6 mo	1266 (50)	765 (50)	501 (50)	
>6 mo	554 (22)	323 (21)	231 (23)	
Fruit (N = 2540)				
0–4 mo	561 (22)	367 (24)	194 (19)	.02
5–6 mo	1318 (52)	774 (50)	544 (54)	
>6 mo	661 (26)	394 (26)	267 (27)	
Cereal (N = 2505)				
0–4 mo	370 (15)	236 (16)	134 (14)	.37
5–6 mo	1272 (51)	765 (50)	507 (51)	
>6 mo	863 (34)	515 (34)	348 (35)	
Meat products (N = 2532)				
0–4 mo	206 (8)	127 (8)	79 (8)	.30
5–6 mo	1011 (40)	625 (41)	386 (38)	
>6 mo	1315 (52)	773 (51)	542 (54)	
Dairy products (N = 2549)				
0–4 mo	101 (4)	71 (5)	30 (3)	.03
5–6 mo	633 (25)	397 (26)	236 (23)	
>6 mo	1815 (71)	1072 (70)	743 (74)	
Other (N = 2533)				
0–6 mo	351 (14)	202 (13)	149 (15)	.26
>6 mo	2182 (86)	1325 (87)	857 (85)	
Egg (N = 2543)				
0–6 mo	168 (7)	109 (7)	59 (6)	.22
>6 mo	2375 (93)	1428 (93)	947 (94)	
Fish (N = 2540)				
0–6 mo	32 (1)	19 (1)	13 (1)	.90
>6 mo	2508 (99)	1516 (99)	992 (99)	
Breastfeeding type at 4 mo (N = 2608)				
Exclusively breastfed	1499 (57)	917 (58)	582 (57)	.73
Mixed	956 (37)	572 (36)	384 (37)	
Exclusively bottle-fed	153 (6)	90 (6)	63 (6)	

Specific food items summarized in food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and other.

^a May not add up to the total number because of missing values.

^b P values are from χ^2 test for the comparison of children with and without early skin or allergic symptoms.

6 or beyond 6 months on this outcome (data not shown).

Analyses for the associations between any solids and solid diversity at ages 4 and 6 months in relation to AD and sensitization outcomes were also repeated within

the subsample of children with a positive family history of atopic diseases. There was no evidence for a protective effect of a delayed introduction of solids on doctor-diagnosed AD, symptomatic AD, and food and any sensitization in these children (data not shown).

TABLE 4 Associations Between the Introduction of Solids and Doctor-Diagnosed AD

	All Doctor-Diagnosed AD Months 0–24, aOR (95% CI) ^a	No Early Skin or Allergic Symptoms Doctor-Diagnosed AD Months 6–24, aOR (95% CI) ^a	Early Skin or Allergic Symptoms Doctor-Diagnosed AD Months 6–24, aOR (95% CI) ^a
Timing of introduction of solids			
Any solids (N = 2474; reference group: 0–4 mo)			
5–6 mo	1.14 (0.86–1.50)	1.02 (0.64–1.62)	1.08 (0.72–1.60)
>6 mo	1.31 (0.93–1.86)	0.96 (0.53–1.74)	1.48 (0.91–2.40)
Solids diversity at 4 mo (N = 2410; reference group: no solid food)			
1–2 groups	0.95 (0.70–1.29)	0.99 (0.59–1.68)	0.98 (0.63–1.51)
3–8 groups	0.71 (0.48–1.04)	0.86 (0.46–1.64)	0.73 (0.42–1.26)
Solids diversity at 6 mo (N = 2407; reference group: no solid food)			
1–2 groups	0.81 (0.57–1.15)	1.10 (0.60–2.02)	0.64 (0.39–1.03)
3–4 groups	0.96 (0.71–1.29)	0.98 (0.57–1.69)	0.91 (0.61–1.37)
5–8 groups	0.66 (0.46–0.94) ^b	1.12 (0.62–2.03)	0.47 (0.28–0.77) ^b
Timing of introduction of single solid food groups			
Vegetables (N = 2540; reference group: 0–4 mo)			
5–6 mo	1.21 (0.91–1.62)	1.14 (0.71–1.83)	1.09 (0.72–1.64)
>6 mo	1.49 (1.06–2.10) ^b	0.97 (0.54–1.76)	1.64 (1.01–2.65) ^b
Fruit (N = 2540; reference group: 0–4 mo)			
5–6 mo	1.14 (0.85–1.53)	0.92 (0.57–1.49)	0.92 (0.60–1.42)
>6 mo	1.11 (0.78–1.57)	0.79 (0.44–1.41)	1.06 (0.65–1.74)
Cereal (N = 2505; reference group: 0–4 mo)			
5–6 mo	1.24 (0.87–1.76)	1.05 (0.58–1.88)	1.23 (0.74–2.03)
>6 mo	1.34 (0.91–1.98)	1.21 (0.63–2.31)	1.34 (0.77–2.34)
Meat products (N = 2532; reference group: 0–4 mo)			
5–6 mo	1.41 (0.89–2.25)	1.64 (0.73–3.67)	1.29 (0.68–2.44)
>6 mo	1.63 (1.00–2.65) ^b	1.27 (0.54–2.99)	1.59 (0.82–3.08)
Dairy products (N = 2549; reference group: 0–4 mo)			
>5–6 mo	1.22 (0.64–2.30)	1.87 (0.63–5.52)	1.24 (0.44–3.49)
>6 mo	1.57 (0.85–2.93)	1.58 (0.54–4.64)	1.96 (0.71–5.37)
Other (N = 2533; reference group: 0–6 mo)			
>6 mo	1.21 (0.86–1.70)	1.81 (0.95–3.42)	1.10 (0.70–1.73)
Egg (N = 2543; reference group: 0–6 mo)			
>6 mo	1.27 (0.80–2.01)	0.93 (0.46–1.87)	1.26 (0.65–2.46)
Fish (N = 2540; reference group: 0–6 mo)			
>6 mo	0.96 (0.38–2.41)	0.74 (0.16–3.41)	1.00 (0.30–3.41)

Specific food items are summarized in food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and other.

^a Adjusted for study center, gender, parental education, parental atopy, birth weight, and breastfeeding type; models might include less than the total number of observations because of missing values.

^b $P < .05$.

DISCUSSION

In this large, population-based, prospective birth cohort study, there was no evidence for a protective effect of a delayed introduction of solids past the sixth month of life on AD and sensitization at 2 years of age. For an introduction of solids past the fourth month of life, this relationship is less clear. A high diversity of introduction of solids within the first 4 months of life increased the odds of symptomatic AD in months 6 to 24. However, this was not seen for doctor-diagnosed AD, combined doctor-diagnosed and symptomatic AD, or sensitization. There was also no evidence for a protective effect of a delayed introduction of solids on AD and sensitization in children of atopic parents. In addition, our results illustrate pitfalls of reverse causality in cohort studies that investigate the relationship between feeding practices and atopic diseases, which we have taken into account in our data analysis.

In this analysis, 2 different definitions of AD (doctor-diagnosed AD and symptomatic AD) were used in parallel and presented for different strata (AD from birth to 2 years of age in all children, from month 6 to 24 with and without early skin or allergic symptoms). The stratum of AD in months 0 to 24 in all children allows a comparison of our results with the results of other studies. Stratification of AD in months 6 to 24 by the presence of skin or allergic symptoms within the first 6 months of life allows the exploration of reverse causality. Strata of children without early skin or allergic symptoms were interpreted as undistorted from reverse causality. This proceeding was based on the assumption that most parents were aware of current prophylactic feeding recommendations and would delay the introduction of solids when they notice symptoms of AD in their child. Consequently, in symptomatic children, a late introduction of solids would be associated with an

TABLE 5 Associations Between the Introduction of Solids and Symptomatic AD

	All Symptomatic AD ^a Months 0–24, aOR (95% CI) ^b	No Early or Allergic Symptoms ^c Symptomatic AD ^a Months 6–24, aOR (95% CI) ^b	Early or Allergic Symptoms ^c Symptomatic AD ^a Months 6–24, ^a aOR (95% CI) ^b
Timing of introduction of solids			
Any solids (N = 2474; reference group: 0–4 mo)			
5–6 mo	1.07 (0.83–1.39)	0.67 (0.44–1.02)	1.08 (0.73–1.59)
>6 mo	1.19 (0.86–1.66)	0.68 (0.40–1.17)	1.51 (0.94–2.45)
Solids diversity at 4 mo (N = 2410; reference group: no solid food)			
1–2 groups	0.83 (0.61–1.12)	0.99 (0.59–1.65)	0.91 (0.59–1.41)
3–8 groups	0.95 (0.68–1.35)	2.17 (1.28–3.69) ^d	0.77 (0.46–1.31)
Solids diversity at 6 mo (N = 2407; reference group: no solid food)			
1–2 groups	0.78 (0.55–1.09)	0.93 (0.52–1.66)	0.63 (0.39–1.03)
3–4 groups	0.98 (0.73–1.30)	1.15 (0.70–1.87)	0.79 (0.52–1.18)
5–8 groups	0.80 (0.57–1.12)	1.06 (0.61–1.83)	0.61 (0.37–0.99) ^d
Timing of introduction of single solid food groups			
Vegetables (N = 2540; reference group: 0–4 mo)			
5–6 mo	1.02 (0.78–1.34)	0.66 (0.43–1.01)	1.03 (0.69–1.54)
>6 mo	1.22 (0.89–1.69)	0.70 (0.41–1.18)	1.46 (0.91–2.35)
Fruit (N = 2540; reference group: 0–4 mo)			
5–6 mo	1.02 (0.78–1.35)	0.65 (0.42–0.99) ^d	0.98 (0.65–1.50)
>6 mo	1.03 (0.75–1.44)	0.59 (0.35–1.00) ^d	1.17 (0.72–1.91)
Cereal (N = 2505; reference group: 0–4 mo)			
5–6 mo	0.94 (0.68–1.29)	0.44 (0.27–0.72) ^d	1.16 (0.71–1.90)
>6 mo	0.99 (0.69–1.41)	0.51 (0.29–0.87) ^d	1.37 (0.80–2.36)
Meat products (N = 2532; reference group: 0–4 mo)			
5–6 mo	1.08 (0.72–1.62)	0.83 (0.44–1.59)	1.17 (0.64–2.13)
>6 mo	1.20 (0.78–1.83)	0.71 (0.35–1.40)	1.48 (0.79–2.77)
Dairy products (N = 2549; reference group: 0–4 mo)			
>5–6 mo	1.39 (0.78–2.50)	0.54 (0.25–1.14)	3.97 (1.15–13.68) ^d
>6 mo	1.35 (0.76–2.40)	0.57 (0.27–1.19)	3.45 (1.01–11.78) ^d
Other (N = 2533; reference group: 0–6 mo)			
>6 mo	0.80 (0.60–1.08)	0.87 (0.52–1.43)	0.86 (0.56–1.32)
Egg (N = 2543; reference group: 0–6 mo)			
>6 mo	1.05 (0.69–1.58)	0.91 (0.48–1.74)	0.84 (0.45–1.54)
Fish (N = 2540; reference group: 0–6 mo)			
>6 mo	0.88 (0.39–2.00)	0.47 (0.15–1.49)	0.89 (0.27–2.99)

Specific food items are summarized in food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and other.

^a Itching eczema that was either recurrent or lasted for >2 weeks and affected the skin creases, face, neck, extremities, hands, feet, or trunk.

^b Adjusted for study center, gender, parental education, parental atopy, birth weight, and breastfeeding type; models might include less than the total number of observations because of missing values.

^c Early skin or allergic symptoms = physician's diagnosis of AD, food allergy, urticaria, milk crust, or any eczema or increase of eczema caused by food intolerance within the first 6 months.

^d $P < .05$.

increased frequency of AD (reverse causality), or a true protective effect would be masked. Possible distortion of studies on infant diet and atopic diseases by reverse causality has been pointed out before.^{5,9} Statistical tests for reverse causality do not exist, and assessment of reverse causality has to be based on indirect evidence only. Because of the large sample size, the prospective cohort design, and the semiannual data collection, we had the opportunity to explore and consider reverse causality in our study. The strong positive association between early skin or allergic symptoms and subsequent AD in our results most likely indicated that early skin or allergic symptoms have already constituted the beginning of AD (“on the causal pathway”) and cannot be adjusted for. It is interesting that all of the investigated single skin or allergic conditions were followed by a

higher frequency of subsequent AD (Table 2) and therefore were included in the stratification variable “early skin or allergic symptoms.” Our results from descriptive and multivariate analyses showed clear evidence for reverse causality. Although cohort studies are seen as the gold standard to assess the temporal sequence of events in observational studies, measures to avoid reverse causality have to be considered in the conduction, analysis, and interpretation of cohort studies that investigate the relationship between feeding practices and AD. To our knowledge, none of the existing studies on solid food introduction and AD has controlled for reverse causality. However, in older studies, reverse causality might not have constituted a problem as public awareness of feeding guidelines would have been smaller at that time.

The results of this cohort study gave no clear evidence

TABLE 6 Associations Between the Introduction of Solids and Atopic Sensitization Against Any and Food Allergens

	Any Sensitization ^a (N = 2086), aOR (95% CI) ^b	Food Sensitization ^c (N = 2094), aOR (95% CI) ^b
Timing of introduction of solids		
Any solids (N = 2474; reference group: 0–4 mo)		
5–6 mo	1.05 (0.74–1.48)	1.04 (0.71–1.53)
>6 mo	0.86 (0.54–1.37)	0.83 (0.49–1.41)
Solids diversity at 4 mo (N = 2410; reference group: no solid food)		
1–2 groups	1.02 (0.68–1.51)	1.04 (0.67–1.61)
3–8 groups	0.98 (0.62–1.56)	0.97 (0.58–1.62)
Solids diversity at 6 mo (N = 2407; reference group: no solid food)		
1–2 groups	1.42 (0.89–2.24)	1.52 (0.90–2.54)
3–4 groups	1.21 (0.79–1.84)	1.20 (0.74–1.94)
5–8 groups	1.02 (0.63–1.64)	1.06 (0.62–1.81)

Specific food items are summarized in food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and other.

^a Any specific IgE \geq 0.35 kU/L against egg, cow milk, wheat, peanut, soybean, cod fish, house dust mites, cockroach, cat, mixed grasses, birch pollen, or mixed moulds at 2 years of age.

^b Adjusted for study center, gender, parental education, parental atopy, birth weight, and breastfeeding type; models might include less than the total number of observations because of missing values.

^c Any specific IgE \geq 0.35 kU/L against egg, cow milk, wheat, peanut, soybean, or cod fish at 2 years of age.

that delaying the introduction of solids beyond 4 months of age would offer protection against the development of AD. Although children had a higher relative risk for symptomatic AD when they had a more diverse diet at 4 months of age and a lower relative risk for symptomatic AD when they have been introduced to solid food groups later than 4 months of age, no such associations could be seen for doctor-diagnosed AD, combined doctor-diagnosed and symptomatic AD, or sensitization. Delaying the introduction of solids beyond 6 months of age clearly had no additional protective effect on the development of AD and sensitization until 2 years of age in our cohort. These results were consistent over all outcome definitions and exposure measures (single food groups, any solid food introduction, and food diversity). For children with atopic parents, there was also no evidence for a protective effect of a delayed introduction of solids on any outcome. Currently, the most reliable results on the relationship between introduction of solids and AD come from a population-based birth cohort study ($n = 1210$) from New Zealand that reported a positive association between solid food diversity at 4 months of age and AD at ages 2 and 10 years.^{10,11} Children were enrolled in this well-conducted study in 1977, at a time when reverse causality was unlikely to have constituted a problem. Unfortunately, the study offers no information on whether a longer avoidance of solid food beyond the sixth month of life would have added an additional protective effect. Subsequent studies on full-term infants failed to reproduce similar results. Only an inconsistent relationship between early solid food introduction and AD at 2 years of age was reported by a Scottish birth cohort study ($n = 671$) of the 1980s.¹² Exposure assessed first introduction of any solid food only, comparing the introduction periods 2 months, 2 to

3 months, and beyond 3 months. Results from a Finnish cohort from the same period that found a protective effect of solid food avoidance during the first 6 months of life (compared with 3 months) on AD at age 1 year (but not 5 years) was limited by methodologic shortcomings. Next to the small study size ($n = 113$), a definition of AD was not given and data were analyzed only descriptively.¹³ An English cohort study ($n = 642$) that recruited children from 1993 to 1995 found no evidence for a protective effect of a delayed introduction of solids on AD at 5 years of age. The introduction of any solids was investigated at 3 months and therefore was not comparable to our results. Reverse causality could have constituted a problem in this study. However, adherence to the feeding guidelines was low in this cohort (only 30% of children were breastfed exclusively until 2 months of age), which might indicate a smaller awareness at that time and place and therefore minimized the problem.¹⁴ The inverse association between food diversity at 6 months of age and incidence of AD at age 1 year in a German intervention study on hydrolyzed milk formulas that recruited from 1995 to 1998 ($n = 1121$) most likely was caused by reverse causality.¹⁵ Another intervention study that recruited 288 children from 1981 to 1984 combined mother's and infant's allergen avoidance measures and found a decreased frequency of AD at age 1 year but not at age 7 years. However, separate assessment of child's diet only was not possible.^{16,17} Evidence that dietary restrictions reduce the prevalence of asthma and sensitization is also lacking.^{14,18} Overall, our data and the existing literature give no evidence for a delayed introduction of solids past the sixth month of life for atopic diseases prevention. We could not exclude that postponing the introduction of solids to the fourth

month of life might offer some protection against AD, but the evidence is weak.

We are aware that the exclusion of children with early skin or allergic symptoms within the first 6 months might have led to a selection of a different subtype of AD as early-onset AD has been linked to both persistence of AD¹⁹ and asthma at school age²⁰ (although the definition of “early” onset usually refers to the first 2 years of life or later). In our study, children with early skin or allergic symptoms were more likely to have a positive family history of atopic diseases and to be sensitized against allergens at 2 years of age (Table 1). The exclusion of these children was the only possibility to rule out reverse causality, which we considered important. Moreover, models for sensitization were calculated with the whole cohort and therefore not prone to this kind of selection bias. Residual confounding might have constituted an additional limitation if there was a history of atopic diseases in the extended family that might have led parents to wean later. However, when we adjusted for the extended family history of AD (any parent or sibling with atopic diseases), the results remained similar. Data were analyzed for the first 2 years of life only. Children might develop AD beyond the age of 2 years. However, previous studies on infant diet and atopic diseases showed a greater effect on short-term outcomes than on long-term outcomes,⁶ and protective effects of combined mother’s and infant’s food interventions on AD and food sensitization that have been seen at age 1 year no longer were significant at 7 years.¹⁶ It seems unlikely that protective effects of a delayed introduction of solids on AD that have not been detectable at an earlier age should appear at an older age. However, this cannot be ruled out completely. The design of this study was population based. However, families in our cohort tended to come from a higher-than-average educational background with a relatively high proportion of atopic parents. This might explain the relatively high proportion of children with early skin or allergic symptoms in our cohort (39%). Participation in blood testing was 68%, with a higher participation of children with parental atopy ($P = .05$), male gender ($P = .02$), and high parental education ($P = .02$). In relation to the timing of introduction of solids, there were no significant differences between children who participated in the blood testing and those who did not. This kind of participation bias in blood testing might result in a reduced generalizability of results to a general population. Participation in questionnaire interviews was good (only 14% had not filled in the questionnaires at 2 years of age), so we would not expect a strong participation bias in relation to questionnaire-derived outcome measures. Finally, negative results of epidemiologic studies always have to be interpreted with caution as they could have resulted from nondifferential misclassification as a result of limited data quality.

CONCLUSIONS

Despite the undisputed benefit of breastfeeding on child’s health, the results of this cohort study provide no evidence supporting a delayed introduction of solids beyond the sixth month of life for the prevention of AD and sensitization. Delaying the introduction of solids for 4 months might provide some benefit for the prevention of AD in the child. Measures to avoid reverse causality have to be considered in the conduction, analysis, and interpretation of cohort studies on the topic.

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Timing of Solid Food Introduction in Relation to Atopic Dermatitis and Atopic Sensitization: Results From a Prospective Birth Cohort Study

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