ARTICLE

Timing of Solid Food Introduction in Relation to Eczema, Asthma, Allergic Rhinitis, and Food and Inhalant Sensitization at the Age of 6 Years: Results From the Prospective Birth Cohort Study LISA

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ABSTRACT

OBJECTIVE. Current prophylactic feeding guidelines recommend a delayed introduction of solids for the prevention of atopic diseases. This study investigates whether a delayed introduction of solids (past 4 or 6 months) is protective against the development of eczema, asthma, allergic rhinitis, and food or inhalant sensitization at the age of 6 years.

METHODS. Data from 2073 children in the ongoing LISA birth cohort study were analyzed at 6 years of age. Multivariate logistic regression analyses were performed for all children and for children without skin or allergic symptoms within the first 6 months of life to take into account reverse causality.

RESULTS. A delayed introduction of solids (past 4 or 6 months) was not associated with decreased odds for asthma, allergic rhinitis, or sensitization against food or inhalant allergens at 6 years of age. On the contrary, food sensitization was more frequent in children who were introduced to solids later. The relationship between the timing of solid food introduction and eczema was not clear. There was no protective effect of a late introduction of solids or a less diverse diet within the first 4 months of life. However, in children without early skin or allergic symptoms were considered, eczema was significantly more frequent in children who received a more diverse diet within the first 4 months.

CONCLUSIONS. This study found no evidence supporting a delayed introduction of solids beyond 4 or 6 months for the prevention of asthma, allergic rhinitis, and food or inhalant sensitization at the age of 6 years. For eczema, the results were conflicting, and a protective effect of a delayed introduction of solids cannot be excluded. Positive associations between late introduction of solids and food sensitization have to be interpreted with caution. A true protective effect of a delayed introduction of solids on food sensitization seems unlikely.

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Key Words
eczema, asthma, hay fever, sensitization, allergy, cohort, reverse causality, solid food

Abbreviations
LISA—Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood
IgE—immunoglobulin E

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CURRENT PROPHYLACTIC FEEDING guidelines recommend a delayed introduction of solids for the prevention of allergic diseases. The World Health Organization,[1] the American Academy of Pediatrics,[2] and the European Academy of Allergology and Clinical Immunology[3] advise avoidance of solids for at least 4 or even 6 months;

however, scientific evidence for this is scarce. A recent review[4] identified only a few studies with conflicting results on the relationship between early introduction of solids and the development of allergic disease.[5–10]

We recently published results of the Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood (LISA) study, a large, prospective, population-based birth cohort study on asthma and allergic disease.[11] In this cohort, there was no clear evidence of a protective effect of a delayed introduction of solids (past 4 or 6 months) on the development of eczema or sensitization at 2 years of age; however, asthma and allergic rhinitis were not investigated because these conditions play a minor role and diagnosis is difficult at this age. We now have data for the first 6 years of life of the LISA cohort. Our aim was to investigate whether a delayed introduction of solid food (past 4 or 6 months) is protective on the development of eczema, asthma, allergic rhinitis, and food and inhalant sensitization at 6 years of age. Because there was clear evidence of reverse causality in our first analysis at 2 years of age, we also accounted for reverse causality in the current analyses and the interpretation of the results.

METHODS

Data from the ongoing birth cohort study LISA were analyzed for the first 6 years of age. The study design of this population-based, prospective birth cohort study has been described elsewhere before.[12,13] In short, 3097 healthy 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. Questionnaires were filled in by the parents at birth and when the children were 0.5, 1, 1.5, 2, 4, and 6 years of age. At age 2 and 6 years, children were invited for blood collection and physical examination. Informed consent was obtained from the parents of all children. Ethical approval for the study was obtained from the local ethics committees.

Food and Inhalant Sensitization

Specific immunoglobulin E (IgE) against common food allergens and inhalant allergens were determined at 2 and 6 years of age by standardized methods with CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany). In the first step, 2 screening tests for atopy were used to detect specific IgE antibodies against inhalant allergens (SX1: timothy, rye, birch, mugwort, house-dust mite, cat, dog, and molds) and food allergens (FX5: egg white, soya protein, cow milk, wheat, peanut, and fish) in the serum. In the second step, only children whose test results were positive for FX5 or SX1 were tested for single specific allergens. These included egg, milk, cod, rye, wheat, soy, and peanut. Inhalant sensitization and food sensitization were defined as a specific IgE value against inhalant allergens (SX1) and food allergens (FX5) $\geq$ 0.35 kU/L, respectively.

Questionnaires

Questionnaires at ages 0.5, 1, 1.5, 2, 4, and 6 years included questions on doctor diagnoses and symptoms of eczema, asthma, allergic rhinitis, and other medical conditions. Questions about feeding practices, child characteristics, lifestyle, and environmental factors were also included depending on the age of the child. Eczema, asthma, and allergic rhinitis were considered to be doctor diagnosed when parents reported a physician's diagnosis of the respective disease in the respective time period. Eczema symptoms were determined when parents reported in the 6-year questionnaire that the child had ever had an itching eczema that lasted for at least 6 months and that had been present in the preceding year and affected the skin creases, face, neck, or joints of hands or feet. Asthma symptoms were determined when parents reported the child's wheezing in the sixth year of life or intake of asthma medication within the fifth and sixth years. The information on medication was available only for the combined time period. Allergic rhinitis symptoms were determined when parents reported sneezing or a blocked or running nose of the child without having a cold in the sixth year of life.

Early skin or allergic symptoms were determined when in the 6-month questionnaire 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 seborrhoic 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 the child's life.

Feeding History

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 comprised 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 mentioned solid food items. Solids diversity was determined summing up the number of different food groups that were included in the child's diet at 4 months of age and subsequent categorization into no solid food, 1 to 2 groups, and 3 to 8 groups (Table 1). Food allergens defined the introduction of soy, wheat, fish, egg, nuts, or dairy products. Breastfeeding was categorized into exclusively breastfed, partly breastfed, and exclusively bottle-fed within the first 4 months irrespective of solid food introduction. Parental allergy was considered positive when either parent ever had eczema, asthma, or hay fever. Parental education was categorized by the highest number of years of school attended by either parent.

TABLE 1 **Characteristics of the LISA Population According to Participation in This Analysis at 6 Years of Age**

Characteristic	Population Analyzed[a]		Population Not Analyzed[a]		*P*[b]
	n/N	%	*n/N*	%	
Population					
Center					
Munich	1115/2073	53.8	352/1024	34.4	<.001
Leipzig	530/2073	25.6	446/1024	43.6	
Wesel	199/2073	9.6	149/1024	14.6	
Bad Honnef	229/2073	11.0	77/1024	7.5	
Female gender	1020/2073	49.2	491/1024	47.9	.51
Parental education					
High school graduate	1450/2056	70.5	516/1004	51.4	<.001
≥10 y	523/2056	25.4	383/1004	38.1	
<10 y	83/2056	4.0	105/1004	10.5	
Parental allergy	1106/2068	53.5	479/1022	46.9	<.001
No. of older siblings					
0	1139/2070	55.0	603/1020	59.1	<.001
1	734/2070	35.5	295/1020	28.9	
2–6	197/2070	9.5	122/1020	12.0	
Early skin or allergic symptoms	795/2057	38.6	308/749	41.1	.235
Feeding practices					
First introduction of any solids					
0–4 mo	663/2073	32.0	275/598	46.0	<.001
5–6 mo	1021/2073	49.3	247/598	41.3	
>6 mo	389/2073	18.8	76/598	12.7	
Solids diversity at 4 mo					
no solid food	1410/2027	69.6	323/568	56.9	<.001
1–2 groups	351/2027	17.3	105/568	18.5	
3–8 groups	266/2027	13.1	140/568	24.6	
Breastfeeding type at 4 mo					
Exclusively breastfed	1224/2071	59.1	367/747	49.1	<.001
Mixed	740/2071	35.7	308/747	41.2	
Exclusively bottle-fed	107/2071	5.2	72/747	9.6	
First introduction of allergens					
<6 mo	811/2061	39.4	382/701	54.5	<.001
>6 mo	1250/2061	60.7	319/701	45.5	
Atopic outcomes					
Doctor diagnosis of eczema at 6 y	174/2043	8.5	13/128	10.2	.521
Doctor diagnosis of asthma at 6 y	42/2043	2.1	3/126	2.4	.804
Doctor diagnosis of allergic rhinitis at 6 y	83/2039	4.1	5/130	3.8	.900
Eczema symptoms at 6 y	83/2040	4.1	5/127	3.9	.942
Asthma symptoms at 6 y	207/2072	10.0	15/130	11.5	.57
Allergic rhinitis symptoms by 6 y	284/2053	13.8	20/130	15.4	.62
Food sensitization at 6 y	135/1123	12.0	8/70	11.4	.882
Inhalant sensitization at 6 y	301/1123	26.8	17/70	24.3	.644

[a] For analysis, population was restricted to children with data on both exposure information and questionnaire information at the age of 6 years. *n* = number of observations; *N* = total number of observations, differences in *N* are attributable to number of missing values.

[b] *P* value from χ^2 test comparing children according to analysis status.

Statistical Analysis

The analysis was restricted to children who had data on solid food and atopic outcomes and participated in the 6-year follow-up investigation ($N = 2073$). Characteristics of children who were involved in this analysis and those who were excluded were compared (Table 1). We examined the 1-year prevalences of doctor diagnoses of eczema, asthma, and allergic rhinitis in relation to the first introduction of any solids in all children and in the subgroup of children without early skin or allergic symptoms (Table 2). The rationale behind this procedure was to avoid a distortion of the results by reverse causality and has been explained in detail before.[11] In short, the underlying assumption is that parents who notice early skin or allergic symptoms (outcome) in their child within the first 6 months of life might start feeding solids later (exposure), resulting in "false" positive association between late introduction of solids and atopic outcomes or masking "true" inverse associations between the 2 (reverse causality). We used early skin or allergic symptoms as the stratifying variable because most par-

TABLE 2 **Associations Between Introduction of Solids and Atopic Conditions at 6 Years of Age: Results From Multivariate Analysis**

Parameter	All Children, aOR (95% CI)[a]	Children Without Early Skin or Allergic Symptoms, aOR (95% CI)[a]
First introduction of any solids[b]		
Doctor diagnosis of eczema		
4–6 mo	0.92 (0.61–1.39)	0.71 (0.39–1.33)
>6 mo	0.82 (0.49–1.40)	0.44 (0.18–1.08)
Eczema symptoms		
4–6 mo	0.92 (0.51–1.68)	0.60 (0.24–1.51)
>6 mo	1.27 (0.63–2.58)	0.51 (0.15–1.70)
Doctor diagnosis of asthma		
4–6 mo	0.86 (0.38–1.96)	1.10 (0.36–3.32)
>6 mo	1.11 (0.42–2.96)	1.20 (0.31–4.70)
Asthma symptoms		
4–6 mo	0.90 (0.61–1.32)	0.76 (0.46–1.27)
>6 mo	0.81 (0.50–1.32)	0.77 (0.40–1.46)
Doctor diagnosis of allergic rhinitis		
4–6 mo	1.35 (0.74–2.46)	1.12 (0.42–2.99)
>6 mo	1.19 (0.56–2.53)	1.45 (0.45–4.63)
Allergic rhinitis symptoms		
4–6 mo	0.90 (0.65–1.25)	1.01 (0.63–1.60)
>6 mo	0.78 (0.50–1.20)	0.63 (0.33–1.21)
Food sensitization		
4–6 mo	2.15 (1.28–3.62)	3.13 (1.45–6.74)
>6 mo	1.88 (0.98–3.58)	3.01 (1.19–7.61)
Inhalant sensitization		
4–6 mo	1.16 (0.81–1.67)	0.92 (0.57–1.49)
>6 mo	1.30 (0.82–2.05)	1.01 (0.54–1.87)
Solids diversity at 4 mo[c]		
Doctor diagnosis of eczema		
1–2 groups	1.01 (0.62–1.62)	1.00 (0.45–2.20)
3–8 groups	1.43 (0.83–2.45)	2.72 (1.24–5.99)
Eczema symptoms		
1–2 groups	1.13 (0.60–2.13)	1.62 (0.59–4.48)
3–8 groups	0.64 (0.25–1.67)	1.38 (0.33–5.74)
Doctor diagnosis of asthma		
1–2 groups	1.31 (0.57–2.99)	1.38 (0.47–4.02)
3–8 groups	0.32 (0.07–1.52)	0.27 (0.03–2.36)
Asthma symptoms		
1–2 groups	1.05 (0.68–1.63)	1.27 (0.72–2.24)
3–8 groups	1.33 (0.80–2.20)	1.53 (0.79–2.96)
Doctor diagnosis of allergic rhinitis		
1–2 groups	0.73 (0.36–1.46)	0.48 (0.13–1.76)
3–8 groups	0.62 (0.25–1.53)	1.03 (0.29–3.70)
Allergic rhinitis symptoms		
1–2 groups	1.29 (0.90–1.85)	1.27 (0.76–2.11)
3–8 groups	1.00 (0.63–1.59)	0.92 (0.47–1.79)
Food sensitization		
1–2 groups	0.38 (0.19–0.73)	0.34 (0.13–0.86)
3–8 groups	0.49 (0.24–0.98)	0.26 (0.09–0.72)
Inhalant sensitization		
1–2 groups	0.77 (0.51–1.17)	0.93 (0.53–1.65)
3–8 groups	0.93 (0.57–1.50)	1.45 (0.78–2.70)

aOR indicates adjusted odds ratio; CI, confidence interval.

[a] Odds ratios with 95% confidence interval adjusted for study center, parental allergy, gender, parental education, and breastfeeding type.

[b] Reference group: first introduction of any solids within the first 4 months.

[c] Reference group: no introduction of solids within the first 4 months.

ents recognize these symptoms as allergic symptoms and know or are informed by their physician that a late introduction of solids is recommended for the protection against allergic disease development.

Multivariate logistic regression analyses were performed to investigate the associations between any solids and solids diversity at 4 months with doctor diagnoses and symptoms of eczema, asthma, allergic rhinitis, and sensitization outcomes at the age of 6 years. For any solids, first introduction of any solids within the first 4 months was taken as the reference group. For solids diversity, no introduction of solids within the first 4 months was taken as the reference group. All models were adjusted for the a priori defined potential confounding factors study center, parental allergy, child's gender, parental education, and breastfeeding type. A possible confounding effect of number of older siblings and mother's smoking in pregnancy on sensitization outcomes was considered; however, testing in multivariate analyses did not considerably change the magnitude of the effect estimates, and therefore no adjustment for these variables was made. Multivariate analyses were performed in parallel for the whole cohort and for the stratum of children without early skin or allergic symptoms. Analyses were also separately performed for children whose parents had allergy to investigate whether these children would react differently and to be able to compare our results with those from high-risk population studies. Results are presented as adjusted odds ratios with 95% confidence intervals. All statistical analysis was performed with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Study Population

Of the 3097 children who were recruited at birth, 2203 (71%) had completed 6-year questionnaires. Information on solid food items and atopic outcomes at 6 years of age was available for 2073 (67% of the original cohort) children and information on food and inhalant sensitization at 6 years of age for 1123 children (36% of the original cohort and 54% of our study population).

Description of Population Characteristics and of Children According to Their Participation Status

The proportion of boys and girls in the study population was nearly equal. Parental education level and the proportion of children with parental allergies were high (Table 1). Solids were introduced within the first 4 months in approximately one third of the children; approximately half were exclusively breastfed within this period. Vegetables and fruit were introduced earliest into the diet, fish and egg latest.[11]

When children who were included in the analysis were compared with those who were not included (children lost to follow-up at 6 years or children without data on solid food introduction), children who were not included in the analysis were more likely to have a lower parental education and fewer parental allergies. Adherence to feeding guidelines was worse than in children who were included in the analysis; that is, solids and allergens were introduced

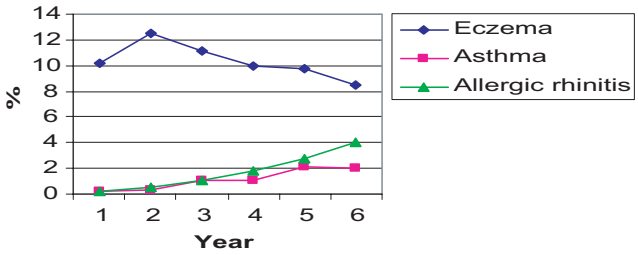

FIGURE 1
One-year prevalences of doctor diagnoses of eczema, asthma, and allergic rhinitis (n = 2073).

earlier and children were breastfed for a shorter duration. There were no clear differences with respect to the allergic outcomes (Table 1).

1-Year Prevalences of Doctor Diagnoses of Eczema, Asthma, and Allergic Rhinitis

Prevalence of eczema ranges between 8% and 12%, with a peak in the second year of life and lowest prevalence in the sixth year of life. Prevalences for both asthma and allergic rhinitis are low with a steady rise from birth to 2% (asthma) and 4% (hay fever) at 6 years (Fig 1).

Description of the Association Between the Timing of Introduction of Solids and Atopic Conditions

Prevalence of doctor diagnosis of eczema, asthma, and allergic rhinitis did not differ substantially between children who were introduced to solids within the first 4 months of life, between months 4 and 6, and after the month 6 (Fig 2, left). When only children without early skin and allergic symptoms were observed, children who were introduced to solids beyond the month 6 had a lower prevalence of eczema and a higher prevalence of allergic rhinitis in years 5 and 6 (Fig 2, right). These associations were not statistically significant.

Multivariate Analyses of the Associations Between the Timing of Introduction of Solids and Atopic Conditions

There was no evidence of a protective effect of a delayed introduction of solids in relation to doctor diagnoses or

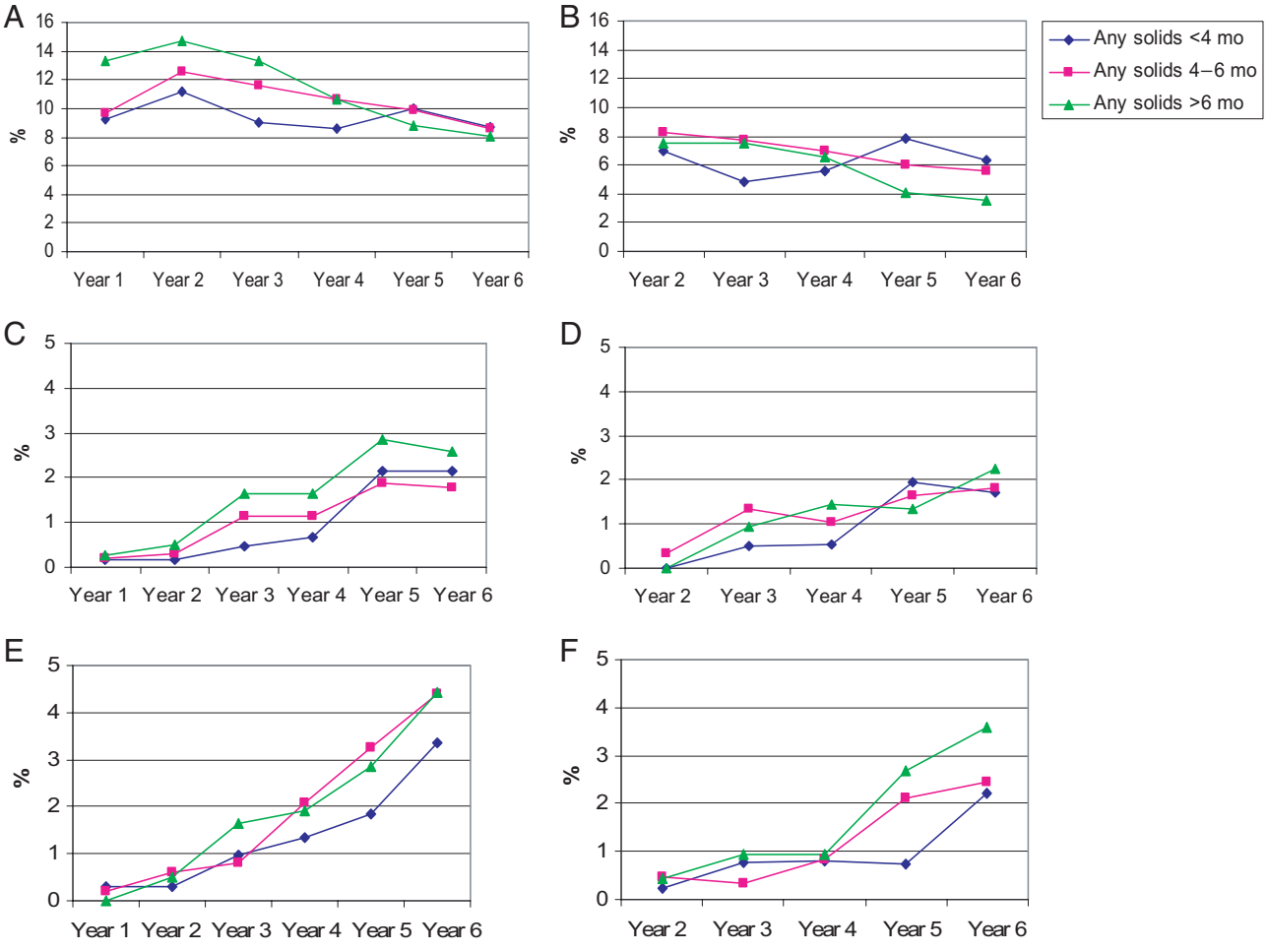

FIGURE 2
Timing of introduction of solids and 1-year prevalences of doctor diagnoses of atopic disease in all children (left) and children without early skin and allergic symptoms (right). On the right, age 1 year was omitted because diagnoses of the first 6 months were excluded per definition. A, Eczema in relation to first introduction of solids; B eczema in relation to first introduction of any solids in children without early symptoms; C, asthma in relation to first introduction of any solids; D, asthma in relation to first introduction of any solids in children without early symptoms; E, allergic rhinitis in relation to first introduction of any solids; F, allergic rhinitis in relation to first introduction of any solids in children without early symptoms.

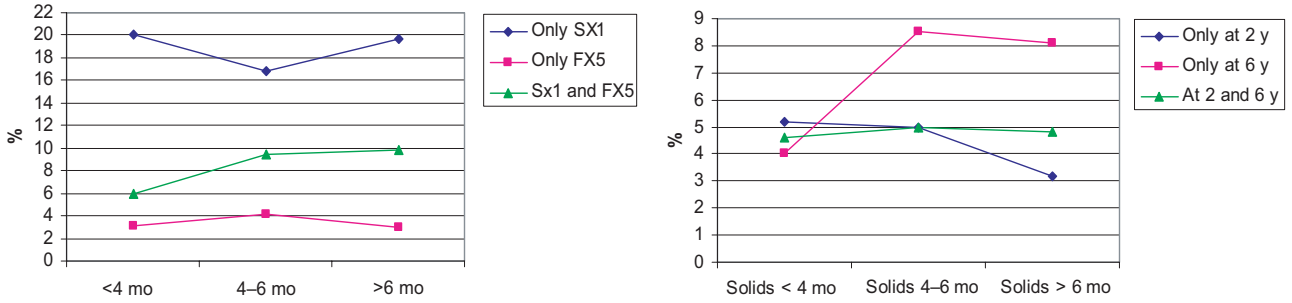

FIGURE 3
Timing of introduction of solids and allergic sensitization; On the left: type of sensitization at 6 years of age; On the right: time of sensitization against food allergens.

symptoms of asthma, allergic rhinitis, and food or inhalant sensitization at 6 years of age (Table 2); however, in children without early skin and allergic symptoms, late introduction of solids borderline significantly decreased the effect estimates for eczema. This effect was statistically significant for the association between solid diversity and doctor-diagnosed eczema. When all children were investigated, there was no protective effect on eczema, possibly indicating distortion of the results by reverse causality. There was an increased risk for food sensitization when solid food was introduced beyond 4 months into the child's diet. In children without early skin and allergic symptoms, this effect was even more pronounced.

Additional Analyses

When we repeated the analyses in children whose parents had allergy, there were also no significant protective effects on atopic outcomes. Only sensitization to food allergens was statistically significantly increased when solids were introduced later (adjusted odds ratio with 95% confidence interval for introduction in months 4–6 and >6: 3.2 [1.5–6.9] and 2.50 [1.03–6.30], respectively).

We also repeated the analyses for lifetime prevalence of eczema and for atopic eczema (eczema plus food or inhalant sensitization). There were no statistically significant associations with the introduction of solids in all children or in children without early skin and allergic symptoms. We also investigated whether a delayed introduction of single food groups was protective for the development of atopic diseases. We tested food allergens, vegetables, fruit, cereal, meat products, dairy products, egg, and fish. A later introduction of meat products, cereal, fruit, and vegetables borderline significantly increased the odds for a sensitization to food allergens (data not shown).

Investigation of the Increased Prevalence of Food Sensitization With Delayed Introduction of Solids

We further investigated the positive associations between late introduction of solids and food sensitization. Food sensitization at 2 years of age was strongly predictive of both sensitization against food and inhalant allergens at 6 years of age. Late introduction of solids increased food sensitization mainly in children who were newly sensitized at 6 years and had not been sensitized at 2 years of age and in children with a double sensitization against food and inhalant allergen (Fig 3). When higher cutoff levels for IgE were selected (≥ 0.7 kU/L), no statistically significant associations between a later introduction of solids and food or inhalant sensitization were seen. When the associations between late introduction of solids and specific IgE against single allergenic food items were investigated, sensitization was more frequent for wheat, soy, and peanut, the last association being statistically significant. The timing of introduction of solids did not influence sensitization against cod, egg, and milk. When only children without early skin and allergic symptoms were examined, the results were similar.

DISCUSSION

In this large, population-based, prospective birth cohort study on asthma and allergic diseases, we found no evidence for a protective effect of a delayed introduction of solids (past 4 or 6 months) on asthma, allergic rhinitis, or food or inhalant sensitization against food or inhalant allergens at 6 years of age. On the contrary, avoidance of solid feeding for the first 4 or 6 months and less diverse diet within the first 4 months were statistically significantly positively associated with food sensitization. The effect estimates further increased when only children without early skin or allergic symptoms or children with parental allergy were examined. The relationship between the timing of solid food introduction and eczema was not clear. In children without early skin and allergic symptoms, a late introduction of solids or a less diverse diet within the first 4 months were partly significantly associated with decreased odds for eczema. This relationship could not be observed in all children, possibly indicating a distortion of the results by reverse causality in all children.

The lack of an association between late introduction of solids and asthma and allergic rhinitis adds important information to the existing literature. Asthma and allergic rhinitis are more prevalent and can be better diagnosed when children are older; therefore, results of cohort studies that have followed children for a considerable amount of time are more meaningful. Only 1 study investigated the associations between the introduction of solids and allergic rhinitis symptoms and

found no association[14]; however, children were younger than 2 years and the study population was very small ($n = 79$). Three cohort studies on asthma were identified.[8–10] In accordance with our results, Fergusson et al, Kajosaari et al, and Wilson et al found no statistically significant associations between early introduction of solids and doctor-diagnosed asthma; however, in the first 2 studies, no adjustments for possible confounding factors were made. Moreover, Fergusson et al investigated young children within the first 4 years of life and also included wheezy bronchitis in the asthma group.[9] The study children were born in the 1970s, when feeding practices differed from today's practices. Kajosaari et al investigated a small group of 113 children at 5 years of age. Asthma and pollen sensitization were more prevalent in those who were introduced to solids earlier.[8] Wilson et al found no statistically significant association between the timing of introduction of solids and asthma at 7 years; however, in contrast to our results, this study found protective effects of an introduction past 15 weeks for wheezing.[10] An English cohort that consisted of 642 children also found no associations between an early introduction of solids and late or persistent wheezing at 5.5 years.[15] Wheezing as a key symptom of asthma is most meaningful from 4 years onward. The prevalence of asthma in our study was low in comparison with other studies. Possibly German doctors are reluctant to label asthma and rather refer to it as obstructive bronchitis because they do not want to concern parents.

There are 2 possible explanations for our findings of increased odds for food sensitization with a delayed introduction of solids. First, the association may be causal and especially children whose parents have allergy would be more likely to develop food sensitization if they are fed solids late. Possibly, early exposure to solid food items induces immune tolerance and thus decreases the development of food sensitization. Second, parents with allergy introduce solids later; therefore, sensitization may appear later; however, the effect in children whose parents have allergy was even stronger. Moreover, for both explanations, it is not clear why this effect would not have been seen at 2 years of age.[11] The second explanation suggests that later introduction of solids would delay but not prevent sensitization. Sensitization may be a physiologic phenomenon without clinical symptoms, whose appearance may depend on the sequence of exposure to different allergens. The interpretation of the implication of food sensitization (at cutoff levels of 0.35 kU/L and 0.7 kU/L) at this age is difficult and has not been linked to clinical conditions. Because we cannot think of a likely explanation, we cannot exclude that our finding might be a chance finding, although the magnitude of the effects makes a chance finding unlikely. Distortion of the results by reverse causality is also possible if parents introduce solids later because of early symptoms of allergy in the child or because of a family history of allergy; however, the increased magnitude of the effect estimates in the subgroups of children whose parents have allergy and children without early skin or allergic symptoms argue against reverse causality. Possibly, residual confounding (for family history of allergy) or residual reverse causality (for first symptoms of allergy) could not be completely avoided. In addition, the introduction of allergens beyond 6 months borderline significantly increased food sensitization at 6 years old; however, parents who follow the feeding guidelines concerning the introduction of any solids are also more likely to follow the guidelines for allergen introduction. Our results are in contrast to results from a Finnish cohort of 113 children at 5 years of age that found increased sensitization frequencies against pollen but not against food allergens when children were fed solids earlier.[8] An English cohort found no association between the timing of introduction of solids and inhalant sensitization at age 5.5 years.[15]

A greater diversity of solid food items introduced until 4 months of age was a risk factor for eczema in children without early skin or allergic symptoms. In contrast, we did not find a protective effect of a delayed introduction of solids on eczema when we investigated all children. This may indicate distortion of the results by reverse causality in all children if parents adhered better to the feeding guidelines because they noticed first eczema symptoms in their children or if doctors advised parents to delay the introduction of solids because of allergic diseases. The protective effect is clearer in doctor diagnosis than in symptoms of eczema. Possible interpretations for this include a stronger effect of reverse causality or better differentiation by the doctor diagnosis variable. Other authors likewise considered reverse causality in their analyses.[16] In our 2-year data, the association between the timing of introduction of solids and eczema was also not clear.[11] Up to now, the strongest evidence for a protective effect of a delayed introduction of solids on eczema comes from an early well-conducted study from New Zealand that found a dosage-response relationship between solids diversity within the first 4 months and eczema when the children were 2 and 10 years of age.[5,7] Subsequent studies did not find clear evidence of a protective effect of a delayed introduction of solids on eczema. A British study found only an inconsistent relationship at 2 years of age.[17] whereas a Finnish study found a protective effect of a delayed introduction of solids on eczema at 1 year of age but not at 5 years of age.[8] No association between the timing of introduction of solids and eczema at <2 years and 5.5 years of age was found in a small Australian birth cohort and in an English cohort that additionally found no association with solids diversity within the first 4 and 6 months.[14,15]

Possible limitations of the study have to be considered in the interpretation of the results. Children who were analyzed and those who were not included in the analysis differed in relation to several confounding factors and the exposure variable; however, they did not differ with respect to the atopic outcomes. These differences are unlikely to influence the validity of the results but limit the generalizability to children from more advantaged families. In relation to sensitization, the proportion of children who were not analyzed is substantial. Although there seems to be no association

between participation and sensitization status, the associations should still be interpreted with caution. Because of the prospective study design, distortion of the results by recall bias was unlikely. Information on the timing of introduction of solids was asked for retrospectively at 6 months of age; therefore, minor misclassification of feeding history might appear, although it is a relatively short period to recall. Information on eczema, asthma, and allergic rhinitis was based on questionnaire results. Physical examinations might have yielded more accurate outcome diagnoses; however, we do not regard this as a major limitation because we largely followed the validated International Study of Asthma and Allergy in Childhood case definitions, which are the most common case definition in epidemiologic studies on allergic diseases. Doctor diagnosis possibly constitutes a more reliable outcome definition than disease symptoms because it is less dependent on parents' educational level. We considered confounding and reverse causality in our analysis strategy by adjusting possible confounding factors and by the additional analysis of children without early skin and allergic symptoms. In the case of eczema, there was some indication of reverse causality. Nevertheless, residual confounding and residual reverse causality cannot be excluded.

CONCLUSIONS

We found no evidence to recommend a delayed introduction of solids beyond 4 or 6 months for the prevention of asthma, allergic rhinitis, and food or inhalant sensitization at the age of 6 years. For eczema, the situation is still unclear. Positive associations between the timing of introduction of solids and food sensitization have to be considered with caution.

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