

Development of atopic dermatitis according to age of onset and association with early-life exposures

Caroline Roduit, MD, MPH,^a Remo Frei, PhD,^b Georg Loss, PhD,^c Gisela Büchele, MPH,^f Juliane Weber, MD,^g Martin Depner, PhD,^g Susanne Loeliger, MLS,^a Marie-Laure Dalphin, MD,^h Marjut Roponen, PhD,ⁱ Anne Hyvärinen, PhD,^j Josef Riedler, MD,^k Jean-Charles Dalphin, MD, PhD,^l Juha Pekkanen, MD,^j Erika von Mutius, MD, MSc,^g Charlotte Braun-Fahrlander, MD,^{c,d} Roger Lauener, MD,^{a,e} and the Protection Against Allergy–Study in Rural Environments study group* Zurich, Basel, and Davos, Switzerland, Ulm and Munich, Germany, Besançon, France, Kuopio, Finland, and Schwarzhach, Austria

Background: Environmental factors can affect the development of atopic dermatitis, and this was described to be already effective during pregnancy and in early life. An important early postnatal exposure is nutrition, although its association with allergic disease remains unclear.

Objective: We sought to determine prospectively whether early postnatal exposures, such as the introduction to complementary food in the first year of life, are associated with the development of atopic dermatitis, taking into account the reverse causality.

Methods: One thousand forty-one children who participated in the Protection Against Allergy–Study in Rural Environments birth cohort study were included in the current study. Atopic dermatitis was defined by a doctor's diagnosis reported by the

parents of children up to 4 years of age, by questionnaires, and/or by positive SCORAD scores from 1 year of age and according to the age of onset within or after the first year of life. Feeding practices were reported by parents in monthly diaries between the 3rd and 12th months of life.

Results: The diversity of introduction of complementary food in the first year of life was associated with a reduction in the risk of having atopic dermatitis with onset after the first year of life (adjusted odds ratio for atopic dermatitis with each additional major food item introduced, 0.76; 95% CI, 0.65–0.88). The introduction of yogurt in the first year of life also reduced the risk for atopic dermatitis (adjusted odds ratio, 0.41; 95% CI, 0.23–0.73).

Conclusion: As early-life exposure, the introduction of yogurt and the diversity of food introduced in the first year of life might have a protective effect against atopic dermatitis. (*J Allergy Clin Immunol* 2012;■■■■:■■■■–■■■■.)

Key words: Atopic dermatitis, diversity, complementary food

From ^athe University of Zurich, Children's Hospital, and the Christine Kühne-Center for Allergy Research and Education, Zurich; ^bthe Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, and the Christine Kühne-Center for Allergy Research and Education, Zurich; ^cthe Swiss Tropical and Public Health Institute, Basel; ^dthe University of Basel; ^eChildren's Allergy and Asthma Hospital, Hochgebirgsklinik, and the Christine Kühne-Center for Allergy Research and Education, Davos; ^fthe Institute of Epidemiology, University of Ulm; ^gUniversity Children's Hospital Munich; ^hthe Department of Pediatrics, University Hospital of Besançon; ⁱthe Department of Environmental Science, University of Eastern Finland, Kuopio; ^jthe Department of Environmental Health, National Institute for Health and Welfare, Kuopio; ^kChildren's Hospital Schwarzhach; and ^lthe Department of Respiratory Disease, UMR/CNRS 6249 Chrono-environnement, University Hospital of Besançon.

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Corresponding author: Caroline Roduit, MD, MPH, Kinderspital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland. E-mail: Caroline.Roduit@kispi.uzh.ch. 0091-6749/\$36.00

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Increasing evidence suggests that prenatal and early-life environmental exposures can influence immune responses and the development of allergic diseases. Atopic dermatitis is a chronic inflammatory skin disease, and in 60% of children, the onset of disease occurs during the first year of life.¹

As early-life exposure, nutrition is a major environmental factor that might have an effect on the immune system and could be a factor that would lead to the prevention of allergic diseases. Studies of the farming environment have shown that consumption of unprocessed farm milk was associated with fewer allergic diseases, although there was some heterogeneity of the effects, especially with atopic dermatitis. In addition, this evidence was based on cross-sectional studies of school-aged children only.^{2–6} First introduction of complementary food in an infant's life and its association with allergic diseases is another aspect of nutrition raising much controversy. Food allergen avoidance during pregnancy or infancy has provided no consistent evidence of allergy prevention^{7,8} and is no longer recommended.⁹ A systematic review of 13 studies of the relationship between early introduction of solid food and the development of allergies concluded that the evidence of this relation is inconsistent and conflicting.¹⁰ Some recent studies even showed that early introduction of complementary food, like the introduction of fish before 1 year of age or early exposure to cow's milk, might have a protective effect against

Abbreviations used

OR: Odds ratio

PASTURE: Protection Against Allergy–Study in Rural Environments

SCFA: Short-chain fatty acid

allergic diseases.^{11–15} One study found a protective effect of the introduction of any complementary food within the first 4 months on atopic dermatitis but only among children with allergic parents.¹⁶ Therefore more evidence with respect to the role of early nutritional exposures is needed.

The birth cohort study Protection Against Allergy–Study in Rural Environments (PASTURE) offered the opportunity to evaluate the effect of prenatal and postnatal exposures on the development of allergic diseases.¹⁷ We previously reported an inverse association between prenatal contact with animals and atopic dermatitis up to 2 years of age.¹⁸ In the present analysis we longitudinally evaluated whether early postnatal exposures, especially food introduction and its diversity, were associated with the development of atopic dermatitis, with data available up to 4 years of age. One major concern with postnatal exposures, especially with the association between feeding practices and atopic dermatitis, is the potential bias caused by the reverse causality effect. This source of bias arises when the reason for introducing or not introducing a certain type of food is strongly associated with the outcome. Among children with early symptoms of the disease, those with allergic parents, or both, introduction of certain complementary food, especially allergenic food, tends to be delayed. We thus focused our analyses on children with atopic dermatitis occurring after the first year of life, ensuring that exposure occurred before onset of the disease.

METHODS

Study design

PASTURE is a prospective birth cohort study involving children from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) designed to evaluate risk factors and preventive factors for atopic diseases. The design of this cohort has been described in detail elsewhere.¹⁷ Briefly, pregnant women were recruited during the third trimester of pregnancy and divided into 2 groups. Women who lived or worked on family-run farms on which any kind of livestock was kept were assigned to the farm group. The reference group was composed of women from the same rural areas not living on a farm. In total, 1133 children were included in this birth cohort. The questionnaires developed within the PASTURE study group used questions on various exposures and outcomes from the Asthma Multicenter Infants Cohort Study,¹⁹ the Allergy and Endotoxin study,² and the Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle study.²⁰ Questionnaires were administered in interviews or self-administered to the mothers within the third trimester of pregnancy; when the children were 2, 12, 18, and 24 months of age; and then yearly up to 4 years of age. Feeding practices and the occurrence of itchy rash were reported by parents between the 3rd and 12th months of life in monthly and weekly diaries, respectively. The study was approved by the local research ethics committees in each country, and written informed consent was obtained from all parents.

Study population

Children from the PASTURE birth cohort with data available on atopic dermatitis up to 4 years of age, farming status, parental allergic history, and feeding practices in the first year of life ($n = 1041$) were included.

Definitions

Children were labeled as having atopic dermatitis when the parents reported in the questionnaires that the child had atopic dermatitis diagnosed by a doctor at least once between 12 months and 4 years of age, positive SCORAD scores (>0) assessed at the age of 1 year during medical examination, or both. Among the 144 children defined as having atopic dermatitis at the age of 1 year, 44 had only a positive SCORAD score, 50 had only a doctor's diagnosis, and 50 had both. Children with no atopic dermatitis but missing information at 1 or more time points were defined as "missing" ($n = 129$) when the prevalence of atopic dermatitis up to 4 years was calculated. In most children atopic dermatitis occurs early in life, and to be able to evaluate exposures occurring before the disease, we used 2 different definitions of atopic dermatitis depending on the occurrence of the disease: atopic dermatitis with onset within the first year of life and atopic dermatitis with onset after the first year of life. Farmer's children were defined as children who were living on a farm on which livestock was held and whose family ran the farm according to parental reports. Maternal farm-related exposures during pregnancy were obtained from the self-reported questionnaires at the third trimester of pregnancy. Prenatal contact with farm animal species was assumed if the mother reported contact at least several times per month in one of the pregnancy trimesters. Postnatal exposures to stables during the first year of life were defined as the child's exposure for at least a quarter of an hour per week. Feeding practices were reported by parents in monthly diaries between the 3rd and 12th months of life. Parents indicated for each food item whether it was given to the child in the last 4 weeks and, if so, how often. A diversity score was calculated, including the major food items, which were defined as the ones introduced in the first year of life to approximately 80% of the children or more. The score included vegetables or fruits, cereals, bread, meat, cake, and yogurt. The same food items were used to define the diversity score within the first 6 months of life. For the association between single food items and atopic dermatitis, we used as reference children for whom the item was not introduced in the first year of life. When it was introduced for less than 15% of the children, cutoffs to earlier time points were used. Introduction of cow's milk was defined as either exclusive consumption of milk purchased in a shop (shop milk) or introduction of milk produced or purchased directly from a farm exclusively or in combination with shop milk and irrespective of whether the milk was boiled or unboiled (any farm milk).

Data on potential confounders, such as smoking during pregnancy, sex, mode of delivery, birth weight, gestational age, maternal education, and duration of breast-feeding were obtained from the self-reported questionnaires at the third trimester of pregnancy and at 2 months and 1 year of age. Duration of breast-feeding was categorized according to the number of months children were breast-fed (not exclusively). Parental history of allergies was defined as ever had asthma, hay fever, or atopic dermatitis, which was self-reported.

Statistical analysis

Data analysis was conducted with SAS software, version 9.2 (SAS Institute, Inc, Cary, NC).

The χ^2 test was used to evaluate the differences between the prevalences of atopic dermatitis depending on parental allergic status and also to compare the diversity score among subgroups of children. Generalized estimating equations were used to investigate the longitudinal effects of prenatal and postnatal exposures on atopic dermatitis with onset after the first year of life, taking into account the correlation between repeated measures (age 18, 24, 36, and 48 months) in the same subject. For the associations between exposures and atopic dermatitis with onset within the first year of life, we used logistic regression because only 1 time point (age 12 months) was taken into account. From these analyses, odds ratios (ORs) with 95% CIs were reported. To avoid reverse causality, with timing of introduction of food in the first year of life, we limited the analyses to children with atopic dermatitis first occurring after the first year of life. For the analysis comparing introduction of food before or after 6 months of age, the analysis was restricted to children without skin symptoms (itchy rash and diary data) within the first 6 months of life. To evaluate the relation between the diversity score and atopic dermatitis, we performed nonparametric smoothing regression analysis. Family history of

TABLE I. Prevalence of atopic dermatitis, according to time of onset and parental allergic status

	Total (n = 912), % (n)	No allergic parents (n = 426), % (n)	Only 1 allergic parent (n = 385), % (n)	Two allergic parents (n = 101), % (n)	P value*
Atopic dermatitis up to age 4 y	27.1 (247)	21.8 (93)	28.3 (109)	44.6 (45)	<.001
Atopic dermatitis with onset within the first year of life	15.9 (144)	12.9 (55)	15.0 (57)	32.0 (32)	<.001
Atopic dermatitis with onset after the first year of life†	10.7 (97)	8.7 (37)	12.6 (48)	12.0 (12)	.18

*Based on χ^2 test between parental allergic status and atopic dermatitis.

†Missing information for the first year of life for 6 children.

allergies is a dominant predictive factor of allergic diseases, particularly atopic dermatitis. Therefore all models were adjusted for parental history of allergy (ever eczema, hay fever, or asthma). For the association between food exposures and atopic dermatitis, we stratified the analyses by this variable. To test for effect modification between food item exposures and parental history of allergy, we calculated terms for interactions in the generalized estimating equation model.

All models were adjusted for study centers as a fixed effect because we did not find heterogeneity between the centers (tested by means of meta-analytic techniques). Multivariate models were further adjusted for farming and duration of breast-feeding in the first year of life because these variables are well known as potential confounders. Smoking during pregnancy and maternal education were added to the model but did not change the results, and therefore they were not kept in the final model. A *P* value of less than .05 was considered statistically significant.

RESULTS

Prevalence of atopic dermatitis

In total, 1041 children were included in this study. The proportion of farmer's children was 47.8%, and 558 (53.6%) had at least 1 allergic parent; among them, 39.1% (218/558) were farmer's children. The general characteristics of this study population were described in our previous analysis.¹⁸ The cumulative prevalence of children with atopic dermatitis in the first 4 years of life was 27.1% (Table I). This prevalence was significantly higher in children with 2 allergic parents than among children with nonallergic parents (44.6% and 21.8%, respectively). For 59.8% (144/241) of these children, the disease appeared in the first year of life. The influence of parental allergy was more pronounced in these children than in those with disease onset after the first year of life (Table I).

Association between early postnatal exposures to farm animals and atopic dermatitis

We did not observe an association between early postnatal contact with farm animals (presence of the child in the stable in the first year of life) and atopic dermatitis with onset after the first year of life. After adjustment for prenatal exposures (adjusted OR, 0.97; 95% CI, 0.53-1.75), unadjusted results were very similar (data not shown). To separate the influence of prenatal and postnatal exposures to farm animals, a variable with 4 mutually exclusive categories was computed: children with both exposures, those with only prenatal or only postnatal exposure, and those not exposed. The negative association between prenatal contact with farm animals and atopic dermatitis was observed only when the disease onset occurred during the first year of life (see Table E1 in this article's Online Repository at www.jacionline.org). By contrast, postnatal exposure was inversely associated with atopic dermatitis with onset after the first year of life, but this analysis was based on small numbers and not statistically significant.

Feeding practices in the first year of life

At 2 months of age, exclusive breast-feeding was observed among 66.0% of the children, and 18.6% were not breast-fed. About half of the children (46.4%) were breast-fed for more than 6 months (not exclusively), and no difference with respect to the parental history of allergy was observed (data not shown).

For only 18 (1.7%) children, no complementary food was introduced in the first year of life (Table II). These children did not differ from those with complementary food introduced in terms of farming status, parental allergic history, maternal education, or duration of breast-feeding (data not shown). In the first year of life, cow's milk was introduced to half of the study population (Table II). Of these children, 43.8% consumed only shop milk, and 56.2% consumed any farm milk, and 118 (37%) of the farm milk drinkers consumed unboiled farm milk.

About 80% of the children consumed vegetables or fruits, cereals, bread, meat, cake, and yogurt during the first year of life. A diversity score including these 6 major food items was calculated, and more than two thirds of the children consumed all 6 items (Table III). Significantly fewer food items were introduced among nonfarmer's children and those with at least 1 parent with a history of allergy. The diversity score showed no difference between children breast-fed for more or less than 6 months. As expected, among children with allergic parents, the allergenic food items, such as dairy products, egg, nut, and soy, were introduced later (data not shown).

Association between complementary food introduction and atopic dermatitis

The analyses of atopic dermatitis with onset within the first year of life showed an inverse association with the introduction in the first year of life for most of the food items, especially the allergenic foods (see Table E2 in this article's Online Repository at www.jacionline.org). This negative association is most likely due to delayed introduction of certain foods in children with early symptoms. Analyses were restricted to children having no atopic dermatitis in the first year of life but who had it later to avoid this form of bias. The introduction of yogurt and shop milk within the first year of life showed an inverse association with the development of atopic dermatitis with onset after the first year of life compared with no introduction, indicating a protective effect (adjusted OR, 0.41; 95% CI, 0.23-0.73 and adjusted OR, 0.52; 95% CI, 0.30-0.92, respectively); unadjusted results were very similar (data not shown). Analyses stratified by parental history of allergy showed similar associations (Fig 1 and see Table E3 in this article's Online Repository at www.jacionline.org). The consumption of farm milk in the first year of life had a tendency to decrease the risk of having atopic dermatitis but only among children with no allergic parents (adjusted OR, 0.49; 95% CI,

TABLE II. Time of first introduction of different food items in the first year of life (n = 1041)

	3-6 mo, % (n)	7-9 mo, % (n)	10-12 mo, % (n)	In total introduced in the first year of life, % (n)
Any food items (15 items)	72.2 (752)	25.6 (267)	0.4 (4)	98.3 (1023)
Any cow's milk	7.2 (75)	20.1 (209)	26.9 (280)	54.2 (564)
Only shop milk (n = 724)*	2.2 (16)	10.6 (77)	21.3 (154)	34.1 (247)
Any farm milk (n = 794)*	6.4 (51)	16.0 (127)	17.5 (139)	39.9 (317)
Yogurt	14.1 (147)	38.4 (400)	26.8 (279)	79.3 (826)
Other milk products	6.7 (70)	30.5 (317)	36.4 (379)	73.6 (766)
Eggs	3.2 (33)	28.1 (292)	36.1 (376)	67.3 (701)
Nuts	0.6 (6)	6.2 (65)	17.6 (183)	24.4 (254)
Vegetables or fruits	71.1 (740)	26.5 (276)	0.6 (6)	98.2 (1022)
Cereals	32.9 (342)	44.3 (461)	10.7 (111)	87.8 (914)
Bread	16.5 (172)	59.1 (615)	18.0 (187)	93.6 (974)
Meat	25.6 (266)	55.6 (579)	11.8 (123)	93.0 (968)
Fish	4.8 (50)	28.7 (299)	23.4 (244)	57.0 (593)
Soy	0.9 (9)	2.0 (21)	2.3 (24)	5.2 (54)
Margarine	8.6 (90)	28.1 (292)	22.0 (229)	58.7 (611)
Butter	6.0 (62)	33.6 (350)	30.2 (314)	69.7 (726)
Cake	11.2 (117)	47.1 (490)	27.9 (290)	86.2 (897)
Chocolate	3.8 (39)	15.2 (158)	27.3 (284)	46.2 (481)

*Reference group: children who did not consume any cow's milk in the first year of life.

TABLE III. Diversity score with major food items introduced in the first year of life among all study populations and subgroups

	Diversity score*			P value†
	0-3 items, % (n)	4-5 items, % (n)	6 items, % (n)	
All study population	5.4 (56)	31.9 (332)	62.7 (653)	
Farmer				
Yes	2.8 (14)	27.9 (139)	69.3 (345)	<.001
No	7.7 (42)	35.5 (193)	56.7 (308)	
Allergic parents (≥1)				
Yes	6.8 (38)	34.4 (192)	58.8 (328)	.007
No	3.7 (18)	29.0 (140)	67.3 (325)	
Breast-feeding >6 mo‡				
Yes	6.3 (30)	31.9 (153)	61.9 (297)	.31
No	4.2 (23)	31.4 (172)	64.4 (352)	

*Diversity score with major food items: vegetables or fruits, any cereals, meat, bread, cake, and yogurt.

†P value based on χ^2 test.

‡Missing information for 14 children.

0.21-1.18). Tests for interaction between parental history of allergy and farm milk showed a *P* value of .08. Introduction of vegetables or fruits in the first 6 months reduced the risk of atopic dermatitis (adjusted OR, 0.56; 95% CI, 0.31-1.00).

A smoothed plot of the prevalence of atopic dermatitis in relation to the diversity score (0-6) was performed to evaluate whether the diversity of foods consumed during the first year of life was associated with atopic dermatitis occurring after the first year of life, showing a decrease in prevalence of the disease with an increasing score (Fig 2). Dividing the diversity score into 3 different categories with the largest as the reference category, we observed a dose-response association with atopic dermatitis (Table IV). For each additional major food item introduced in the first year of life, we observed a significant reduction of 25% in the development of atopic dermatitis. Similar results were obtained in separate analyses stratified by parental history of allergy (adjusted OR for each food item introduced among children with parents with no allergy, 0.70; 95% CI, 0.56-0.87; among those

with at least 1 parent with allergy: adjusted OR, 0.81; 95% CI, 0.65-1.01). The score was recalculated excluding yogurt to evaluate the influence of the yogurt item in this score and showed the same association with atopic dermatitis (Table IV). Moreover, yogurt remained significantly associated with atopic dermatitis after adjustment for the reduced score. Smoothed plots with a diversity score including all 15 food items also showed a decrease in prevalence of the disease with an increasing score most strongly with up to 6 items (see Fig E1 in this article's Online Repository at www.jacionline.org). When the major food items were excluded from the score, no association was observed (see Fig E2 in this article's Online Repository at www.jacionline.org).

Additionally, we evaluated the association between the introduction of food in the first 6 months of life and atopic dermatitis with onset within the first year of life in the subgroup of children and no symptoms of atopic dermatitis (itchy rash) within the first 6 months (60.3% of the children with atopic dermatitis with early onset). We could also observe a decreased risk of atopic dermatitis with increasing numbers of major food introduced in the first 6 months, indicating a dose-response effect (Table V). We also observed similar results in separated analyses stratified by the parental history of allergy, as well as in unadjusted analyses (data not shown).

DISCUSSION

Our study shows a strong association between the family history of allergies and atopic dermatitis with early onset but not with onset occurring after the first year of life. The previously reported protective prenatal effect of exposure to farm animals was limited to atopic dermatitis occurring during the first year of life. The postnatal exposure to farm animals was not significantly associated with atopic dermatitis.

Feeding practices in the first year of life seem to be associated with atopic dermatitis. We showed that the diversity of food items introduced in the first year of life reduces the risk of atopic dermatitis later in life. Introduction of yogurt in the first year of life showed a strong protective effect against atopic dermatitis with onset after the first year of life independently of the diversity of food.

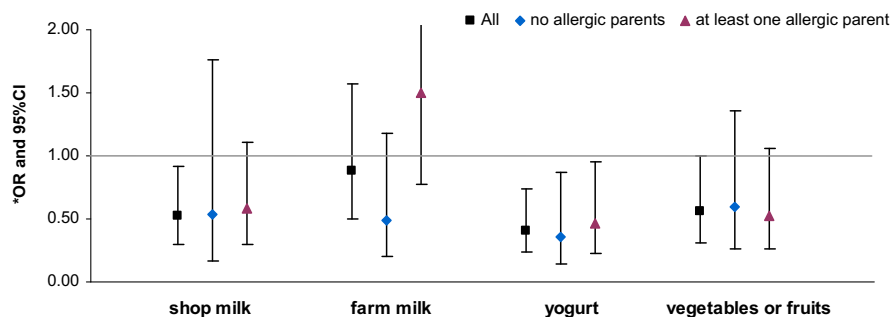


FIG 1. Association between food item introduction in the first year of life and atopic dermatitis with onset after the first year of life stratified by parental allergies. *Adjusted for farmer, center, breast-feeding, and parental history of allergies (ever eczema, hay fever, or asthma). For dairy products: introduction in the first year of life compared with no introduction before 1 year of age. For vegetables or fruits: introduction in the first 6 months of life compared with no introduction before 6 months of age.

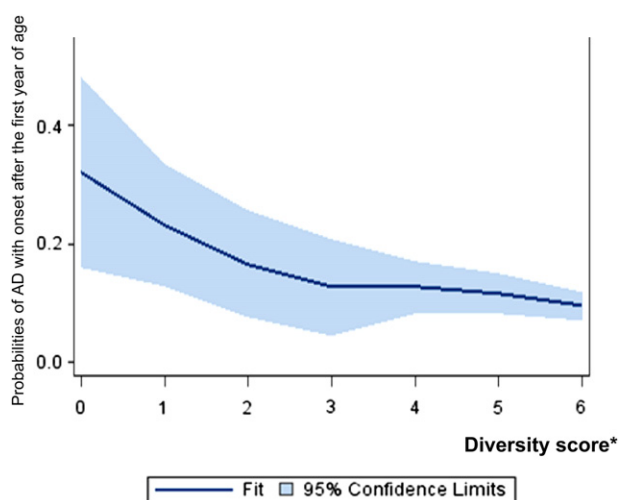


FIG 2. Association between increasing numbers of different major food items ($n = 6$) introduced in the first year of life and atopic dermatitis (AD) with onset after the first year of life. *Diversity score with major food items: vegetables or fruits, any cereals, meat, bread, cake, and yogurt.

Our results suggest that the association between genetic factors and prenatal exposures is stronger with atopic dermatitis with onset early in life than with late-onset atopic dermatitis. In a Dutch birth cohort study it was shown that filaggrin gene mutations were associated with atopic dermatitis when the occurrence of the disease was in the first year of life but not after²¹ and that cat exposure increased the effect of filaggrin gene mutations on atopic dermatitis, indicating a gene-environment interaction.²² Epigenetic mechanisms in the development of allergic diseases have recently raised much interest.²³ Our finding that the protective effect of prenatal exposures was not observed in children with atopic dermatitis occurring after the first year of life challenges the idea of epigenetic mechanisms underlying the association between prenatal contact with animals and atopic dermatitis with late onset. It might be that atopic dermatitis depending on the age of onset represents 2 different phenotypes of the disease and that genetic and epigenetic mechanisms influence mainly the early onset. However, our study was not sufficiently powered to evaluate the independent role of postnatal exposure to farm animals on atopic dermatitis occurring after the first year of life.

Our results support recent studies showing an inverse association between early introduction of complementary food, such as fish and cow's milk, and allergic diseases and highlight the role of the diversity of environmental exposures for the development of allergic diseases. We have previously shown that the diversity of maternal exposure to different farm animal species during pregnancy had a protective effect on atopic dermatitis early in life.¹⁸ Moreover, recent findings have shown that the diversity of microbial exposures might play a role in the protective effect with regard to asthma.²⁴ Bacterial diversity of the intestinal flora has also been suggested to be associated with atopic diseases, even though its association with atopic dermatitis remains unclear.²⁵ Food is a major environmental factor, especially for infants who encounter large quantities of new food components during their first year of life. Diversity of food seems to be protective against the development of atopic dermatitis. This was observed only when the diversity score was composed of major food items. This might be due to the fact that the number of children exposed to the other items was too small to show an effect or that these items had no effect. Our findings on the diversity of food introduced in the first year of life might support the hypothesis that exposure to a variety of antigens, such as food protein, during a specific time window early in life might be essential for the development of immune tolerance.²⁶

The strengths of this study are the prospective design and the detailed data collection of feeding practices in the first year of life. Focusing the analyses on atopic dermatitis occurring after the first year of life allowed us to avoid the reverse causality effect. However, this focus also reduced the number of affected children because the onset of this disease occurred in the first year of life for most of the children, thus limiting the power of the present analysis. Food exposures early in life might differently affect the disease with early or late onset. However, when we restricted our analyses to children without symptoms of atopic dermatitis during the first 6 months but atopic dermatitis with onset within the first year of life, similar associations with introduction of food in the first 6 months were found as in patients with late onset of the disease.

Yogurt is produced by bacterial fermentation of milk by lactic acid bacteria. Many of these bacterial strains have been selected as probiotics. The strong protective effect of consumption of yogurt in the first year of life on atopic dermatitis could be due to these bacteria. In the present study, unfortunately, no information on children's consumption of yogurt with or without live

TABLE IV. Association between the diversity score with major items introduced in the first year of life and atopic dermatitis with onset after the first year of life

	Atopic dermatitis with onset after the first year of life			
	No.	OR*	95% CI	P value†
Diversity score with major food items‡ (0-6)				
No. of items introduced in the first year				
0-3	56	2.87	1.26-6.56	.01
4-5	332	1.2	1.06-2.80	.03
6, reference	653	1	—	
For each major food item introduced§	1041	0.76	0.65-0.88	<.001
Diversity score with major food items, without yogurt (0-5)				
For each major food items introduced§	1041	0.75	0.62-0.91	.003

Boldface values are significant ($P < .05$).

*Adjusted for farmer, center, duration of breast-feeding, and parents with atopy (eczema, asthma, or hay fever).

†P value based on generalized estimating equation analysis.

‡Diversity score with major food items: vegetables or fruits, any cereals, meat, bread, cake, and yogurt.

§OR for atopic dermatitis with each additional food item introduced in the first year of life.

TABLE V. Association between the diversity score with major items introduced in the first 6 months and atopic dermatitis with onset within the first year of life but no symptoms in the first 6 months

	Atopic dermatitis with onset within the first year of life but no symptoms (itchy rash) in the first 6 mo			
	No.	OR*	95% CI	P value†
Diversity score with major food items‡ (0-6)				
No. of items introduced in the first 6 mo				
0-1	532	2.12	1.12-4.03	.02
2	190	1.76	0.85-3.69	.16
≥3, reference	319	1	—	
For each major food item introduced§	1041	0.88	0.73-1.05	.16
Diversity score with major food items, without yogurt (0-5)				
For each major food item introduced§	1041	0.85	0.70-1.04	.12

Boldface values are significant ($P < .05$).

*Adjusted for farmer, center, duration of breast-feeding, and parents with atopy (eczema, asthma, or hay fever).

†P value based on logistic regression analysis.

‡Diversity score with major food items: vegetables or fruits, any cereals, meat, bread, cake, and yogurt.

§OR for atopic dermatitis with each additional food items introduced in the first 6 months of life.

bacterial cultures was available. One of the first randomized controlled trials, which was conducted by Kalliomäki et al²⁷ in pregnant women with a family history of allergy, showed a 50% reduction in clinical eczema among the probiotic group. Even though several other studies and meta-analyses on probiotics and the prevention of allergic diseases have been conducted, most of them concluded that there is insufficient evidence to recommend probiotics for prevention. Recently, a Finnish study observed that probiotics were protective for allergic disease only among children born by means of cesarean section.²⁸ In our study we observed the same protective effect of the introduction of yogurt on atopic dermatitis when analyses were restricted to children born by means of vaginal delivery, arguing against effect modification by mode of delivery in the present study (data not shown).

Levels of metabolites produced by intestinal microbiota, such as short-chain fatty acids (SCFAs), have been shown to be increased in fecal and plasma samples after yogurt consumption.^{29,30} Moreover, it has been suggested that SCFAs might have anti-inflammatory properties,^{31,32} and thus it has been proposed that factors that influence the intestinal microbiota and the production of SCFAs might have an effect on immune and inflammatory responses. Interestingly, more fecal SCFAs were found among children from rural Africa compared with those from

urban Europe, providing indirect evidence of a role of SCFAs. As among children from Africa, a lower prevalence of allergic diseases was observed compared with the prevalence seen in children from western Europe.^{33,34}

The protective effect of cow's milk in the present study was mainly related to consumption of shop milk. Previously, cross-sectional studies on farm milk consumption and allergies suggested a protective effect of farm milk consumption on asthma, whereas the association with atopic dermatitis was more controversial.^{5,6,35} In the present study the relationship between farm milk consumption in the first year of life and atopic dermatitis tended to be modified by parental history of allergies, which has not been observed in the cross-sectional studies.^{6,35} A tendency toward a decreased risk of atopic dermatitis with consumption of farm milk was observed only among children with parents without allergies. These results could be explained by a gene-environment interaction effect, which is supported by a previous study showing that a polymorphism in the gene encoding CD14 modified the effect of farm milk consumption on allergic diseases and CD14 gene expression.³⁶ With other complementary foods, we did not have evidence for effect modification by parental allergies in the association with atopic dermatitis.

Children exposed to complementary foods, especially yogurt, and an increased diversity of foods within the first year of life have

a reduced risk of atopic dermatitis independently of parental history of allergies.

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Clinical implications: The diversity of food introduced in the first year of life might decrease the risk of atopic dermatitis in children.

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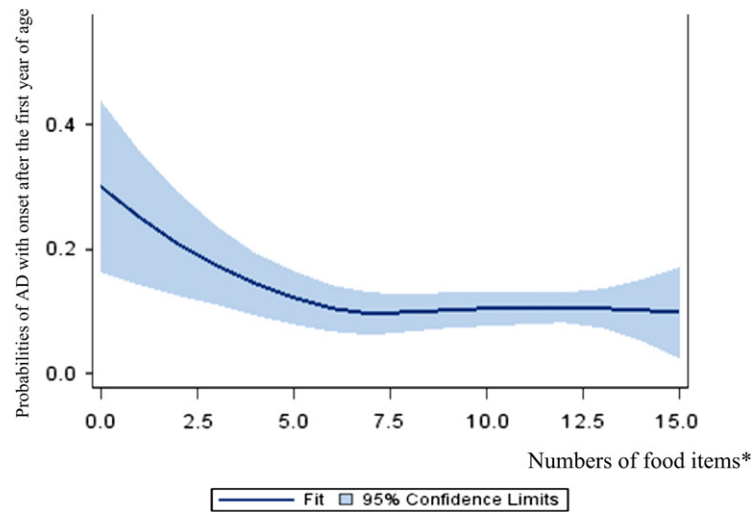


FIG E1. Association between increasing numbers of all different food items ($n = 15$) introduced in the first year of life and atopic dermatitis (AD) with onset after the first year of life. *Food items ($n = 15$): any cow's milk, yogurt, other milk products, eggs, nuts, vegetables or fruits, cereals, bread, meat, fish, soy, margarine, butter, cake, and chocolate.

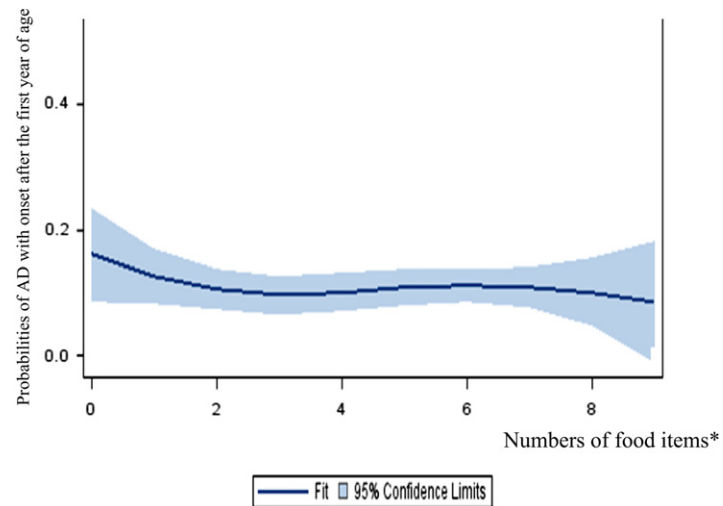


FIG E2. Association between increasing numbers of all different food items excluding major foods ($n = 9$) introduced in the first year of life and atopic dermatitis (AD) with onset after the first year of life. *Food items ($n = 9$): any cow's milk, other milk products, eggs, nuts, fish, soy, margarine, butter, and chocolate.

TABLE E1. Association between prenatal and postnatal exposures to farm animals and atopic dermatitis with different time of onset

		Atopic dermatitis with onset within the first year of life		Atopic dermatitis with onset after the first year of life	
	Percent (n)	OR*	95% CI	OR*	95% CI
Contact with farm animal					
Prenatal and postnatal combined					
Prenatal and postnatal	37.7 (345)	0.51	0.26-1.00	1.20	0.53-2.71
Only prenatal	22.8 (209)	0.61	0.35-1.08	1.09	0.56-2.14
Only postnatal	2.9 (26)	2.01	0.78-5.15	0.34	0.03-3.75
No contact, reference	36.6 (335)	1			

Postnatal: presence of the child in the stable within the first year of life.

*Adjusted for farmer, center, parents with atopy, smoking during pregnancy, and duration of breast-feeding.

TABLE E2. Association between introduction of food items in the first year of life and atopic dermatitis up to 4 years of age and with onset within the first year of life

	Atopic dermatitis up to 4 y of age		Atopic dermatitis with onset within the first year of life		Atopic dermatitis with onset within the first year of life but no symptoms of itchy rash in the first 6 mo	
	OR*	95% CI	OR*	95% CI	OR*	95% CI
Dairy items						
Cow's milk						
3-12 mo	0.46	0.32-0.65	0.60	0.41-0.87	0.65	0.40-1.05
Not in first year, reference†	1.00	—	1.00		1.00	
Only shop's milk						
3-12 mo	0.31	0.20-0.49	0.54	0.33-0.87	0.57	0.31-1.07
Not in first year, reference†	1.00	—	1.00		1.00	
Any farm's milk						
3-12 mo	0.61	0.39-0.95	0.63	0.38-1.03	0.67	0.36-1.24
Not in first year, reference†	1.00		1.00		1.00	
Yogurt						
3-12 mo	0.31	0.20-0.46	0.52	0.34-0.82	0.60	0.33-1.07
Not in first year, reference	1.00		1.00		1.00	
Other milk products (eg, cheese and quark)						
3-12 mo	0.62	0.41-0.94	0.60	0.40-0.90	0.58	0.35-0.96
Not in first year, reference	1.00		1.00		1.00	
Other food items						
Nuts						
3-12 mo	0.99	0.62-1.57	0.54	0.33-0.90	0.51	0.26-0.99
Not in first year, reference	1.00		1.00		1.00	
Eggs						
3-12 mo	0.76	0.51-1.12	0.55	0.38-0.80	0.61	0.38-1.00
Not in first year, reference	1.00		1.00		1.00	
Fish						
3-12 mo	0.45	0.29-0.69	0.52	0.35-0.77	0.51	0.30-0.87
Not in first year, reference	1.00		1.00		1.00	
Meat						
3-8 mo	0.75	0.49-1.14	0.71	0.47-1.08	0.77	0.46-1.31
Not in first 8 mo, reference	1.00		1.00		1.00	
Cereals						
3-8 mo	0.95	0.62-1.44	1.14	0.74-1.74	1.29	0.75-2.21
Not in first 8 mo, reference	1.00		1.00		1.00	
Vegetables or fruits						
<6 mo	0.46	0.31-0.70	0.81	0.53-1.25	0.67	0.38-1.15
Not in first 6 mo, reference	1.00		1.00		1.00	
Bread						
3-8 mo	0.82	0.57-1.17	0.80	0.55-1.16	0.63	0.39-1.02
Not in first 8 mo, reference	1.00		1.00		1.00	
Soy						
3-12 mo	0.78	0.35-1.75	1.13	0.53-2.41	1.16	0.43-3.13
Not in first year, reference	1.00		1.00		1.00	
Margarine						
3-12 mo	0.72	0.48-1.07	0.76	0.51-1.14	0.75	0.45-1.26
Not in first year, reference	1.00		1.00		1.00	
Butter						
3-12 mo	0.89	0.60-1.30	0.78	0.52-1.16	0.83	0.50-1.41
Not in first year, reference	1.00		1.00		1.00	
Cake						
3-8 mo	0.70	0.47-1.02	0.72	0.49-1.07	0.66	0.40-1.10
Not in first 8 mo, reference	1.00		1.00		1.00	
Chocolate						
3-12 mo	0.53	0.36-0.77	0.66	0.45-0.98	0.95	0.58-1.54
Not in first year, reference	1.00		1.00		1.00	

Boldface values are significant ($P < .05$).

*Adjusted for farmer, center, breast-feeding (duration), and parental history of allergies (ever eczema, hay fever, or asthma).

†Reference = no introduction of any cow's milk in the first year of life.

TABLE E3. Association between introduction of food items in the first year of life and atopic dermatitis with onset after the first year of life stratified by parents with or without allergies

	Entire study population			Parents without allergy			At least 1 parent with allergy		
	No.	Atopic dermatitis, with onset after the first year of life		No.	Atopic dermatitis, with onset after the first year of life		No.	Atopic dermatitis, with onset after the first year of life	
		OR*	95% CI		OR*	95% CI		OR*	95% CI
Dairy items									
Cow's milk									
3-12 mo	564	0.68	0.44-1.05	289	0.49	0.24-1.01	275	0.86	0.51-1.45
Not in first year, reference†	477	1.00	–	194	1.00		283	1.00	
Only shop's milk									
3-12 mo	247	0.52	0.30-0.92	98	0.54	0.17-1.77	149	0.58	0.30-1.10
Not in first year, reference†	477	1.00	–	194	1.00		283	1.00	
Any farm's milk‡									
3-12 mo	317	0.88	0.49-1.57	191	0.49	0.21-1.18	126	1.50	0.77-2.89
Not in first year, reference†	477	1.00		194	1.00		283	1.00	
Yogurt									
3-12 mo	826	0.41	0.23-0.73	411	0.36	0.15-0.87	415	0.46	0.23-0.95
Not in first year, reference	215	1.00		72	1.00		143	1.00	
Other milk products (eg, cheese and quark)									
3-12 mo	766	1.07	0.59-1.91	373	1.25	0.47-3.34	393	1.00	0.47-2.13
Not in first year, reference	275	1.00		110	1.00		165	1.00	
Other food items									
Nuts									
3-12 mo	254	1.35	0.79-2.31	135	1.49	0.66-3.37	119	1.28	0.62-2.61
Not in first year, reference	787	1.00		348	1.00		439	1.00	
Eggs									
3-12 mo	701	1.02	0.63-1.66	353	1.08	0.46-2.53	348	1.01	0.55-1.85
Not in first year, reference	340	1.00		130	1.00		210	1.00	
Fish									
3-12 mo	593	0.73	0.43-1.24	288	1.09	0.43-2.75	305	0.58	0.31-1.09
Not in first year, reference	448	1.00		195	1.00		253	1.00	
Meat									
3-8 mo	697	0.87	0.50-1.54	333	1.01	0.42-2.42	364	0.81	0.37-1.77
Not in first 8 mo, reference	344	1.00		150	1.00		194	1.00	
Cereals									
3-8 mo	700	0.72	0.42-1.25	304	0.79	0.35-1.80	396	0.70	0.36-1.37
Not in first 8 mo, reference	341	1.00		179	1.00		162	1.00	
Vegetables or fruits									
<6 mo	462	0.56	0.31-1.00	218	0.59	0.26-1.36	244	0.52	0.26-1.06
Not in first 6 mo, reference	579	1.00		265	1.00		314	1.00	
Bread									
3-8 mo	787	0.84	0.52-1.35	378	0.70	0.36-1.35	409	0.96	0.51-1.81
Not in first 8 mo, reference	254	1.00		105	1.00		149	1.00	
Soy									
3-12 mo	54	0.92	0.39-2.17	18	0.88	0.12-6.65	36	0.92	0.38-2.21
Not in first year, reference	987	1.00		465	1.00		522	1.00	
Margarine									
3-12 mo	611	0.69	0.41-1.16	267	0.62	0.24-1.62	344	0.74	0.40-1.34
Not in first year, reference	430	1.00		216	1.00		214	1.00	
Butter									
3-12 mo	726	1.00	0.64-1.55	358	0.87	0.41-1.83	368	1.09	0.63-1.89
Not in first year, reference	315	1.00		125	1.00		190	1.00	
Cake									
3-8 mo	444	0.75	0.47-1.21	239	0.75	0.37-1.51	205	0.76	0.41-1.44
Not in first 8 mo, reference	597	1.00		244	1.00		353	1.00	
Chocolate									
3-12 mo	481	0.73	0.47-1.15	251	0.86	0.41-1.82	230	0.67	0.38-1.17
Not in first year, reference	560	1.00		232	1.00		328	1.00	

Boldface values are significant ($P < .05$).

*Adjusted for farmer, center, breast-feeding (duration), and parental history of allergies (ever eczema, hay fever, or asthma).

†Reference = no introduction of any cow's milk in the first year of life.

‡Interaction term between parents with atopy and food item ($P = .08$).