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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Impaired skin barrier and allergic sensitization in early infancy

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Abstract

Background: Factors predicting allergic sensitization in the first 6 months of life are poorly understood. We aimed to determine whether eczema, dry skin, and high transepidermal water loss (TEWL) at 3 months were associated with allergic sensitization at 6 months of age and, secondarily, to establish whether these characteristics predicted sensitization from 3 to 6 months of age.

Methods: At 3 months of age, 1,994 infants from the population-based PreventADALL birth cohort in Norway and Sweden were assessed for eczema and dry skin on the cheeks and/or extensors; impaired skin barrier function, defined as TEWL in the upper quartile (>9.4 g/m^2/h), and allergen-specific IgE levels <0.1 kU$_A$/L, available in 830. At 6 months, we assessed allergic sensitization to any food (egg, cow's milk, peanut, wheat, soy) or inhalant (birch, timothy grass, dog, and cat) allergen by a skin prick test wheal diameter ≥2 mm larger than negative control.

Results: Any sensitization was found in 198 of the 1,994 infants (9.9%), the majority to food allergens (n = 177, 8.9%). Eczema, dry skin, and high TEWL at 3 months increased

Abbreviations: AD, atopic dermatitis; GA, gestational age; IgE, immunoglobulin E; kU$_A$/L, kilounits of allergen-specific IgE per liter; SPT, skin prick test; TEWL, transepidermal water loss.

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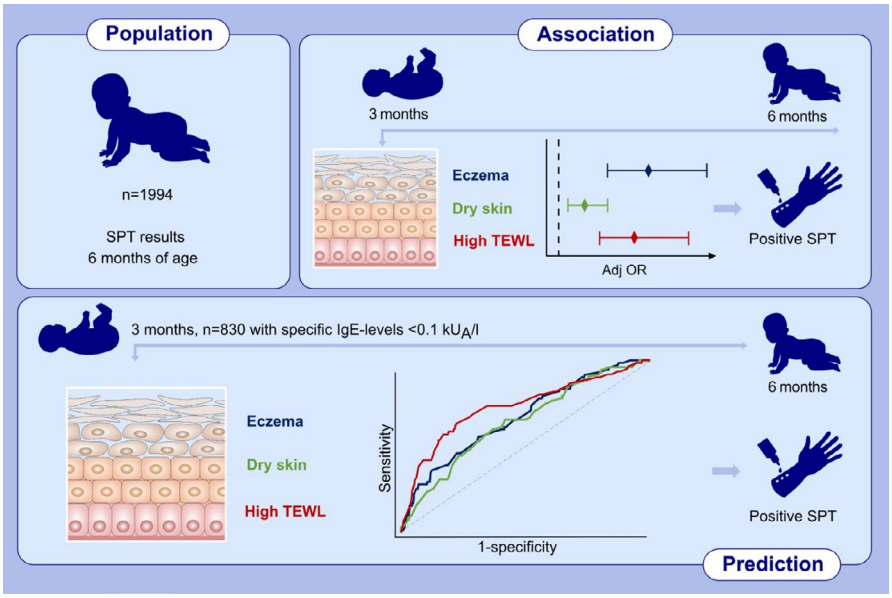
the risk of sensitization at 6 months; adjusted odds ratios 4.20 (95% CI 2.93–6.04), 2.09 (95% CI 1.51–2.90) and 3.67 (95% CI 2.58–5.22), respectively. Eczema predicted sensitization with 55.6% sensitivity and 68.1% specificity; dry skin with 65.3% sensitivity and 57.3% specificity; and high TEWL with 61.7% sensitivity and 78.1% specificity.

Conclusion: Eczema, dry skin, and high TEWL at 3 months predicted allergic sensitization at 6 months of age.

KEYWORDS
allergic sensitization, infancy, PreventADALL, skin barrier



GRAPHICAL ABSTRACT

At 6 months, 198/1994 infants (9.9%) had any sensitization, the majority to food. Eczema, dry skin, and high TEWL at 3 months increased the risk of sensitization at 6 months of age. Eczema, dry skin, and high TEWL at 3 months predicted incident sensitization at 6 months of age (n = 87/830, 10.5%).

Abbreviations: Adj, adjusted; kU_A/L, kilounits of allergen-specific IgE per liter; OR, odds ratio; SPT, skin prick test; TEWL, transepidermal water loss.

1 | INTRODUCTION

Allergic disease often begins early in life, typically with eczema (atopic dermatitis) in infancy, which may be followed by food allergies, allergic rhinitis, and asthma, a pattern referred to as the atopic march.[1] Early allergic sensitization is a major risk factor for chronic allergic disease in children.[2,3] It is not clear what initiates allergic sensitization development, but sensitization to a single food allergen typically starts in infancy.[4]

Atopic dermatitis (AD), an inflammatory skin disorder characterized by itchy eczematous lesions, is associated with reduced skin barrier function and the development of allergic sensitization.[5–8] The timing and severity of AD manifestations appear to be crucial in allergic disease development because the risk of food sensitization and, therefore, of food allergy increases with the earlier onset and greater severity of AD.[4,6,7]

The Childhood Asthma Prevention Study, including children with a history of asthma in their family, reported that AD at 18 months can predict allergic sensitization at 5 years of age.[2] However, the evidence of early predictors for allergic sensitization in the first 6 months of life is not well established. Previously, studies have shown a strong association between AD and sensitization or food

allergy in infancy,[6,7] but without controlling for potential reverse causation. To our knowledge, no previous studies have predicted the development of allergic sensitization in the first 6 months of life by analyzing the presence of potential markers of impaired skin barrier in non-sensitized infants. Identifying appropriate predictors of allergic sensitization may guide novel strategies for the prevention of food allergy.[9,10]

The first aim of the present study was to determine whether eczema, dry skin and high transepidermal water loss (TEWL) at 3 months of age were associated with allergic sensitization at 6 months of age. The second aim was to establish whether eczema, dry skin, or high TEWL in non-sensitized infants at 3 months predicted incident allergic sensitization at 6 months of age.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study addressed observational research questions by using prospectively collected information from the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) study, a factorial, multicenter, cluster-randomized controlled trial and observational, population-based mother-child birth cohort.[11]In total, 2,697 pregnant women were enrolled in the PreventADALL study at the routine 18-gestational-weeks ultrasound screening in Oslo and Østfold in Norway as well as in Stockholm, Sweden, from December 2014 until October 2016.[11] Women with insufficient skills in Nordic languages, as well as those carrying more than two fetuses or a fetus with severe disease or malformation, were excluded, together with infants born before 35.0 weeks of gestational age (GA).[11]

At birth, the child was randomly assigned (1:1:1:1) to one of the four groups 'no intervention'; 'skin care'; 'early complementary feeding'; and 'combined skin and food interventions', as described in detail elsewhere.[11,12]Briefly, the effect of the skin intervention has been reported previously, with no reduction of AD at 12 months of age.[12]

The present study population consisted of all 1,994 infants with information on skin prick test (SPT) results at 6 months of age. A flow chart of the study population is shown in Figure 1.

2.2 | Data sources

2.2.1 | *Electronic questionnaires*

Information about socio-demographic characteristics, lifestyle and environmental factors in the families, and parental heredity regarding atopic disease was available at recruitment, as well as from electronic questionnaires filled out by the parents at 34 weeks of pregnancy and when the infants were 3 and 6 months old.

2.2.2 | *Skin examination and transepidermal water loss*

The skin examination and TEWL measurements were performed at 3-month clinical visits by trained study personnel, who were blinded to the intervention. Dry skin was documented in line with the principles of the Dry skin/Ichtyosis and Severity Index (DASI), without the score of erythema.[13]Parents had been instructed not to bathe their infant or use emollients 24 h prior to the visit.[14]After the infant had been acclimatized for 15 min wearing a diaper only, TEWL was measured on the left lateral upper arm using an open-chamber DermaLab USB (Cortex).[14]Only measurements performed at room temperature between 20 and 25°C were included in the present analysis, in line with general practical recommendations.[15] The room humidity ranged from 6.9% to 73.1% (mean 29.9%, standard deviation 13.0). All TEWL values presented are the mean of three successfully performed measurements.

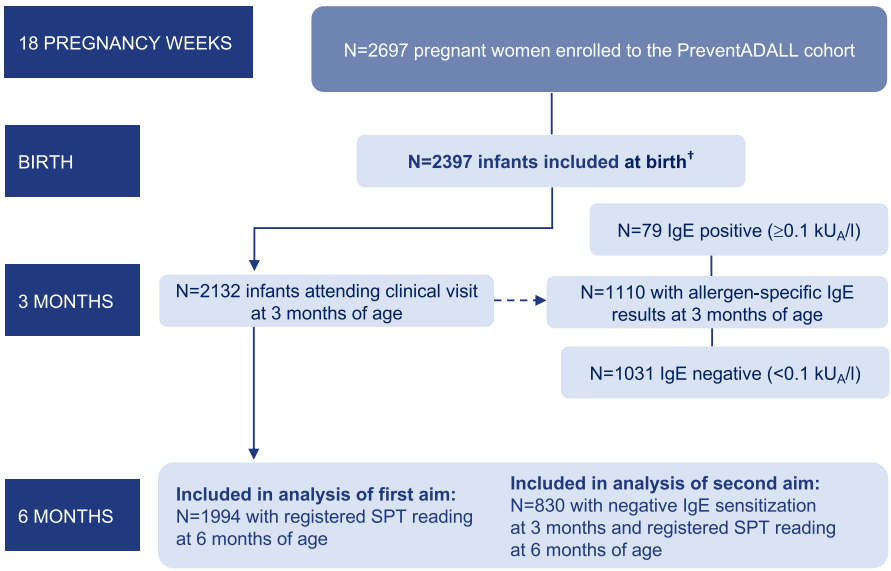


FIGURE 1 Flow chart for the study population derived from the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) study. †3 participants withdrew consents

2.2.3 | *Skin prick tests and allergen-specific IgE levels*

At the 6-month clinical visit, SPTs against egg, cow's milk, peanut, wheat, soy, birch, timothy grass, dog, and cat (Soluprick ALK-Albelló, Hørsholm, Denmark) were conducted as part of the study protocol for all children. The assessment of the skin wheal was performed after 10 and/or 15 min. At 3 months of age, sera were analyzed against Phadiatop Infant®, which includes egg white, cow's milk, peanut, birch, timothy grass, dog, and cat, and against wheat extract (ImmunoCAP System, Thermo Fisher Scientific). Sensitization was defined as IgE ≥ 0.1 kU_A/l. Median s-IgE levels among the sensitized infants were 0.23 kU_A/l, IQR 0.16–0.81 kU_A/l.[16] Further information regarding allergic sensitization at 3 months of age in PreventADALL can be found elsewhere.[16]

2.3 | Definitions

2.3.1 | *Allergic sensitization*

At least one SPT reaction to any specific allergen with wheal diameter exceeding that of the negative control by at least 2 mm.[17,18]

2.3.2 | Polysensitization

Positive allergen-specific SPT reactions to at least two allergens.[4]

2.3.3 | Multisensitization

Positive allergen-specific SPT reaction to at least one food allergen and at least one inhalant allergen.

2.3.4 | Eczema

Clinical observation of eczematous lesions by trained physicians, excluding common differential diagnoses for eczema, such as seborrheic dermatitis and irritative contact dermatitis.[14]

2.3.5 | *Dry skin*

Clinically observed dry skin, defined as the presence of scaling and roughness on cheeks and/or extensor surfaces of the extremities.[5]

2.3.6 | *High TEWL*

TEWL in the upper quartile[19](>9.4 $g/m^2/h$ in the present study population at 3 months of age).

2.4 | Statistical analysis

Continuous variables are presented as means and standard deviations (SDs) if normally distributed, and descriptive comparisons of these were conducted with independent samples t-tests, whereas categorical variables are presented as numbers and percentage and examined through Chi-squared tests and Fisher's exact tests when absolute counts were less than five.

The associations between exposures (eczema, dry skin, and high TEWL) and outcome were evaluated in a complete case logistic regression analysis. A univariate analysis was conducted in the first step. In the second step, sex,[20–22] any parental heredity regarding atopic disease,[22,23] low household income (<600,000 NOK/SEK per year, ie, approximately 58,800 EUR per year),[24-26] caesarian section,[22,27,28]and low GA[20,29,30] (<37 weeks) were treated as confounders in a multivariate analysis, along with intervention group allocation to ensure external validity. Separate multivariate models were created for each exposure. An interaction analysis was conducted between pre-specified exposures and confounders, in which no interaction was found. As we found no significant interaction between the skin and/or the food intervention and eczema, dry skin or high TEWL, respectively (p-values >0.06), with the exception of a possible interaction between high TEWL and the skin intervention observed in the crude analysis, although not statistically significant in the multivariate analysis (Table S1 in the online repository), we included all infants in our analyses, regardless of intervention group allocation.

In the analysis of the second aim, the predictive accuracy of the multivariate logistic regression models was tested among the subsample of infants who were non-sensitized at 3 months of age ($n = 830$, Figure 1) using receiver operating characteristics (ROC) curve analysis. An observation was classified as positive if the predicted probability was above 0.1. A ROC curve analysis was also conducted to determine the optimal threshold of TEWL (as a continuous variable) at 3 months for differentiating sensitization from non-sensitization at 6 months of age. The optimal threshold was derived by estimating the Youden Index.

Finally, a sensitivity analysis was undertaken to evaluate our choice of the definition of allergic sensitization. Additional analyses were performed, with the SPT reaction wheal diameter cutoffs at ≥1- and ≥3 mm.

All analyses were carried out using Stata/MP 16 software. *p*-values of less than .05 were considered significant.

2.5 | Ethical approval

The PreventADALL study was approved by The Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518) and The Swedish Ethical Review Authority in Stockholm (2014/2242-31/4). Study participation was voluntary, and written informed consent was collected from the parents at study enrolment.

TABLE 1 Distribution in general characteristics of the study population at birth and at 3- and 6 months of age

	All infants *N* = 1994 no (%)	Any sensitization 6 months of age[a] *N* = 198 no (%)	Negative sensitization 6 months of age *N* = 1796 no (%)	*p*-value[e]	Negative IgE 3 months of age[b] *N* = 830 no (%)
Infants' characteristics					
Sex					
Boys	1047 (52.5)	110 (55.6)	937 (52.2)		430 (51.8)
Girls	947 (47.5)	88 (44.4)	859 (47.8)	0.365	400 (48.2)
Study country					
Sweden	438 (22.0)	55 (27.8)	383 (21.3)		153 (18.4)
Norway	1556 (78.0)	143 (72.2)	1413 (78.7)	0.037	677 (81.6)
Delivery mode					
Vaginal birth	1674 (84.1)	161 (81.3)	1513 (84.4)		703 (84.9)
Caesarian section	317 (15.9)	37 (18.7)	280 (15.6)	0.262	125 (15.1)
Gestational age at birth, days					
Mean ± SD	280.5 ± 9.4	279.9 ± 9.4	280.5 ± 9.4		280.4 ± 9.3
Min, max	245, 298	247, 298	245, 297	0.380	245, 297
Birth weight (g)					
Mean ± SD	3571.4 ± 480.4	3564.2 ± 476.3	3572.2 ± 481.0		3567.8 ± 482.3
Min, max	1794, 5632	2280, 4800	1794, 5632	0.824	1933, 5016
Household smoking during late pregnancy					
Yes	77 (4.1)	9 (4.7)	68 (4.0)		23 (2.9)
No	1818 (95.9)	182 (95.3)	1636 (96.0)	0.632	765 (97.1)
Household pet ownership[c]					
Yes	463 (25.2)	43 (24.2)	420 (25.3)		181 (23.8)
No	1373 (74.8)	135 (75.8)	1238 (74.7)	0.732	579 (76.2)
Living environment					
Urban	1406 (76.9)	142 (75.5)	1264 (77.0)		591 (78.7)
Rural	423 (23.1)	46 (24.5)	377 (23.0)	0.645	160 (21.3)
Eczema, 3 months					
Yes	247 (12.6)	69 (35.4)	178 (10.1)		113 (13.9)
No	1714 (87.4)	126 (64.6)	1588 (89.9)	<0.001	702 (86.1)
Dry skin cheeks and/or extensors, 3 months					
Yes	915 (46.1)	128 (65.3)	787 (44.0)		407 (49.2)
No	1071 (53.93)	68 (34.7)	1003 (56.0)	<0.001	421 (50.8)
High TEWL, 3 months					
Yes	426 (24.7)	83 (49.7)	343 (22.0)		175 (24.1)
No	1300 (75.3)	84 (50.3)	1216 (78.0)	<0.001	552 (75.9)
TEWL 3 months, g/m^2/h					
Mean ± SD	8.3 ± 5.9	13.3 ± 10.8	7.8 ± 4.8		8.2 ± 5.6
Min, max	0, 58.0	2, 58.0	0, 46.2	<0.001	0, 58.0
Parents' characteristics					
Firstborn child of the mother					
Yes	1202 (60.3)	124 (62.6)	1078 (60.1)		488 (58.8)
No	790 (39.7)	74 (37.4)	716 (39.9)	0.657	342 (41.2)

TABLE 1 (Continued)

	All infants *N* = 1994 no (%)	Any sensitization 6 months of age[a] *N* = 198 no (%)	Negative sensitization 6 months of age *N* = 1796 no (%)	*p*-value[e]	Negative IgE 3 months of age[b] *N* = 830 no (%)
Mother's educational level					
Preliminary school or High school	188 (10.3)	23 (12.3)	165 (10.1)		72 (9.7)
Higher education or PhD	1631 (89.7)	164 (87.7)	1467 (89.9)	0.352	674 (90.3)
Co-parent's educational level					
Preliminary school or High school	331 (19.1)	38 (21.1)	293 (18.8)		125 (17.7)
Higher education or PhD	1406 (80.9)	142 (78.9)	1264 (81.2)	0.458	582 (82.3)
Household income					
Low, <600 000 NOK/SEK per year	238 (13.2)	30 (16.4)	208 (12.9)		96 (13.0)
High, ≥600,000 NOK/SEK per year	1561 (86.8)	153 (83.6)	1408 (87.1)	0.183	641 (87.0)
Doctor-diagnosed allergic disease in mother[d]					
Yes	753 (41.2)	86 (45.7)	667 (40.7)		305 (40.6)
No	1076 (58.8)	102 (54.3)	974 (59.3)	0.178	446 (59.4)
Doctor-diagnosed allergic disease in father[d]					
Yes	643 (35.2)	80 (43.7)	563 (34.2)		263 (34.4)
No	1186 (64.8)	103 (56.3)	1083 (65.8)	0.011	501 (65.6)

Note: Eczema was defined as the clinical observation of eczematous lesions by trained physicians, excluding common differential diagnoses for eczema. Dry skin was defined as clinically observed dry skin, that is, the presence of scaling and roughness on the cheeks and/or extensors, by trained study personnel. High TEWL was defined as TEWL in the upper quartile (>9.4 g/m^2/h). The different denominators are due to missing data.

Abbreviation: TEWL, transepidermal water loss.

[a]Any sensitization was defined as at least one SPT reaction to egg, cow's milk, peanut, wheat, soy, birch, timothy grass, dog or cat, with a wheal diameter exceeding that of the negative control by at least 2 mm.

[b]Those infants included in the second aim had an allergen-specific IgE level <0.1 kU$_A$/l at 3 months of age.

[c]Household pet/s at 6 months or during the first 6 months of life.

[d]Self-reported information on doctor-diagnosed asthma, atopic dermatitis, allergic rhinitis, and/or food allergies.

[e]The *p*-value for independent samples *t*-tests and Chi-squared tests for differences in distributions between the group with any sensitization at 6 months of age (*N* = 198) and negative sensitization at 6 months of age (*N* = 1,796).

3 | RESULTS

The general characteristics of the 1,994 included infants and their parents are presented in Table 1. The included subjects were largely similar to those who did not have available SPT results, with some exceptions for parental demographic factors and caesarian section being slightly more common among non-included infants (Table S2 in the online repository).

Overall, at 6 months of age, 198 infants (9.9%) were sensitized to any allergen, 177 infants (8.9%) were sensitized to any food, and 39 infants (1.9%) were sensitized to any inhalant allergen. Among infants with negative IgE at 3 months of age, 87/830 (10.5%) infants had a positive SPT at 6 months of age. The distribution of positive SPT reactions at 6 months of age among the 1994 infants is described in detail in Table 2.

Among the 79 infants with positive IgE (>0.1 kU$_A$/l) at 3 months of age, 70 had an SPT reading at 6 months of age, and 6/70 infants (8.6%) had a positive SPT at 6 months of age.

3.1 | Eczema, dry skin, and high TEWL at 3 months and allergic sensitization at 6 months of age

The proportions of infants with allergic sensitization at 6 months stratified by eczema, dry skin, and high TEWL, respectively, are described in Figure 2 for all infants, as well as for the 830 infants who had negative IgE (<0.1 kU$_A$/L) to the Phadiatop Infant and wheat extract at 3 months of age.

The risk of any allergic sensitization at 6 months was significantly increased by observed eczema, dry skin, and high TEWL at

TABLE 2 Prevalence of allergic sensitization at 6 months of age in all infants, as well as according to presence of eczema, dry skin on the cheeks and/or extensors, and high TEWL at 3 months of age

	All infants *N* = 1994 no (%)	Eczema 3 months *N* = 247 no (%)	Dry skin 3 months *N* = 915 no (%)	High TEWL 3 months *N* = 426 no (%)
Any sensitization[a]	198 (9.9)	69 (27.9)	128 (14.0)	83 (19.5)
Food	177 (8.9)	65 (26.3)	114 (12.5)	73 (17.2)
Inhalant	38 (1.9)	7 (2.8)	21 (2.3)	21 (5.0)
Specific allergen				
Egg	131 (6.6)	52 (21.1)	90 (9.9)	56 (13.2)
Cow's milk	35 (1.8)	10 (4.1)	21 (2.3)	18 (4.3)
Peanut	47 (2.4)	20 (8.1)	33 (3.6)	20 (4.7)
Wheat	11 (0.6)	4 (1.6)	8 (0.9)	6 (1.4)
Soy	7 (0.4)	1 (0.4)	3 (0.3)	4 (0.9)
Birch	5 (0.3)	0 (0.0)	1 (0.1)	2 (0.5)
Timothy	4 (0.2)	1 (0.4)	0 (0.0)	2 (0.5)
Dog	16 (0.8)	4 (1.6)	10 (1.1)	11 (2.6)
Cat	20 (1.0)	3 (1.2)	11 (1.2)	8 (1.9)
Any polysensitization[b]	56 (2.8)	19 (7.7)	36 (3.9)	27 (6.3)
Any multisensitization[c]	17 (0.9)	3 (1.2)	7 (0.8)	11 (2.6)

Note: Differences in proportions of infants with any sensitization, comparing those with eczema, dry skin, and high TEWL, respectively, to all infants ($N = 1{,}994$), were statistically significant (p-values ≤ .001 for Chi-squared tests). Eczema was defined as the clinical observation of eczematous lesions by trained physicians, excluding common differential diagnoses for eczema. Dry skin was defined as clinically observed dry skin, that is, the presence of scaling and roughness on the cheeks and/or extensors, by trained study personnel. High TEWL was defined as TEWL in the upper quartile (>9.4 g/m^2/h).

Abbreviation: TEWL, transepidermal water loss.

[a]At least one SPT reaction to egg, cow's milk, peanut, wheat, soy, birch, timothy grass, dog or cat, with wheal diameter exceeding that of the negative control by at least 2 mm.

[b]At least two positive allergen-specific SPT reactions.

[c]Positive SPT reaction to at least one food allergen and at least one inhalant allergen.

3 months. Results among all 1,994 infants are given as crude ORs in Table S3A in this article's online repository. After adjusting for sex, any parental heredity regarding atopic disease, low household income, caesarian section, low GA, and intervention group allocation, the risk of allergic sensitization at 6 months increased, with an OR of 4.20 (95% CI 2.93–6.04) for eczema at 3 months ($n = 247$), 2.09 (95% CI 1.51–2.90) for dry skin ($n = 915$), and 3.67 (95% CI 2.58–5.22) for high TEWL ($n = 426$), see Figure 3A and Table S3A. Similar odds were observed for sensitization to food allergens, with adjusted OR illustrated in Figure 3C and presented in Table S3A, in this article's online repository.

Among non-sensitized infants at 3 months ($n = 830$), eczema, dry skin on the cheeks and/or extensors, and high TEWL at 3 months increased the risk of any incident sensitization, as well as sensitization to food allergens, at 6 months, with the highest OR observed for high TEWL, OR 6.06 (95% CI 3.34–11.00), as illustrated in Figure 3B and described in detail in Table S3B in the online repository.

The risk of polysensitization (sensitization to at least two allergens) was increased among infants who, at 3 months, had eczema, dry skin, and/or high TEWL (Table S3A and S3B in this article's online repository).

Seventeen infants were multisensitized at 6 months, that is, sensitized to both food and inhalant allergens. We found no significant association between eczema, dry skin, or high TEWL at 3 months and multisensitization (data not shown).

3.2 | Prediction of allergic sensitization at 6 months based on eczema, dry skin and high TEWL at 3 months of age

The predictive values among all 1994 infants as well as among the 830 infants with negative IgE at 3 months are presented in Table S4A and Table S4B, respectively, in the online repository.

Among infants who were IgE negative at 3 months, eczema at 3 months predicted any incident allergic sensitization at 6 months with 55.6% sensitivity, 68.1% specificity, and a ROC-AUC of 0.67 (95% CI 0.60–0.73). Dry skin at 3 months predicted any sensitization at 6 months with 65.3% sensitivity, 57.3% specificity, and a ROC-AUC of 0.64 (95% CI 0.57–0.71). High TEWL at 3 months predicted any sensitization at 6 months of age with 61.7% sensitivity, 78.1% specificity, and a ROC-AUC of 0.73 (95% CI 0.65–0.80). When

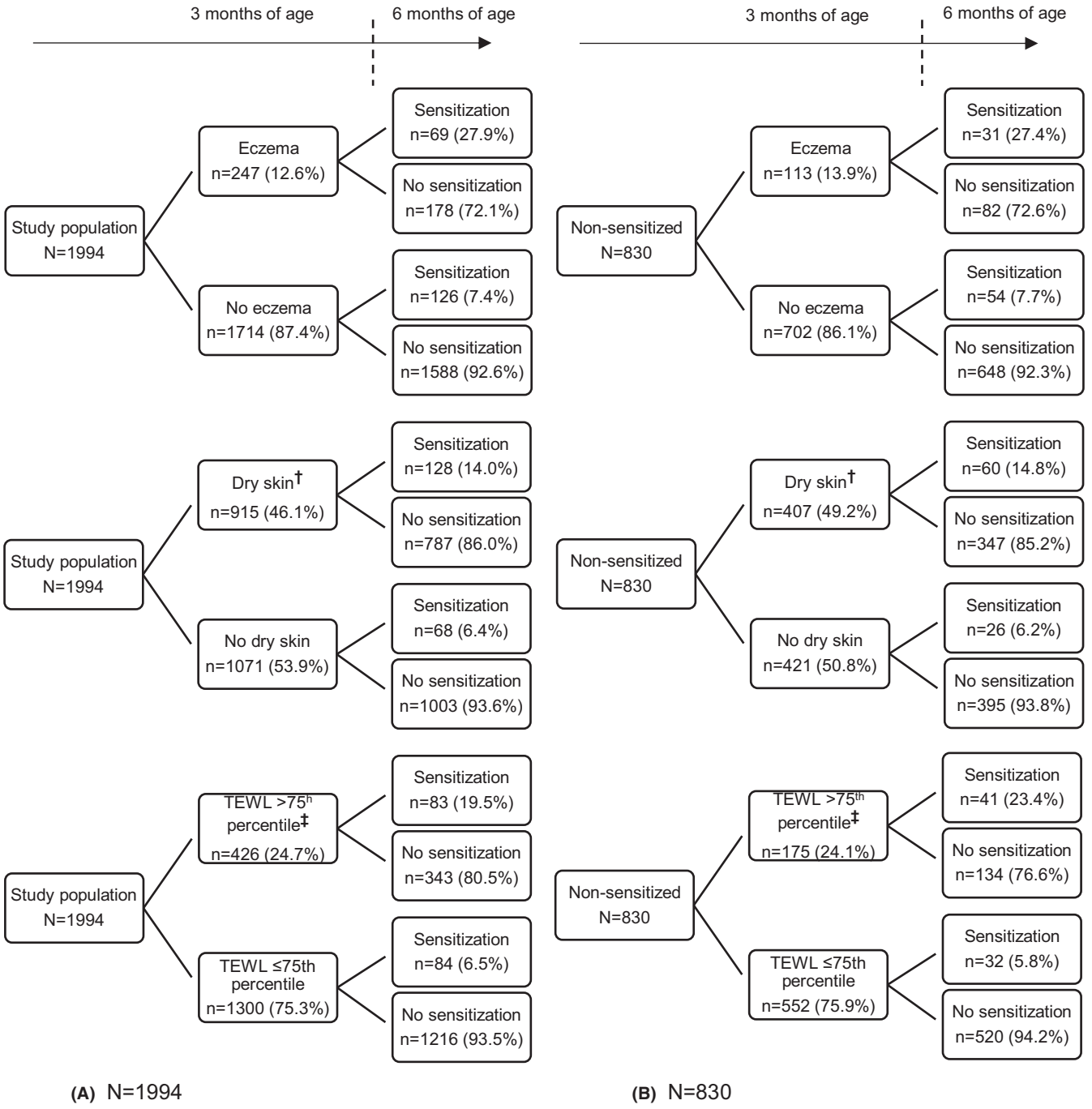


FIGURE 2 Illustration of the proportion of infants with allergic sensitization at 6 months in the presence of impaired skin barrier exposure at 3 months of age among (A) all infants (N = 1,994) and (B) infants with negative IgE (<0.1 kU_A/L) to the Phadiatop Infant and wheat extract at 3 months of age (N = 830). †Dry skin on cheeks and/or extensors, ‡>9.4 $g/m^2/h$ in the present study population

excluding those infants with eczema and/or dry skin at 3 months (56/175 infants with high TEWL had neither eczema, nor dry skin), high TEWL at 3 months predicted any sensitization at 6 months of age with 50.0% sensitivity, 85.6% specificity, and a ROC-AUC of 0.72 (95% CI 0.65–0.79). Finally, TEWL >90th percentile (>13.7 $g/m^2/h$ in the present study population) predicted any sensitization with 40.0% sensitivity, 91.9% specificity, and a ROC-AUC of 0.70 (95% CI 0.62–0.78).

When treating TEWL as a continuous variable, a TEWL of 9.3 $g/m^2/h$ at 3 months of age was the optimal threshold for differentiating positive from negative sensitization at 6 months of age, with a sensitivity of 60.3% and a specificity of 78.6% (AUC = 0.70 [95% CI 0.63–0.77], see Figure 4).

3.3 | Sensitivity analysis

The prevalence of any sensitization at 6 months of age among the 1,994 infants was slightly lower when using 3 mm as the cutoff value for SPT wheal diameter as compared to 2 mm (6.9% vs. 9.9%,

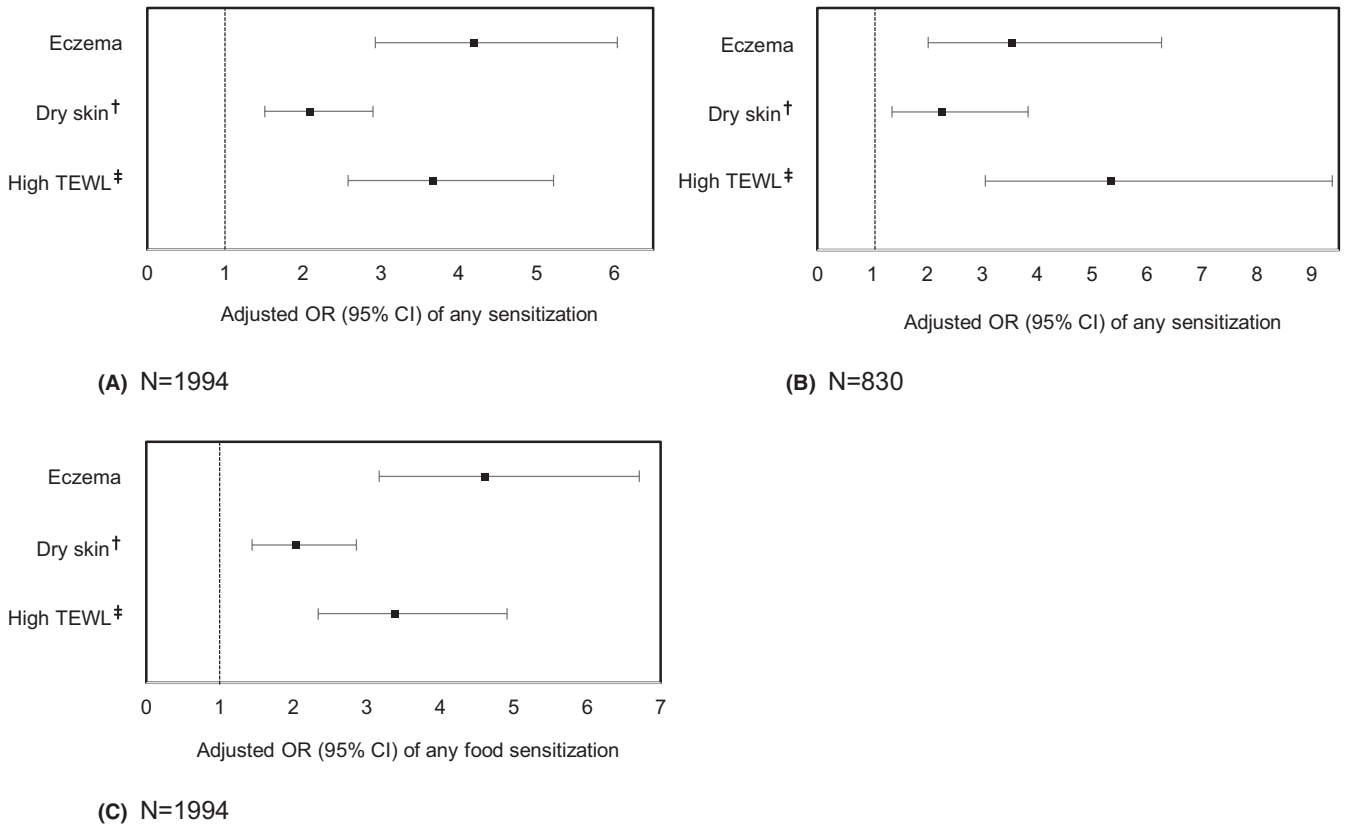


FIGURE 3 Adjusted OR (95% CI) of any sensitization at 6 months of age in (A) all infants (N = 1,994) and (B) the subsample of infants with negative IgE (<0.1 kU_A/L) to the Phadiatop Infant and wheat extract at 3 months of age, included in the analysis of the second aim (N = 830), according to presence of eczema, dry skin and high transepidermal water loss (TEWL) at 3 months of age. (C) Illustrates the adjusted OR (95% CI) of any food sensitization at 6 months of age in all infants (N = 1,994). The confounders adjusted for are sex, any parental heredity regarding atopic disease, low household income (<600,000 NOK/SEK per year), caesarian section, low gestational age (<37 weeks), and intervention group allocation. Any sensitization was defined as at least one SPT reaction to egg, cow's milk, peanut, wheat, soy, birch, timothy grass, dog, or cat, with a wheal diameter exceeding that of the negative control by at least 2 mm. †Dry skin on cheeks and/or extensors, ‡A TEWL value in the upper quartile (>9.4 $g/m^2/h$)

p = .001, see Table S5 in the online repository). Furthermore, all three impaired skin barrier exposures were associated with a slightly higher crude OR for any sensitization with 3 mm as compared to 2 mm (Table S6 in the online repository).

4 | DISCUSSION

In this general population study of almost 2000 infants in Norway and Sweden, eczema, dry skin, and high TEWL at 3 months of age increased the risk of any allergic sensitization, food sensitization, and polysensitization at 6 months of age. Eczema, dry skin, and an impaired skin barrier function, measured as TEWL, at 3 months of age predicted allergic sensitization at 6 months, with the highest predictive accuracy (ROC-AUC) observed for high TEWL. A TEWL value of 9.3 $g/m^2/h$ at 3 months in infants with no sensitization was the optimal threshold for differentiating between sensitization and no sensitization at 6 months of age.

The 9.9% prevalence of any allergic sensitization at 6 months of age in PreventADALL is higher than the 5.3% of 6-month-old infants with food sensitization, and 1.5% sensitized to inhalant allergens, observed in the Copenhagen Prospective Study on Asthma in $Childhood_{2000}$ high-risk birth cohort.[31] In the high-risk Melbourne Atopy Cohort study, 26% of 560 included infants with SPT at 6 months of age were sensitized to at least one allergen by that age.[32] Both these cohorts used the same definition of positive SPT reaction as in the present study.[31,32] Few large population-based studies have reported sensitization in early infancy. When using the stricter definition of a positive SPT reaction, that is, a wheal diameter of ≥3 mm, the 6.9% prevalence of sensitization at 6 months of age in PreventADALL is higher than the 3.5% value for the 404 infants included in the Danish Allergy Research Centre birth cohort study, which analyzed infants born from 1998 to 1999.[33] The majority of the sensitized infants in the present study were sensitized to only one allergen, most of them to a food allergen, which agrees well with previous studies of sensitization patterns in infants in their first year of life.[33–35]

Our finding of a significant association between eczema at 3 months of age and allergic sensitization at 6 months of age is supported by other comparable studies.[6,7,36] The Australian

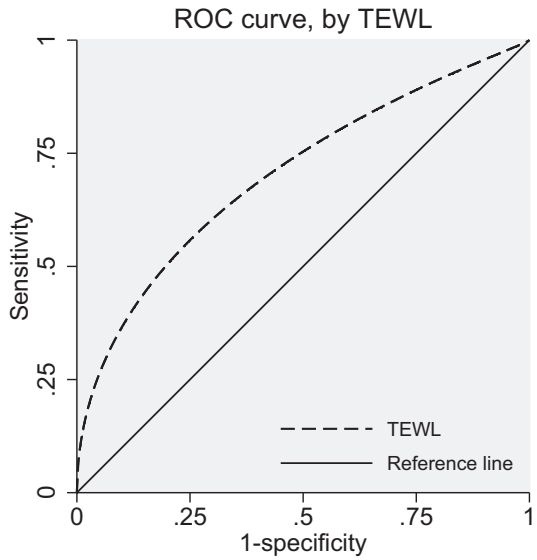


FIGURE 4 ROC curve, AUC 0.70 (95% CI 0.63–0.77), of optimal thresholds for transepidermal water loss (TEWL) at 3 months of age, as a continuous variable, for differentiating between allergic sensitization and no allergic sensitization at 6 months of age. Allergic sensitization was defined as at least one SPT reaction to egg, cow's milk, peanut, wheat, soy, birch, timothy grass, dog, or cat, with a wheal diameter exceeding that of the negative control by at least 2 mm ($N = 830$)

HealthNuts study demonstrated that eczema was a strong risk factor for food sensitization and food allergies in infancy.[6] Also, the international study Early Prevention of Asthma in the Atopic Child reported a strong association between eczema and food sensitization in young children,[7] and the Enquiring about Tolerance (EAT) trial found a significant association between eczema at 3 months and food allergy between 1 and 3 years of age.[36]The Melbourne Atopy Cohort study suggested that eczema with an onset before 6 months of age predicted incident sensitization both at 1 and 2 years of age.[37]

The increased risk of allergic sensitization by dry skin has, to the best of our knowledge, not been reported in early infancy. We have previously shown that dry skin in at least one of eleven predefined skin areas, had a prevalence of 59% in infants at 3 months of age (the cheeks and extremities' extensor surfaces being the most common areas).[5]Dry skin without the presence of eczema doubled the risk of eczema 3 months later in our cohort.[14] These findings indicate that dry skin in infancy is common and may also predict later disease. Our finding of dry skin being associated with an increased risk of sensitization is supported by the theory that a reduced epithelial barrier plays a crucial role in immune responses and the initiation of allergic diseases.[38]

Our finding of TEWL in the upper quartile as well as TEWL >90th percentile predicting allergic sensitization is in agreement with a French study including 59 infants with AD and 30 controls reporting increased likelihood of sensitization to two or more inhalant allergens by increasing TEWL.[39]However, our mean TEWL of 8.3 (±SD 5.9) g/m^2/h at 3 months was lower than that of the French study reporting a mean of 11.1 g/m^2/h in control infants aged 3–12 months without AD,[39]but similar to the reported 7.06 ± SD 3.41 g/m^2/h in full-term infants at birth.[40]

Our data showed that 10.5% of non-sensitized infants developed sensitization between 3 and 6 months of age, which is novel information regarding sensitization incidence at this early age. We have further demonstrated a clinical phenotype, allergic sensitization at 6 months of age, that was preceded by the early presentation of eczema, dry skin, and impaired skin barrier function, irrespective of the presence of clinically symptomatic skin barrier impairment. This is in line with previous observations of epicutaneous sensitization, suggesting a role for an impaired skin barrier in early sensitization to allergens, where the skin can be a potential target for strategies aiming to prevent food allergies.[9,10]Although our data do not extend sufficiently into childhood to shed light on future diseases reflected in the atopic march concept,[1] they suggest the potential of identifying infants who are at a high risk of developing clinically relevant sensitization and future allergic disease. Furthermore, skin barrier impairment may contribute to the burden of disease at a young age, and therefore, these infants may be targets for allergic disease prevention.[1,8,9,41]Future analyses in the PreventADALL study will assess the role of impaired skin barrier exposures in relation to food allergy and asthma development later in childhood.

The large sample size and the fact that the study is based on general populations from both Norway and Sweden is a major strength, as compared to other studies in the research field that are limited to children at a high risk of allergic disease.[2,7,42,43] Other strengths of the study include the thorough clinical assessments performed at the 3-month visit, including objective observation of eczema and dry skin by trained nurses and physicians, as well as TEWL measurement, which is a well-established method of assessing skin barrier function.[15]Also, by excluding infants known to be sensitized at 3 months of age from the analysis of the second aim, we could eliminate possible reverse causation between allergic sensitization and pre-specified exposures as a potential underlying mechanism influencing the interpretation of the results. Our study represents infants recruited from a general population, although with a somewhat higher educational level than a non-selected general Scandinavian population, and few ethnic minority subjects were enrolled.[11]The fact that 75% of the infants were randomized to skin and/or food intervention may limit the generalizability of our results, although the skin intervention has not been shown to affect AD development by 12 months of age.[12]Severity of dry skin was recorded in line with the principles of DASI. However, we did not use corneometry, which could be a limitation as it is an objective assessment of dry skin. In addition, the finding of the exposures being only moderate predictors of sensitization at 6 months of age in our study, although slightly higher predictive values were observed among the 830 infants with negative IgE at 3 months compared to all 1994 infants, may be due to the short time-span of 3 months in this section of the analysis.

In conclusion, this study demonstrates that eczema, dry skin on the cheeks and/or extensors, and high TEWL at 3 months of age precede and predict allergic sensitization, mainly to food allergens, at 6 months of age. Our results suggest that clinical features of atopic dermatitis, dry skin and impaired skin barrier function can be used to target infants who may be particularly relevant for allergy prevention strategies.

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CONFLICT OF INTEREST

A Asarnoj reports personal fees from Orion Pharma, Novartis, and MEDA, outside this work. MP Borres is an employee of Thermo Fisher Scientific. KC. Lødrup Carlsen reports an honorarium to the institution provided by Thermo Fisher Scientific for a symposium talk by the author in 2019; EM Rehbinder reports honoraria for lectures from Sanofi-Genzyme, Novartis, Leo-Pharma, Perrigo and The Norwegian Asthma and Allergy Association, and M van Hage reports personal fees from Thermo Fisher Scientific, outside this work. The other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

S Wärnberg Gerdin participated in design of the study, analysis and interpretation of data, and manuscript writing. A Lie contributed to the data analysis and critically revised the manuscript. A Asarnoj contributed to data collection and critically revised the manuscript. MP Borres contributed to analysis and interpretation of data, and critically revised the manuscript. KC Lødrup Carlsen—principal investigator of the PreventADALL study—contributed to the design of the study, and critically revised the manuscript. M Färdig contributed to data collection and critically revised the manuscript. JR Konradsen contributed to analysis and interpretation of data, and critically revised the manuscript. C Monceyron Jonassen—local principal investigator in Østfold—contributed to the conception and design of the PreventADALL study and critically revised this manuscript. C-A Olsson Mägi contributed to data collection and critically revised the manuscript. EM Rehbinder—local principal investigator in Oslo—contributed to the study design, data collection, and critically revised the manuscript. K Rudi contributed to the conception and design of the PreventADALL study and critically revised this manuscript. HO Skjerven—co-principal investigator of the PreventADALL study—critically revised this manuscript. AC Staff contributed to the conception and design of the PreventADALL study and critically revised this manuscript. C Söderhäll contributed to the conception and design of the PreventADALL study and critically revised this manuscript. SG Tedner contributed to data collection and critically revised the manuscript. M van Hage contributed to analysis and interpretation of data, and critically revised the manuscript. R Vettukattil—principal investigator bioinformatics—critically revised this manuscript. B Nordlund—local principal investigator of the PreventADALL study in Stockholm—participated in design of the study, analysis and interpretation of data, and manuscript writing. All listed authors approved the final version of the manuscript before submission and agreed to be accountable for all aspects of the work.

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