

# The Effect of Early Food Introduction and Skin Emollients on Pollen Sensitization: A Randomized Trial (PreventADALL) Sub-Study



Sabina Wärnberg Gerdin, MSc<sup>a,b</sup>, Håvard O. Skjerven, PhD<sup>d,e</sup>, Jon R. Konradsen, PhD<sup>a,b</sup>, Magnus P. Borres, PhD<sup>o,f</sup>, Berit Granum, PhD<sup>g</sup>, Christine Monceyron Jonassen, PhD<sup>h,i</sup>, Marissa LeBlanc, PhD<sup>i,k</sup>, Morten Nilsen, PhD<sup>l</sup>, Eva Maria Reh binder, PhD<sup>d,m</sup>, Knut Rudi, PhD<sup>l</sup>, Anne Cathrine Staff, PhD<sup>d,n</sup>, Cilla Söderhäll, PhD<sup>a,b</sup>, Marianne van Hage, PhD<sup>o,p</sup>, Riyas Vettukattil, PhD<sup>c,d</sup>, Karin C. Lødrup Carlsen, PhD<sup>c,d</sup>, and Björn Nordlund, PhD<sup>a,b</sup>  
Stockholm and Uppsala, Sweden; and Oslo, Kalnes, and Ås, Norway

**What is already known about this topic?** An impaired skin barrier early in life increases the risk of allergic sensitization. The route of exposure to pollens that may induce initial sensitization to pollens remains largely unknown.

**What does this article add to our knowledge?** This study provides important insights into the potential disadvantages of frequent emollient use in healthy infants, and later pollen sensitization as a possible consequence of this.

**How does this study impact current management guidelines?** Interventions aimed at restoring the skin barrier function in early infancy could offer a strategy to prevent respiratory allergies.

**BACKGROUND:** Pollen sensitization may be directed toward proteins also found in plant foods.

**OBJECTIVE:** We explored whether early food introduction and skin emollients prevented birch and grass sensitization at age 3

years and whether the effect was mediated by skin barrier function or modified by season of birth.

**METHODS:** In the population-based, randomized, controlled Preventing Atopic Dermatitis and Allergy in Children trial,

<sup>a</sup>Lung and Allergy Department for Children, Astrid Lindgren's Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

<sup>b</sup>Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>c</sup>Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

<sup>d</sup>Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>e</sup>Thermo Fisher Scientific, Uppsala, Sweden

<sup>f</sup>Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

<sup>g</sup>Department of Chemical Toxicology, Norwegian Institute of Public Health, Oslo, Norway

<sup>h</sup>Center for Laboratory Medicine, Østfold Hospital Trust, Kalnes, Norway

<sup>i</sup>Department of Virology, Norwegian Institute of Public Health, Oslo, Norway

<sup>j</sup>Oslo Centre for Biostatistics and Epidemiology, University of Oslo, Oslo, Norway

<sup>k</sup>Department of Method Develop and Analytics, Norwegian Institute of Public Health, Oslo, Norway

<sup>l</sup>Department of Chemistry, Biotechnology, and Food Science, Norwegian University of Life Sciences, Ås, Norway

<sup>m</sup>Department of Dermatology, Oslo University Hospital, Oslo, Norway

<sup>n</sup>Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway

<sup>o</sup>Department of Medicine Solna, Division of Immunology and Respiratory Medicine, Karolinska Institutet and Karolinska University Hospital, Solna, Stockholm, Sweden

<sup>p</sup>Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden

The PreventADALL study has received support from several public and private funding bodies: the Regional Health Board South East, the Norwegian Research Council, Oslo University Hospital, the University of Oslo, Health and Rehabilitation Norway, the Foundation for Healthcare and Allergy Research in Sweden—Vårdalstiftelsen, the Swedish Asthma and Allergy Association's Research Foundation, the Swedish Research Council—the Initiative for Clinical Therapy Research, the Swedish Heart-Lung Foundation, SFO-V Karolinska Institutet,

Østfold Hospital Trust, the European Union (MeDALL project), the Norwegian Association of Asthma and Allergy, the Kloster foundation, Thermo Fisher Scientific (through supplying allergen reagents), Først Medical Laboratory, Oslo, Norway (through performing IgE analyses), Norwegian Society of Dermatology and Venereology, Arne Ingel's legat, Forte, Swedish Order of Freemasons Foundation Barnhuset, the Sven Jerring Foundation, the Hesselman foundation, the Magnus Bergwall Foundation, the Konsul Th C Bergh's Foundation, Her Royal Highness Crown Princess Lovisa's Association for Child Health Care, Cancer and Allergy Foundation, Region Stockholm (ALF project), KI Foundations & Funds (KID), and the Pediatric Research Foundation at Astrid Lindgren Children's Hospital.

Conflicts of interest: E.M. Reh binder has received honoraria for lectures from Sanofi Genzyme, Leo Pharma, Novartis, the Norwegian Psoriasis and Eczema Association, and the Norwegian Asthma and Allergy Association. M. van Hage has received lecture fees from Thermo Fisher Scientific and AstraZeneca outside the submitted work. C. Söderhäll has received nonfinancial support from Thermo Fisher Scientific outside the submitted work. K.C. Lødrup Carlsen has received honorarium from Thermo Fisher Scientific for symposium presentation. M. LeBlanc reports personal fees from Merck Sharp & Dohme. M. Nilsen has received honoraria for lectures from Nestlé. C. Monceyron Jonassen has received honoraria for lectures from the Norwegian Medical Association outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 22, 2024; revised manuscript received and accepted for publication March 25, 2025.

Available online April 7, 2025.

Corresponding author: Sabina Wärnberg Gerdin, MSc, Department of Women's and Children's Health, Karolinska Institutet, KPE Lung Allergi Barn, Karolinska vägen 37A, SE-171 64 Solna, Sweden. E-mail: [sabina.warnberg.gerdin@ki.se](mailto:sabina.warnberg.gerdin@ki.se). 2213-2198

© 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2025.03.046>

*Abbreviations used**AD*-A atopic dermatitis*PreventADALL*-Preventing Atopic Dermatitis and Allergy in Children*SPT*-Skin prick test*TEWL*-Transepidermal water loss

information on allergic sensitization by age 3 years was available in 2,066 children. Newborns were randomized (1:1:1:1) to no (controls); to food (tastes of peanut, cow's milk, wheat, and egg from 3 months) or skin (oil baths and facial cream from 2 weeks); or to both interventions. Sensitization was defined as specific IgE 0.1 kU<sub>A</sub>/L or greater and/or skin prick test wheal 3 mm or greater. A mediator analysis assessed the skin intervention's effect through transepidermal water loss at 3 months. An interaction analysis estimated effect modification by month of birth.

**RESULTS:** At age 3 years, 117 of 1,492 children (7.8%) were sensitized to birch and 40 of 1,482 children (2.7%) to timothy. Compared with controls, crude odds ratio (95% CI) in the food, skin, and combined intervention groups, respectively, was 1.10 (0.63-1.93), 2.38 (1.43-3.95), and 0.70 (0.37-1.34) for birch, and 0.58 (0.21-1.60), 1.73 (0.77-3.91), and 1.00 (0.40-2.49) for grass sensitization. A significant indirect effect of the skin intervention through transepidermal water loss was observed, but there was no significant modification by month of birth for either intervention.

**CONCLUSIONS:** Early food introduction did not affect the risk of pollen sensitization. Infants with skin intervention had increased risk only of birch sensitization, mediated by reduced skin barrier function in early infancy. © 2025 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2025;13:1325-34)

**Key words:** Allergic Sensitization; Food introduction; Inhalant allergens; Skin barrier function; Skin emollients

## INTRODUCTION

Pollen allergy, causing seasonal allergic symptoms, is a significant health concern.<sup>1,2</sup> With no primary prevention strategies available, early life presents a unique opportunity to modulate immune responses and promote tolerance against pollen allergens.<sup>3</sup> The risk of allergy development is dependent on the route of exposure to the sensitizing allergen. An impaired skin barrier increases the risk of allergic sensitization<sup>4</sup> and allergy.<sup>5</sup> Conversely, oral exposure to food allergens early in life reduces the risk of developing allergic sensitization to foods and food allergy.<sup>6-8</sup> However, the route of exposure to pollens that may induce initial sensitization to pollens remains largely unknown.

Pollen allergy frequently induces secondary allergic reactions to plant-derived foods through cross-reactive IgE antibodies.<sup>2,9</sup> The cross-reactivity between birch and peanut, for instance, is explained by primary sensitization to the major birch allergen component Bet v 1 and the cross-reactive peanut allergen component Ara h 8, both of which belong to pathogenesis-related protein family number 10.<sup>9</sup> A study of

peanut-sensitized children and adolescents in a birch-endemic area indicated that protein family number 10 sensitization was equally common in peanut-tolerant and peanut-allergic individuals.<sup>10</sup> Another example of cross-reactivity involves timothy grass and wheat, both originating from the common Poaceae family. A potential strategy for preventing pollen allergy could involve leveraging the cross-reactive effects between food and pollen allergens.

A disrupted skin barrier, as in atopic dermatitis (AD), is often the first step in a commonly seen progression of allergic diseases, called the atopic march.<sup>11</sup> Because emollients are the baseline treatment of AD, there has been significant interest in studying the effect of emollients on primary prevention of AD<sup>12,13</sup> and food allergy.<sup>14-16</sup> However, a Cochrane review and meta-analysis composed of 11 randomized controlled trials (RCTs), including the Preventing Atopic Dermatitis and Allergy in Children (PreventADALL) study, concluded that emollients are most likely ineffective in preventing AD and may increase the risk of food allergy.<sup>17</sup> In the PreventADALL study, frequent mineral-based oil baths from age 2 weeks resulted in higher transepidermal water loss (TEWL) both at age 3 months and over time through the first year of life,<sup>18</sup> which is in line with several other studies.<sup>19-21</sup> The general population Enquiring About Tolerance study showed increasing sensitization rates to aeroallergens at age 3 years with increasing moisturization frequency at age 3 months, in a dose-response manner.<sup>21</sup> However, whether emollients have a role in the development of pollen sensitization by affecting the skin barrier function remains unknown.

In line with other studies,<sup>8,22</sup> the PreventADALL study has demonstrated a reduced risk of peanut allergy and peanut sensitization at age 3 years, by small tastes of peanut, cow's milk, wheat, and egg, from age 3 months.<sup>7</sup> In the current study, our hypothesis was that optimizing the skin barrier, alone or combined with introducing cross-reactive foods, influences the risk of pollen sensitization. Thus, this study aimed primarily to investigate the effect of early food introduction, including peanut and wheat, and skin emollient use on birch and timothy grass pollen sensitization at age 3 years. Secondly, it aimed to determine whether the skin intervention effect was mediated by skin barrier function or whether either intervention effect was modified by the season of birth.

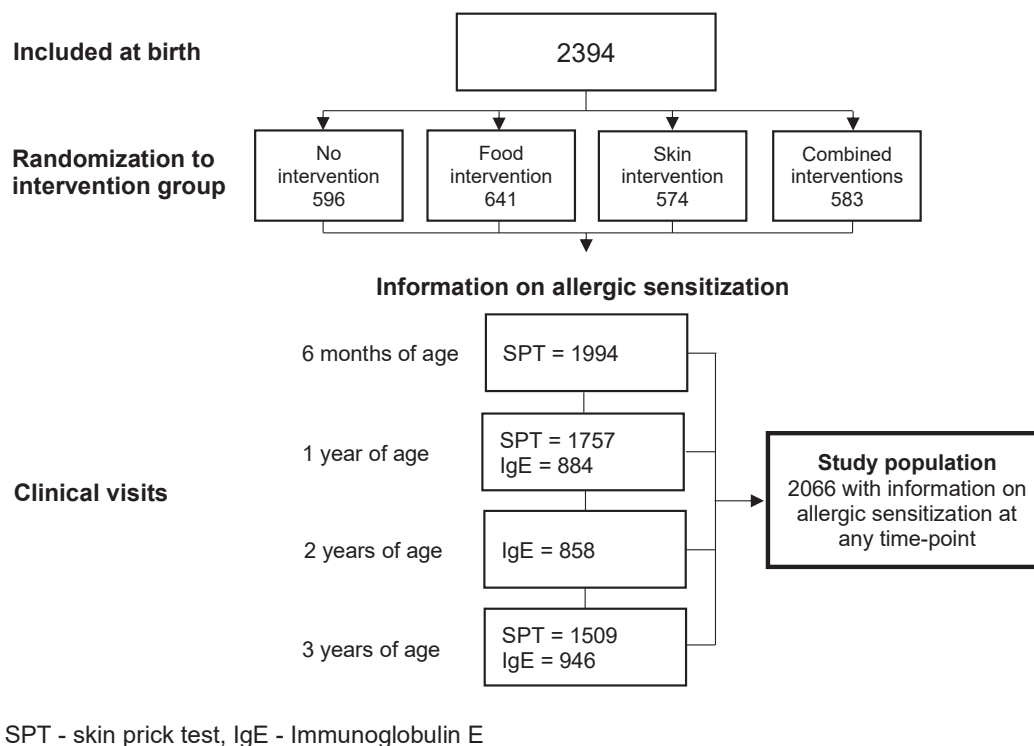
## METHODS

The PreventADALL trial design, randomization, and procedures are described in detail elsewhere<sup>7,23</sup> and are briefly outlined here. We obtained informed consent from the parent(s) at study enrollment.

The PreventADALL study was ethically approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and the Swedish Ethical Review Authority in Stockholm (2014/2242-31/4 and 2018/1437-32), and is registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT02449850).

## Study design

The PreventADALL study is a 2 × 2 factorially designed cluster-RCT including 2,397 mother-child pairs recruited antenatally, with the newborn infants allocated in a 1:1:1:1 ratio to no intervention (controls), early food introduction or skin emollient intervention, or both interventions. The cluster randomization was based on 92 geographic areas and eight 3-month time blocks.<sup>7,23</sup> Three participants later withdrew consent. Recruitment, inclusion, and clinical investigations, including assessment of skin barrier function and



**FIGURE 1.** Flowchart of the study population including 2,066 children from the Preventing Atopic Dermatitis and Allergy in Children study.

allergic sensitization, were conducted in Norway (Oslo University Hospital and Østfold Hospital Trust) and Sweden (Karolinska Institutet).

### Participants, randomization, and masking

Pregnant women were invited at their routine ultrasound investigation at 18 weeks of pregnancy (range, 16-22 weeks). Healthy newborns, gestational age at least 35.0 weeks, were randomized to one of the four intervention groups. The allocation was done by computer-generated cluster randomization based on geographic residential area and time block.<sup>7</sup> Study personnel conducting clinical examinations of the children were blinded to the intervention group allocation.

This exploratory PreventADALL subanalysis included 2,066 of 2,394 randomized children with information on allergic sensitization (specific IgE [s-IgE] and/or skin prick test [SPT]) to birch and/or timothy grass at age 6 months and 1, 2, and/or 3 years. Figure 1 presents a flowchart of the study population.

### Procedures

**Interventions.** The parents of infants in the control (no intervention) group were given no additional advice on skin care or food introduction other than to follow the general national guidelines and recommendations.

The food intervention consisted of the introduction of peanut, milk, wheat, and egg between ages 3 and 4 months, complementary to regular feeding. The foods were introduced as small tastes, one at a time with 1-week intervals, and were given at least 4 days/week until age 6 months, but they were encouraged to be part of the infant's diet after the intervention period.

The skin intervention consisted of oil baths (oil consisting of paraffinum liquidum and 1% trilaureth-4-phosphate produced specifically for PreventADALL; 0.5 dL/8 L water) and paraffin-based facial cream (Ceridal, GlaxoSmithKline Consumer Healthcare, Philadelphia, Pa) from age 2 weeks through age 8 months, at least 4 days/week. Parents were told not to use soaps.

**Data sources.** The children attended clinical investigations at age 3 and 6 months and at age 1, 2, and 3 years.

Information on background characteristics was available from electronic questionnaires, filled in by the mother at around 18 and 34 weeks of gestation, then every 3 months during the child's first year of life and subsequently every 6 months until age 3 years. Adherence to the interventions was reported as the number of days each week per intervention. This was filled in weekly in electronic diaries from age 2 to 26 weeks by parents in all four intervention groups.<sup>7</sup>

Skin barrier function, assessed by TEWL at age 3 months, is reported as the mean of three measurements on the left lateral upper arm, using an open chamber DermaLab USB (Cortex, Hadsund, Denmark).<sup>24,25</sup> Parents were told not to bathe their children within 24 hours before the clinical visit, and measurements were standardized to room temperature between 20 and 25 degree Celsius, in line with general recommendations.<sup>25,26</sup>

Skin prick tests (Soluprick ALK-Abelló, Hørsholm, Denmark) assessed allergic sensitization to birch and timothy grass, among other allergens, at the 6-months and 1- and 3-year clinical visits.<sup>27</sup> Blood sampling for IgE analyses were performed at the 1-, 2-, and 3-year clinical visits. Sera were analyzed against the panel Phadiatop Infant (at 1 year) (Thermo Fisher Scientific, Uppsala, Sweden) or

Phadiatop (at ages 2 and 3 years) (Thermo Fisher Scientific, Uppsala, Sweden). Specific IgEs to single allergen extracts were analyzed if the panel test was positive ( $\geq 0.1$  kU<sub>A</sub>/L). Allergen extracts were supplied by Thermo Fisher Scientific (Uppsala, Sweden), and analyses were performed by Frst Laboratory in Oslo (Norway).

## Outcomes

Primary outcomes were allergic sensitization (s-IgE  $\geq 0.1$  kU<sub>A</sub>/L and/or SPT wheal  $\geq 3$  mm) to birch pollen and timothy grass, respectively, at age 3 years.

Secondary outcomes were allergic sensitization by age 3 years of age (at any of time points including age 6 months or 1, 2, and/or 3 years) to birch pollen and timothy grass, respectively, defined as s-IgE 0.1 kU<sub>A</sub>/L or greater (at age 1, 2, and/or 3 years) and/or SPT wheal 2 mm or greater (at ages 6 months and 1 year,<sup>28-30</sup> and a wheal greater than 3 mm at age 3 years).<sup>7</sup> Another secondary outcome was allergic sensitization using an s-IgE cutoff of 0.35 kU<sub>A</sub>/L.

A potential mediator of the skin intervention effect was skin barrier function (TEWL) at age 3 months<sup>18</sup> and the potential effect modifier was the month of birth.

## Statistical analysis

We used Stata/MP software (version 16, StataCorp LLC, TX) for all analyses. Categorical data are presented as numbers and percentages. Continuous data are presented as means, SDs, and range. Pearson  $\chi^2$  tests, Fisher exact tests, and independent-samples *t* tests for differences in distributions or means between groups were conducted, as appropriate.

We conducted the primary analysis with a modified intention-to-treat (mITT) approach. To compare the risk of allergic sensitization at age 3 years between the intervention groups, simple logistic regression modelling was performed. The intervention group was included as the independent variable, with one category for each intervention group. The no intervention group (controls) was used as the comparison group. We assessed interactions between the two interventions on allergic sensitization at age 3 years to birch and timothy grass, respectively, in separate models through adjusted logistic regression, with the food and skin intervention as two independent binary variables, followed by the interaction term between the skin and food intervention.

Descriptive statistics presented the prevalence of allergic sensitization according to season of birth, born during the pollen season or not. To estimate different intervention effects on allergic sensitization by month of birth, an interaction term between birth month (categorical variable with one category/mo) and intervention group allocation was added in the primary analysis logistic regression models, adjusted for birth month.

The clustering variables were not included in the logistic regression models. This was owing to failure of the mixed effects logistic regression models, with clusters by residential postal code and randomization time period as random effects, to converge. Therefore, we omitted the random effects from the models.

A mediator analysis using a generalized structural equation model assessed the direct, indirect, and total effect of the skin intervention through TEWL at age 3 months on allergic sensitization at age 3 years (see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

We conducted longitudinal modeling in terms of interval-censored Weibull proportional hazards regression for the secondary outcome of allergic sensitization by age 3 years (from age 6 months

to 3 years), reported as the hazard ratio (95% CI). The Cox-Snell residuals versus the residuals themselves were plotted to assess the fit of the parametric survival model visually.

We performed two sensitivity analyses to analyze the effect of the interventions on the risk of allergic sensitization. The first included all individuals with data on IgE and/or SPT at all time points (*n* = 642 for birch and 638 for timothy grass), and then a per-protocol group included individuals with full protocol adherence to the skin and food interventions. Defined as reported baths with oil additive and the Cerdal facial creme for a mean of at least 3.5 days per week in 16 of the first 25 first weeks of life, and as reported intake of the food for minimum 3-5 days/week in at least 5 weeks, between age 19 and 26 weeks.

**Handling of missing data.** Across all four intervention groups, the pattern of missing data concerning allergic sensitization had a similar structure (see Figure E2, *A* and *B* in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). No imputation for missing data was performed.

## RESULTS

There were no statistically significant differences among the four intervention groups regarding the background characteristics of the included children, except it was less common in the food intervention group for the child to be the mother's firstborn compared with the other groups (Table I). When we compared the children with available data on allergic sensitization up to age 3 (*n* = 2,066) with those with missing information (*n* = 328), the included children were less frequently delivered via caesarian section, and their caregivers tended to have higher educational levels (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Sensitization information at all time points (age 6 months and 1, 2, and 3 years) was available in 642 children.

### Allergic sensitization prevalence and patterns

At age 3 years, birch sensitization was found in 7.8% of children (117 of 1,492) and timothy grass sensitization in 2.7% (40 of 1,482). Polysensitization to birch and timothy at age 3 years was found in 2.1% of children (31 of 1,482). At ages 6 months, 1 year, and 2 years, respectively, birch sensitization was present in 0.3%, 1.0%, and 2.6% of children (see Table E2A in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) and grass sensitization in 0.2%, 1.7%, and 1.7% (Table E2B).

Among the children with birch sensitization at any time point (*n* = 55 of 642 children with information at all time points), 27.3% (15 of 55) were sensitized first at age 2 years, and 58.2% (32 of 55) first at age 3 years. Conversely, transient timothy grass sensitization, appearing solely at age 1 year, was observed in 12 of 33 children (36.4%) who were sensitized to grass at any time point.

### Effect of food and skin interventions on allergic sensitization

Birch pollen sensitization was significantly more common in the skin intervention group (13.9%) compared with the other groups (4.6% to 7.0%) at age 3 years (Table E2A). Timothy grass sensitization (s-IgE  $\geq 0.35$  kU<sub>A</sub>/L) was significantly less common in the food intervention group at age 1 (0.0%) and 3 years (0.8%) compared with controls (2.7% and 3.3%, respectively) (Table E2B). Compared with controls, the crude odds ratios (ORs) and 95% CIs for birch sensitization at age 3 years

**TABLE I.** Background characteristics of study population (n = 2,066) according to intervention group allocation in Preventing Atopic Dermatitis and Allergy in Children study

Characteristics	No intervention (n = 556), n (%)	Food intervention (n = 559), n (%)	Skin intervention (n = 475), n (%)	Combined interventions (n = 476), n (%)
<b>Sex</b>				
Boy	288 (51.8)	304 (54.4)	235 (49.5)	262 (55.0)
Girl	268 (48.2)	255 (45.6)	240 (50.5)	214 (45.0)
<b>Gestational age at birth, d</b>				
Mean ± SD	280.6 ± 9.7	280.5 ± 9.5	279.7 ± 9.2	281.0 ± 9.2
Range	245-297	250-298	253-297	247-296
<b>Study country</b>				
Norway	453 (81.5)	430 (76.9)	372 (78.3)	360 (75.6)
Sweden	103 (18.5)	129 (23.1)	103 (21.7)	116 (24.4)
<b>Delivery method</b>				
Vaginal delivery	469 (84.4)	478 (85.5)	399 (84.2)	389 (82.1)
Caesarean delivery	87 (15.6)	81 (14.5)	75 (15.8)	85 (17.9)
<b>Firstborn child of mother</b>				
Yes	340 (61.2)	307 (55.1)	298 (62.9)	303 (63.7)
<b>Maternal educational level</b>				
Primary school or high school only	51 (10.1)	53 (10.4)	43 (10.2)	47 (10.7)
Higher education or PhD	456 (89.9)	457 (89.6)	380 (89.8)	391 (89.3)
<b>Paternal educational level</b>				
Primary school or high school only	91 (18.7)	88 (18.4)	76 (18.9)	87 (20.4)
Higher education or PhD	397 (81.4)	390 (81.6)	325 (81.0)	339 (79.6)
<b>Doctor diagnosed allergic disease*</b>				
Maternal	219 (42.9)	220 (42.9)	171 (40.1)	174 (39.6)
Paternal	180 (34.6)	181 (36.3)	154 (35.5)	149 (34.1)

Different denominators are due to missing data.

\*Doctor-diagnosed asthma, atopic dermatitis, allergic rhinitis, and/or food allergy at enrollment (self-reported).

were 1.10 (0.63-1.93) in the food intervention group, 2.38 (1.43-3.95) in the skin intervention group, and 0.70 (0.37-1.34) in the combined interventions group. For timothy grass sensitization at age 3 years, the corresponding ORs (95% CI) were 0.58 (0.21-1.60), 1.73 (0.77-3.91), and 1.00 (0.40-2.49). Table E3A and B (in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) lists the crude ORs at each time point. A significant interaction ( $P < .01$ ) between the two interventions was observed at age 3 years for the outcome of birch sensitization, but not for timothy grass.

The hazard ratios (95% CI) for allergic sensitization to birch by age 3 years in the food, skin, and combined intervention groups, respectively, compared with controls, were 1.10 (0.68-1.80), 2.11 (1.35-3.31), and 0.78 (0.45-1.36), and for timothy grass sensitization by age 3 years were 0.65 (0.31-1.34), 1.70 (0.93-3.09), and 1.47 (0.79-2.72). The corresponding plots of the hazard regression models are displayed in Figure E3, A and B (in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

### Transepidermal water loss and allergic sensitization

Transepidermal water at age 3 months was significantly higher in the skin intervention group compared with the control group ( $P < .001$ ), food group ( $P < .001$ ), and combined interventions group ( $P = .0038$ ) (see Table E4 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Birch-sensitized children at age 3 years had significantly higher TEWL ( $\text{g}/\text{m}^2$  per h [95% CI]) at age 3 months (11.4 [9.8-12.9]) compared with non-sensitized children (8.1 [7.8-8.4];  $P < .001$ ), as we also observed in children sensitized to timothy at age 3 years (12.9 [9.5-16.3]),

compared with non-timothy sensitized children (8.2 [7.9-8.5];  $P < .001$ ). Among sensitized children at age 3 years, the skin and combined intervention groups had the highest TEWL at 3 months compared with controls (Figure 2 and Table E4), with a significant indirect effect, but not a direct or total effect, through TEWL at 3 months on allergic sensitization at 3 years (Table II).

### Season of birth and allergic sensitization

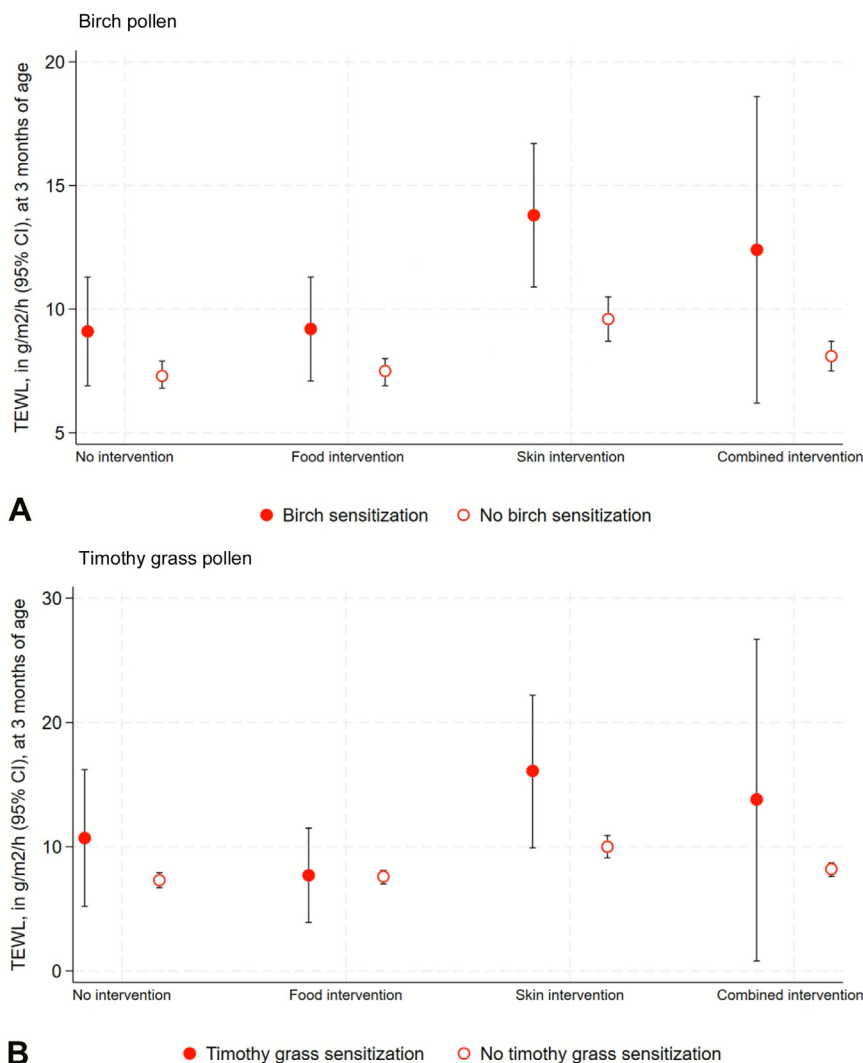
The prevalence of allergic sensitization at age 3 years was not associated in any of the intervention groups with being born during the pollen seasons (see Table E5A and B in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Furthermore, no significant effect modification by month of birth was observed for either intervention (interaction term  $P$  values of .47 and .53 for birch and timothy grass, respectively).

### Complete case analysis

In children with information on allergic sensitization at all time points, 55 of 642 (8.6%) were sensitized to birch by age 3 years (at any time point), and 33 of 637 (5.2%) to timothy grass by 3 years (see Table E6A and B in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The intervention group allocations were associated with similar crude ORs and risk differences for birch and timothy grass sensitization, respectively, in the complete case analysis compared with the mITT analysis (Table III).

### Per-protocol analysis

Among the 315 of 951 children (33.1%) randomized to skin intervention who were fully protocol adherent to the use of both



**FIGURE 2.** Transepidermal water loss (TEWL) (g/m<sup>2</sup> per h [95% CI]) at age 3 months in relation to (A) birch and (B) timothy grass pollen sensitization (specific IgE ≥0.1 kU<sub>A</sub>/L and/or SPT ≥3 mm) at age 3 years and intervention group allocation.

**TABLE II.** Mediator analysis of direct, indirect, and total effect of skin intervention through transepidermal water loss at 3 mo on allergic sensitization at 3 y

Analysis	Birch sensitization at 3 y (n = 117/1,492; 7.8%)			Timothy grass sensitization at 3 y (n = 40/1,482; 2.7%)		
	Direct effect	Indirect effect	Total effect	Direct effect	Indirect effect	Total effect
Coefficient	0.24	0.08	0.32	0.33	0.08	0.41
P	.253	.001	.128	.346	.002	.233

A total of 951 out of 2,066 children (46%) were exposed to the skin intervention. Mediator: Transepidermal water loss at 3 mo (g/m<sup>2</sup> per h).

bath oil and facial cream, an increased prevalence (Table E7A), as well as risk of birch sensitization at age 3 years was observed in the skin intervention group, similar to the mITT population (Table III). Although birch sensitization was less common in those with full peanut protocol adherence in the combined interventions group (Table E7B), the risk was not significantly reduced in regression analysis (Table III). Similarly, whereas timothy grass sensitization was less common in children with full wheat protocol adherence in the food intervention group

(Table E7D), the risk estimate was not statically significant (Table III).

**DISCUSSION**

In this explorative subanalysis of a Scandinavian population-based randomized trial, 7.8% of children were sensitized to birch and 2.7% to timothy grass pollen at age 3 years. We found no evidence for a preventive effect of early food introduction on

**TABLE III.** Crude OR (95% CI) and risk difference (95% CI) for allergic sensitization (specific IgE  $\geq 0.1$  kU<sub>A</sub>/L and/or skin prick test  $\geq 3$  mm) at age 3 y, comparing populations in intention-to-treat, complete case, and per-protocol analysis

Populations	Birch pollen sensitization			Timothy grass pollen sensitization		
	n (%)	Risk difference (95% CI)	Crude OR (95% CI)	n (%)	Risk difference (95% CI)	Crude OR (95% CI)
<b>Skin intervention group</b>						
Modified intention-to-treat population	48 (13.9)	7.6% (3.2-11.9)	2.38 (1.43-3.95)	15 (4.4)	1.8% (-0.9 to 4.5)	1.73 (0.77-3.91)
Complete case population	24 (16.0)	10.3% (3.4-17.2)	3.15 (1.41-7.03)	7 (4.7)	1.5% (-2.9 to 5.9)	1.49 (0.46-4.80)
Full protocol adherence						
Skin intervention adherence*	18 (14.6)	8.3% (1.6-15.0)	2.52 (1.33-4.80)	4 (3.3)	0.7% (-2.8 to 4.2)	1.28 (0.40-4.17)
<b>Food intervention group</b>						
Modified intention-to-treat population	28 (7.0)	0.6% (-2.9 to 4.1)	1.10 (0.63-1.93)	6 (1.5)	-1.1% (-3.0 to 0.9)	0.58 (0.21-1.60)
Complete case population	14 (7.5)	1.8% (-3.5 to 7.0)	1.33 (0.56-3.17)	0	-3.2% (-6.0 to -0.4)	—
Full protocol adherence						
Peanut (birch)/wheat (timothy) introduction†	12 (6.1)	-0.3% (-4.4 to 3.8)	0.95 (0.47-1.93)	1 (0.4)	-2.2% (-3.9 to -0.4)	0.16 (0.02-1.24)
<b>Combined interventions group</b>						
Modified intention-to-treat population	16 (4.6)	-1.8% (-5.1 to 1.4)	0.70 (0.37-1.34)	9 (2.6)	0.0% (-2.3 to 2.3)	1.00 (0.40-2.49)
Complete case population	3 (2.1)	-3.6% (-7.9 to 0.6)	0.35 (0.09-1.31)	2 (1.4)	-1.8% (-5.2 to 1.5)	0.42 (0.08-2.21)
Full protocol adherence						
Skin intervention adherence*	6 (4.6)	-1.8% (-6.1 to 2.5)	0.70 (0.29-1.75)	3 (2.3)	-0.3% (-3.3 to 2.7)	0.89 (0.24-3.28)
Peanut (birch)/wheat (timothy) introduction†	3 (2.1)	-4.3% (-7.6 to 0.9)	0.31 (0.09-1.05)	3 (1.7)	-0.8% (-3.3 to 1.7)	0.67 (0.18-2.46)

OR, odds ratio.

Reference: no intervention.

\*Defined as "reported baths with the Preventing Atopic Dermatitis and Allergy in Children oil additive and Cerdial facial cream for mean of at least 3.5 d/wk in 16 of the 25 first weeks of life. Emollients had to be applied for the first time by 4 wk of age and could not be missed in two of three consecutive weeks."<sup>2,3</sup>

†Full food intervention adherence was defined as introduction of the food between ages 13 and 18 wk and intake of the food for a minimum of 3-5 d/wk in at least 5 wk between ages 19 and 26 wk.<sup>7</sup>

pollen sensitization at age 3 years. Birch pollen sensitization was most common among children assigned to mineral-based oil baths and facial cream 4 times/week starting at age 2 weeks. This was confirmed among those who adhered fully to the skin intervention protocol. In addition, the skin intervention increased the risk of allergic sensitization to birch over time, from age 6 months to 3 years. At age 3 months, TEWL was higher among children with pollen sensitization at age 3 years, and highest in the skin and combined intervention groups. We found a significant indirect effect of the skin intervention through TEWL at age 3 months. No significant effect modification by month of birth was observed for either intervention.

The observed prevalence of birch and timothy grass pollen sensitization, respectively, at age 3 years in the PreventADALL study is similar to what was observed in the German Multicenter Allergy Study.<sup>31</sup> In contrast, the prevalence in the current study was slightly lower than what was reported in another Swedish large population-based birth cohort<sup>32</sup> and compared with a study of 7- to 8-year-olds in Northern Sweden, with a prevalence measured by SPT.<sup>33</sup> However, this was expected, because an increase in the aeroallergen sensitization rate through childhood is commonly seen.<sup>34</sup>

We found no effect of the food intervention on the risk of birch sensitization at or by age 3 years, whereas a significantly lower number of children with full protocol wheat adherence were sensitized to timothy grass in the food intervention group compared with the controls. This finding partly supports our hypothesis of a cross-reactive allergen prevention effect between pollen and plant foods early in life. An observational population-based prospective cohort of 5,000 children, conducted in the Netherlands, reported that neither the timing nor the diversity of food introduction was consistently associated with allergic manifestations or sensitization to inhalant allergens at age 10 years, although a decreased risk of inhalant allergy, but not of sensitization to inhalant allergens assessed by SPT, was observed by introducing three or more foods before age 6 months.<sup>35</sup>

To the best of our knowledge, the increased risk of birch pollen sensitization at age 3 years by the use of skin emollients from age 2 weeks is novel. In addition, our data suggest a dose-response effect, with the lowest prevalence of birch sensitization in the no skin intervention groups, a bit higher in the skin intervention group in the mITT population, and highest among those who were fully compliant with the protocol in the skin intervention group. Our finding in this randomized trial with careful monitoring of the intervention adherence in weekly diaries from age 2 to 26 weeks,<sup>7</sup> is supported by the early food introduction randomized Enquiring About Tolerance trial, in which parent-reported frequency of moisturization use at age 3 months was positively associated with the risk of aeroallergen sensitization at age 3 years.<sup>21</sup>

It may seem unexpected that the risk of birch sensitization is increased in the skin intervention—only group but not in the group with both skin and food interventions. We observed a statistically significant interaction between the interventions. Although this could be a chance finding, it may also be explained by the indirect effect through TEWL at age 3 months. The TEWL values at 3 months were significantly higher in the skin intervention—only group compared with the other groups.

Our finding that children with pollen sensitization at age 3 years had higher TEWL in early infancy, compared with those

without pollen sensitization, is supported by the increasing body of evidence of epicutaneous sensitization through an impaired skin barrier.<sup>15,36</sup> In the PreventADALL study, we previously showed that TEWL in the upper quartile at 3 months predicted allergic sensitization (food or inhalant) already at age 6 months.<sup>4</sup> In the current study, the significant indirect effect of the skin intervention through TEWL suggests that the emollients reduced the skin barrier function, facilitating the penetration of pollen allergens through the skin. Studies of different skin care regimes have shown conflicting results on the effect on TEWL. Some studies, including our own,<sup>18</sup> demonstrated increased TEWL at some point during infancy by either emollient baths or different leave-on emollients.<sup>16,19-21</sup> Other studies including neonates have reported decreased TEWL by bathing at different frequencies with or without emollient additives.<sup>37,38</sup>

### Clinical implications

This study identifies a gap in knowledge in terms of the effect of emollient use through infancy on the skin barrier function, and later pollen sensitization as a potential consequence of this.

Overall, this study suggests that the infant skin is a highly relevant route of exposure to pollens. The findings further suggest that the disruption of the skin barrier caused by frequent skin emollient use also means higher exposure to pollens through the skin. With this knowledge, future studies should focus on the skin barrier function, and how it can be modified, to prevent allergic rhinitis later in childhood. Because the disease burden of pollen allergy is increasing, partly owing to climate change and global warming making the pollen seasons more intense and longer,<sup>39</sup> the study findings highlight the importance of preventive measures of pollen sensitization that might be caused by a disrupted skin barrier.

This study focused on measured s-IgE and SPT reactivity, and it did not include the presence of pollen-related allergic symptoms. Because in many cases pollen sensitization can be demonstrated years before the onset of clinical disease,<sup>40</sup> and allergic rhinitis is not common at preschool age, the effect of early interventions on pollen allergy will be more meaningful to study later in childhood.

### Strengths and limitations

The children were recruited from the general population, so factors such as heredity for atopic disease were equally distributed across the intervention groups. Also, the RCT design indicated a higher level of evidence compared with non-RCT studies. Another advantage was the use of TEWL as an objective, well-established measure of skin barrier function. In addition, that both the complete case and per-protocol analysis showed a similar tendency of the risk of allergic sensitization as the primary analysis suggests that the results are robust.

Although a large sample size, the low number of participants with timothy grass sensitization limits the possibility of drawing conclusions from the analysis with that outcome. Additionally, the generalizability of findings might be limited to populations in Northern Europe, because the timing of pollen seasons, and the numbers and types of pollen, vary across geographic regions. Additional limitations are the proportion of children with available s-IgE and SPT results (40% and 63%, respectively, of 2,394 randomized children) at age 3 years, and the proportion of children who were fully adherent to the skin intervention protocol (33.1% in the current study population). Also, although

the mediator analysis results provide valuable insights, confounding might have influenced the findings and should be addressed in future studies.

## Conclusions

In this study, we found no effect of early tastes of four allergenic foods, alone or combined with the skin intervention, on the risk of birch or timothy grass sensitization at age 3 years. Infants randomized to the skin intervention had an increased risk only of birch sensitization at age 3 years, and over time from age 6 months to 3 years. The skin intervention effect was mediated by a reduced skin barrier function in early infancy. None of the intervention effects were modified by the season of birth.

## Acknowledgments

We would like to thank all PreventADALL participants, as well as the individuals who have contributed to the study: H. Aaneland, F. Andersson, S. Asad, A. Asarnej, K.E.S. Bains, A. Berglind, A. Bergström, J. Björk, M. Hauger Carlsen, O.C. Lødrup Carlsen, Å. Wik Desprée, K.M.A. Endre, T. Aspelund Fatnes, M. Färdig, P.A. Granlund, M. Gudbrandsgard, H.K. Gudmundsdóttir, S. Götberg, G. Haugen, G. Hedlin, K. Hilde, M. Ingemansson, S. Sperstad Kennelly, M. Rønning Kjendsli, I. Kreyberg, V. Østberg Landaas, L. Landrø, A. Lie, C.A. Olsson Mägi, N. Nilsson, M. Nordenbrand, L.S. Nordhagen, C.M. Saunders, K. Sedergren, N. Sedergren, S. Sjelmo, I. Skrindo, L.J. Sørdal, P. Söderman, S. Ganrud Tedner, E. Tegnerud, S. Thompson, M.R. Værnesbranden, and J. Wiik, and in memoriam, K.H. Carlsen.

## REFERENCES

1. Kiotseridis H, Cilio CM, Bjermer L, Tunsater A, Jacobsson H, Dahl A. Grass pollen allergy in children and adolescents-symptoms, health related quality of life and the value of pollen prognosis. *Clin Transl Allergy* 2013;3:19.
2. Biedermann T, Winther L, Till SJ, Panzner P, Knulst A, Valovirta E. Birch pollen allergy in Europe. *Allergy* 2019;74:1237-48.
3. Pierau M, Arra A, Brunner-Weinzierl MC. Preventing atopic diseases during childhood - early exposure matters. *Front Immunol* 2021;12:617731.
4. Warnberg Gerdin S, Lie A, Asarnej A, Borres MP, Lodrup Carlsen KC, Färdig M, et al. Impaired skin barrier and allergic sensitization in early infancy. *Allergy* 2022;77:1464-76.
5. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;127:661-7.
6. du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol* 2016;137:998-1010.
7. Skjerven HO, Lie A, Vettukattil R, Reh binder EM, LeBlanc M, Asarnej A, et al. Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2022;399:2398-411.
8. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
9. Tolkki L, Alanko K, Petman L, Skydtsgaard MB, Milvang PG, Seppala U, et al. Clinical characterization and IgE profiling of birch (*Betula verrucosa*)-allergic individuals suffering from allergic reactions to raw fruits and vegetables. *J Allergy Clin Immunol Pract* 2013;1:623-31.e1.
10. Uotila R, Kukkonen AK, Blom WM, Remington B, Westerhout J, Pelkonen AS, et al. Component-resolved diagnostics demonstrates that most peanut-allergic individuals could potentially introduce tree nuts to their diet. *Clin Exp Allergy* 2018;48:712-21.
11. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69:17-27.
12. Zhong Y, Samuel M, van Bever H, Tham EH. Emollients in infancy to prevent atopic dermatitis: a systematic review and meta-analysis. *Allergy* 2022;77:1685-99.
13. Ni Chaoimh C, Lad D, Nico C, Puppels GJ, Wong X, Common JE, et al. Early initiation of short-term emollient use for the prevention of atopic dermatitis in high-risk infants-the STOP-AD randomised controlled trial. *Allergy* 2023;78:984-94.
14. Yamamoto-Hanada K, Kobayashi T, Mikami M, Williams HC, Saito H, Saito-Abe M, et al. Enhanced early skin treatment for atopic dermatitis in infants reduces food allergy. *J Allergy Clin Immunol* 2023;152:126-35.
15. Marques-Mejias A, Bartha I, Ciaccio CE, Chinthrajah RS, Chan S, Hershey GKK, et al. Skin as the target for allergy prevention and treatment. *Ann Allergy Asthma Immunol* 2024;133:133-43.
16. Kelleher MM, Cro S, Cornelius V, Lodrup Carlsen KC, Skjerven HO, Reh binder EM, et al. Skin care interventions in infants for preventing eczema and food allergy. *Cochrane Database Syst Rev* 2021;2:CD013534.
17. Kelleher MM, Phillips R, Brown SJ, Cro S, Cornelius V, Carlsen KCL, et al. Skin care interventions in infants for preventing eczema and food allergy. *Cochrane Database Syst Rev* 2022;11:CD013534.
18. Reh binder EM, Warnberg Gerdin S, Hoyer A, Bradley M, Lodrup Carlsen KC, Granum B, et al. Frequent oil-baths and skin barrier during infancy in the PreventADALL study. *Br J Dermatol* 2024;191:49-57.
19. O'Connor C, Livingstone V, O'B Hourihane J, Irvine AD, Boylan G, Murray D. Early emollient bathing is associated with subsequent atopic dermatitis in an unselected birth cohort study. *Pediatr Allergy Immunol* 2023;34:e13998.
20. Wilborn D, Amin R, Kottner J, Blume-Peytavi U. Skin care in neonates and infants: a scoping review. *Skin Pharmacol Physiol* 2023;36:51-66.
21. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Boyle RJ, et al. Association of frequent moisturizer use in early infancy with the development of food allergy. *J Allergy Clin Immunol* 2021;147:967-76.e1.
22. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733-43.
23. Skjerven HO, Reh binder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Early skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020;395:951-61.
24. Reh binder EM, Winger AJ, Landro L, Asarnej A, Berents TL, Carlsen KH, et al. Dry skin and skin barrier in early infancy. *Br J Dermatol* 2019;181:218-9.
25. Reh binder EM, Advocaat Endre KM, Lodrup Carlsen KC, Asarnej A, Stensby Bains KE, Berents TL, et al. Predicting skin barrier dysfunction and atopic dermatitis in early infancy. *J Allergy Clin Immunol Pract* 2020;8:664-73.e5.
26. Rogiers V, Group E. EEMCO guidance for the assessment of transepidermal water loss in cosmetic sciences. *Skin Pharmacol Appl Skin Physiol* 2001;14:117-28.
27. Lie A, Warnberg Gerdin S, Skrindo I, Reh binder EM, Jonassen CM, LeBlanc M, et al. Evaluation of skin prick test reading time at 10 versus 15 min in young infants. *Int Arch Allergy Immunol* 2022;183:824-34.
28. Ansoategui JJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. *World Allergy Organ J* 2020;13:100080.
29. Alduraywish SA, Lodge CJ, Vicendese D, Lowe AJ, Erbas B, Matheson MC, et al. Sensitization to milk, egg and peanut from birth to 18 years: a longitudinal study of a cohort at risk of allergic disease. *Pediatr Allergy Immunol* 2016;27:83-91.
30. Tran MM, Lefebvre DL, Dharmia C, Dai D, Lou WYW, Subbarao P, et al. Predicting the atopic march: results from the Canadian Healthy Infant Longitudinal Development Study. *J Allergy Clin Immunol* 2018;141:601-7.e8.
31. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;103:1173-9.
32. Asarnej A, Ostblom E, Kull I, Lilja G, Pershagen G, Hedlin G, et al. Sensitization to inhalant allergens between 4 and 8 years of age is a dynamic process: results from the BAMSE birth cohort. *Clin Exp Allergy* 2008;38:1507-13.
33. Ronmark E, Warm K, Bjerg A, Backman H, Hedman L, Lundback B. High incidence and persistence of airborne allergen sensitization up to age 19 years. *Allergy* 2017;72:723-30.
34. Koet LBM, Brand PLP. Increase in atopic sensitization rate among Dutch children with symptoms of allergic disease between 1994 and 2014. *Pediatr Allergy Immunol* 2018;29:78-83.
35. Elbert NJ, Kieffe-de Jong JC, Voortman T, Nijsten TEC, de Jong NW, Jaddoe VVW, et al. Allergenic food introduction and risk of childhood atopic diseases. *PLoS One* 2017;12:e0187999.
36. Brough HA, Nadeau KC, Sindher SB, Alkotob SS, Chan S, Bahnson HT, et al. Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? *Allergy* 2020;75:2185-205.

37. Yonezawa K, Haruna M, Matsuzaki M, Shiraishi M, Kojima R. Effects of moisturizing skincare on skin barrier function and the prevention of skin problems in 3-month-old infants: a randomized controlled trial. *J Dermatol* 2018;45:24-30.
38. Garcia Bartels N, Scheufele R, Prosch F, Schink T, Proquitte H, Wauer RR, et al. Effect of standardized skin care regimens on neonatal skin barrier function in different body areas. *Pediatr Dermatol* 2010;27:1-8.
39. D'Amato G, Chong-Neto HJ, Monge Ortega OP, Vitale C, Ansotegui I, Rosario N, et al. The effects of climate change on respiratory allergy and asthma induced by pollen and mold allergens. *Allergy* 2020;75:2219-28.
40. Hatzler L, Panetta V, Lau S, Wagner P, Bergmann RL, Illi S, et al. Molecular spreading and predictive value of preclinical IgE response to *Phleum pratense* in children with hay fever. *J Allergy Clin Immunol* 2012;130:894-901.e5.