THE ROLE OF THE SKIN IN ALLERGY

EVIDENCE OVERVIEW

THE SKIN STILL HOLDS SURPRISES

- The traditional view of allergy holds that sensitization occurs at the site of symptoms: atopic dermatitis (AD) is triggered through skin contact, food allergies are triggered by ingesting the offending substance and respiratory allergies are triggered via inhalation.
- The contemporary model of allergy challenges this understanding. **Research increasingly confirms that the skin is a major route to all types of allergy, regardless of where allergy symptoms eventually occur.**
- Impaired skin barrier function is a key part of the process. When this critical barrier is disrupted, allergens pass into the dermis and come into contact with the immune cells of this skin. It is this contact that can cause sensitization. For reasons that are complex and not yet fully elucidated, the immune cells may overreact, treating the allergen as a harmful substance and triggering the production of allergen-reactive cells in the lymph nodes.
- While the skin–allergy link has been known for some time, it has only recently become a hot area of research. Most studies are from the past 5 years. Large, robust studies have now been conducted across a range of allergens and allergic diseases which have confirmed and strengthened the contemporary view.
- **We are please to offer you this Evidence Overview** to guide you through the science behind this exciting field. The document is organized into two sections: clinical/preclinical studies and review articles. Note that several studies included patients with AD as a proxy for compromised skin barrier function. As the studies themselves show, AD itself is not the driving force behind allergy. Patients who have compromised skin barrier function for any reason have increased allergic risk.
- If you have any questions or comments, we would be happy to discuss them with you. Please contact your LA ROCHE-POSAY medical representative.

PUBLICATION OVERVIEW (1/2)

Page	Publication	Allergic disease	Allergen	No. patients	Key finding
CLINICAL/PRECLINICAL STUDIES					
6	Lack 2003	Food allergy	Peanut	49	Sensitization to peanut can be triggered by the application of peanut oil to the skin
7	Brough 2014	Food allergy	Peanut	623	Impaired skin barrier function increases the risk of peanut allergy via household dust
8	Brough 2015	Food allergy	Peanut	512	Severe AD increases the risk of sensitization to peanut dust more than overall AD
9	Kelleher 2016	Food allergy	Multiple	1260	Skin barrier impairment at birth, not AD per se, predicts development of food allergy
10	Flohr 2014	Food allergy	Multiple	619	Exposure of the gut to food antigens is not necessary for sensitization to foods
11	Marenholz 2009	Asthma	*Not applicable*	871	Skin barrier impairment plus food allergy predicts asthma development with 100% accuracy
12	Grant 2018	Allergic rhinitis	Mouse	394	New allergy development via the skin can occur throughout life
13	Yokooji 2013	Food allergy	Wheat	32	New allergy development via the skin can occur throughout life
14	Wisniewski 2013	Allergic march	Multiple	66	The allergic march is initiated in the skin

PUBLICATION OVERVIEW (2/2)

Page	Publication	Allergic disease	Allergen	No. patients	Key finding
CLINICAL/PRECLINICAL STUDIES (cont.)					
15	Simpson 2014	Atopic dermatitis	*Not applicable*	124	Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention
16	Chalmers 2017	Atopic dermatitis	*Not applicable*	1400 (anticipated)	The effect of emollients on prevention of AD and allergies is the topic of a major study
17	Dunkin 2011	IgE response	Milk protein	*Not applicable*	While sensitization can occur via all routes of exposure, the skin shows the highest response
18	Noti 2014	Food allergy	Ovalbumin	*Not applicable*	The skin's own immune response initiates food allergy when first exposure occurs via the skin
REVIEW ARTICLES					
20	Kim 2018	*Not applicable*			The epidermis provides both a physical and functional barrier to the skin
21	Wesemann 2016	*Not applicable*			Allergy risk could essentially be a function of barrier integrity
22	Han 2017	*Not applicable*			Skin barrier function could help explain progression of the allergic march
23	Natsume 2018	*Not applicable*			Early skin protection with emollients could help slow the allergic march

CLINICAL/PRECLINICAL STUDIES

SENSITIZATION TO FOODS CAN OCCUR VIA THE SKIN

The NEW ENGLAND JOURNAL of MEDICINE

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Factors Associated with the Development of Peanut Allergy in Childhood

Gideon Lack, M.B., B.Ch., Deborah Fox, B.A., Kate Northstone, M.Sc., and Jean Golding, Ph.D., for the Avon Longitudinal Study of Parents and Children Study Team

ABSTRACT

BACKGROUND

The prevalence of peanut allergy appears to have increased in recent decades. Other than a family history of peanut allergy and the presence of atopy, there are no known risk factors.

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METHODS

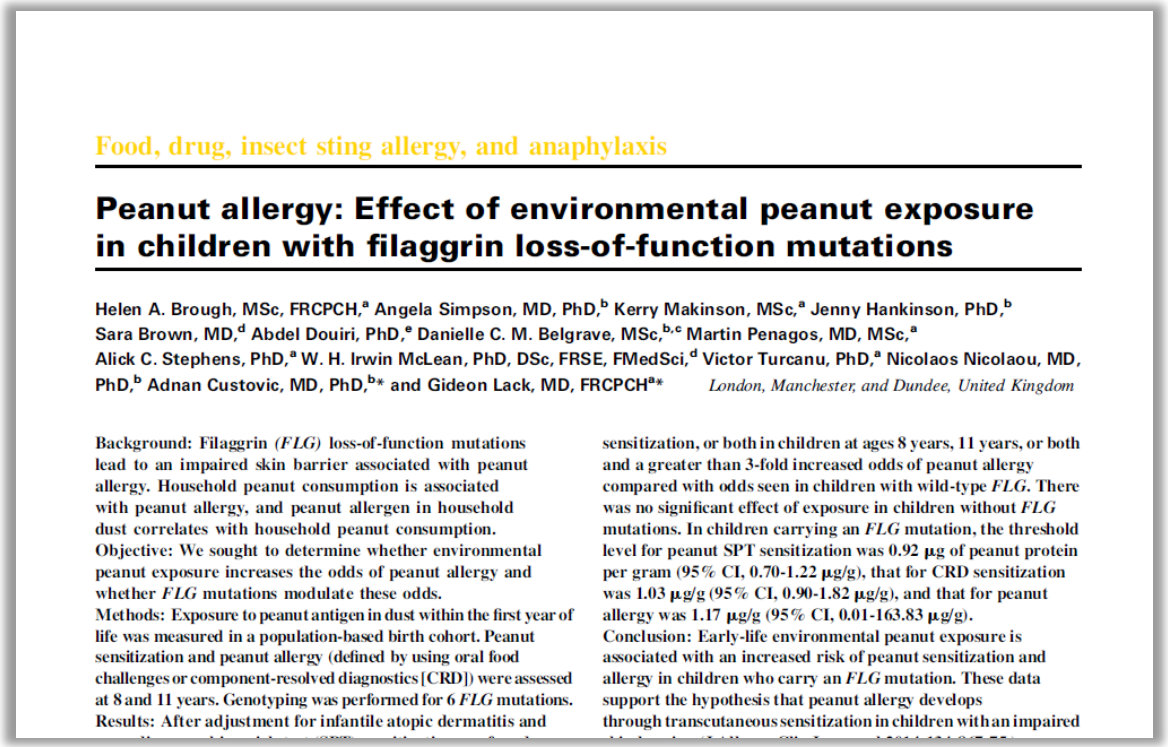
Lack G, *et al.* Factors associated with the development of peanut allergy in childhood. *N Engl J Med.* 2003;348(11):977-985.

Sensitization to peanut can be triggered by the application of peanut oil to the skin

Peanut oil skin products used in young infants increases the risk of peanut allergy at preschool age

- The use of skin preparations containing peanut oil (e.g. diaper rash creams) increased the risk of peanut allergy by 6.8-fold in preschool children *vs* no use
- Risk of peanut allergy was NOT associated with:
  - Consumption of peanuts during pregnancy or breastfeeding
  - Use of peanut oil-containing breast creams
  - High peanut consumption by infants

IMPAIRED SKIN BARRIER FUNCTION INCREASES RISK OF SENSITIZATION



Food, drug, insect sting allergy, and anaphylaxis

Peanut allergy: Effect of environmental peanut exposure in children with filaggrin loss-of-function mutations

Helen A. Brough, MSc, FRCPCH,[a] Angela Simpson, MD, PhD,[b] Kerry Makinson, MSc,[a] Jenny Hankinson, PhD,[b] Sara Brown, MD,[d] Abdel Douiri, PhD,[e] Danielle C. M. Belgrave, MSc,[b,c] Martin Penagos, MD, MSc,[a] Alick C. Stephens, PhD,[a] W. H. Irwin McLean, PhD, DSc, FRSE, FMedSci,[d] Victor Turcanu, PhD,[a] Nicolaos Nicolaou, MD, PhD,[b] Adnan Custovic, MD, PhD,[b]* and Gideon Lack, MD, FRCPCH[a]* *London, Manchester, and Dundee, United Kingdom*

Background: Filaggrin *(FLG)* loss-of-function mutations lead to an impaired skin barrier associated with peanut allergy. Household peanut consumption is associated with peanut allergy, and peanut allergen in household dust correlates with household peanut consumption.
Objective: We sought to determine whether environmental peanut exposure increases the odds of peanut allergy and whether *FLG* mutations modulate these odds.
Methods: Exposure to peanut antigen in dust within the first year of life was measured in a population-based birth cohort. Peanut sensitization and peanut allergy (defined by using oral food challenges or component-resolved diagnostics [CRD]) were assessed at 8 and 11 years. Genotyping was performed for 6 *FLG* mutations.
Results: After adjustment for infantile atopic dermatitis and sensitization, or both in children at ages 8 years, 11 years, or both and a greater than 3-fold increased odds of peanut allergy compared with odds seen in children with wild-type *FLG*. There was no significant effect of exposure in children without *FLG* mutations. In children carrying an *FLG* mutation, the threshold level for peanut SPT sensitization was 0.92 μg of peanut protein per gram (95% CI, 0.70-1.22 μg/g), that for CRD sensitization was 1.03 μg/g (95% CI, 0.90-1.82 μg/g), and that for peanut allergy was 1.17 μg/g (95% CI, 0.01-163.83 μg/g).
Conclusion: Early-life environmental peanut exposure is associated with an increased risk of peanut sensitization and allergy in children who carry an *FLG* mutation. These data support the hypothesis that peanut allergy develops through transcutaneous sensitization in children with an impaired

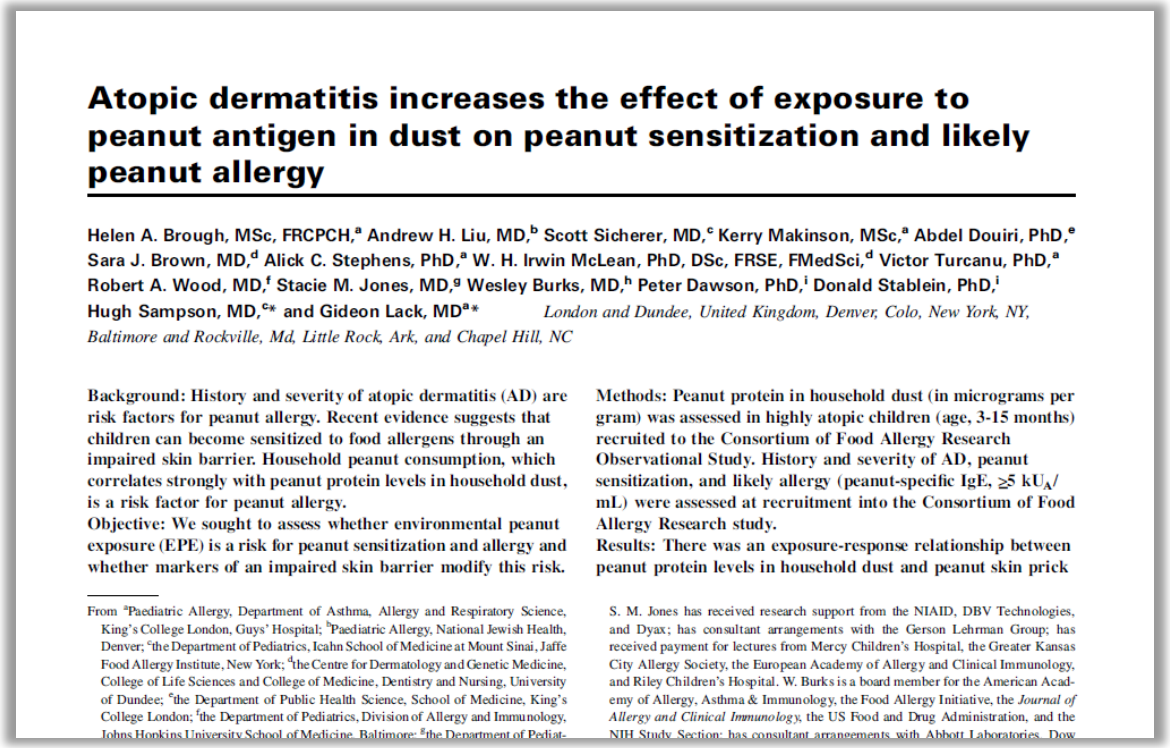
1. Brough HA, *et al.* Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol.* 2014;134(4):867-875.e1.
2. Barker JNWN, *et al.* Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol.* 2007;127(3):564-567.

Impaired skin barrier function increases the risk of peanut allergy via household dust

In children with impaired skin barrier function, early exposure to peanut antigen in household dust is a risk factor for peanut allergy[1]

- Filaggrin (FLG) null mutations prevent the formation of a structurally sound stratum corneum (the uppermost layer of the epidermis)[2]
  - Such mutations are associated with impaired skin barrier function and an increased risk of atopic dermatitis
- For each *ln* unit increase in peanut protein levels in household dust, children with *FLG* mutations showed[1]:
  - >6-fold higher odds of peanut SPT sensitization*
  - >3-fold higher odds of peanut of peanut allergy†
- There was no significant effect of exposure in children without FLG mutations[1]

SEVERE AD PROMOTES ALLERGY TO AN EVEN GREATER DEGREE



Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy

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Background: History and severity of atopic dermatitis (AD) are risk factors for peanut allergy. Recent evidence suggests that children can become sensitized to food allergens through an impaired skin barrier. Household peanut consumption, which correlates strongly with peanut protein levels in household dust, is a risk factor for peanut allergy.
Objective: We sought to assess whether environmental peanut exposure (EPE) is a risk for peanut sensitization and allergy and whether markers of an impaired skin barrier modify this risk.
Methods: Peanut protein in household dust (in micrograms per gram) was assessed in highly atopic children (age, 3-15 months) recruited to the Consortium of Food Allergy Research Observational Study. History and severity of AD, peanut sensitization, and likely allergy (peanut-specific IgE, ≥5 kU_A/mL) were assessed at recruitment into the Consortium of Food Allergy Research study.
Results: There was an exposure-response relationship between peanut protein levels in household dust and peanut skin prick

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S. M. Jones has received research support from the NIAID, DBV Technologies, and Dyax; has consultant arrangements with the Gerson Lehrman Group; has received payment for lectures from Mercy Children's Hospital, the Greater Kansas City Allergy Society, the European Academy of Allergy and Clinical Immunology, and Riley Children's Hospital. W. Burks is a board member for the American Academy of Allergy, Asthma & Immunology, the Food Allergy Initiative, the *Journal of Allergy and Clinical Immunology*, the US Food and Drug Administration, and the NIH Study Section; has consultant arrangements with Abbott Laboratories, Dow

Brough HA, *et al.* Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol*. 2015;135(1):164-70.

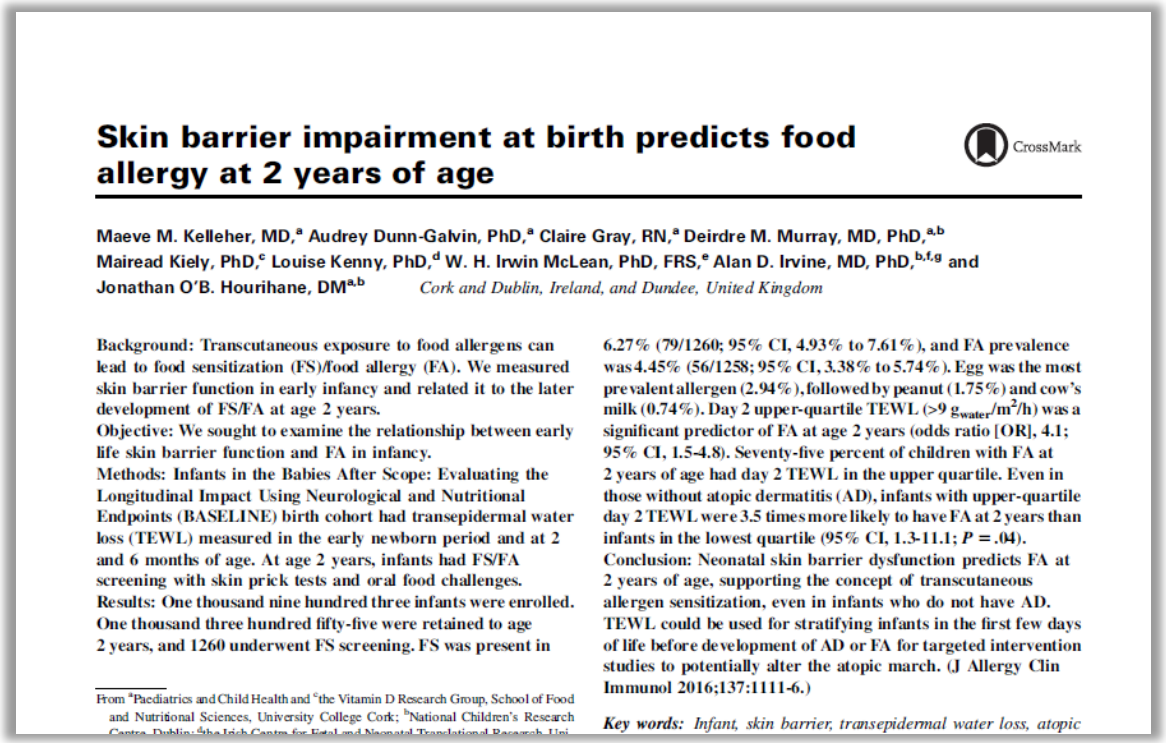
Severe AD increases the risk of sensitization to peanut dust more than overall AD

The risk of peanut allergy is increased in children with AD, and even more so when AD is severe

- The incidence of peanut SPT sensitization* was 2-fold higher in children with impaired skin barrier function due to AD, *vs* no AD (odds ratio 1.97, $p<0.01$)
- The incidence was even higher in children with severe AD, *vs* no AD (odds ratio 2.41, $p<0.01$)

*Children with peanut skin prick test (SPT) responses of 3 mm or greater were described as peanut SPT sensitized.
†Children with serum sIgE levels to peanut of 5 kUA/mL or greater were described as having a serologic diagnosis of likely peanut allergy (PA); this was postulated as in previous studies, 70% to 90% of 5- to 7-year-old children had positive diagnostic peanut challenge results with this level of peanut sIgE.

ALLERGY RISK IS A DIRECT EFFECT OF SKIN BARRIER IMPAIRMENT



Skin barrier impairment at birth predicts food allergy at 2 years of age

Maeve M. Kelleher, MD,[a] Audrey Dunn-Galvin, PhD,[a] Claire Gray, RN,[a] Deirdre M. Murray, MD, PhD,[a,b] Mairead Kiely, PhD,[c] Louise Kenny, PhD,[d] W. H. Irwin McLean, PhD, FRS,[e] Alan D. Irvine, MD, PhD,[b,f,g] and Jonathan O'B. Hourihane, DM[a,b] *Cork and Dublin, Ireland, and Dundee, United Kingdom*

Background: Transcutaneous exposure to food allergens can lead to food sensitization (FS)/food allergy (FA). We measured skin barrier function in early infancy and related it to the later development of FS/FA at age 2 years.
Objective: We sought to examine the relationship between early life skin barrier function and FA in infancy.
Methods: Infants in the Babies After Scope: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints (BASELINE) birth cohort had transepidermal water loss (TEWL) measured in the early newborn period and at 2 and 6 months of age. At age 2 years, infants had FS/FA screening with skin prick tests and oral food challenges.
Results: One thousand nine hundred three infants were enrolled. One thousand three hundred fifty-five were retained to age 2 years, and 1260 underwent FS screening. FS was present in 6.27% (79/1260; 95% CI, 4.93% to 7.61%), and FA prevalence was 4.45% (56/1258; 95% CI, 3.38% to 5.74%). Egg was the most prevalent allergen (2.94%), followed by peanut (1.75%) and cow's milk (0.74%). Day 2 upper-quartile TEWL (>9 $g_{water}/m^2/h$) was a significant predictor of FA at age 2 years (odds ratio [OR], 4.1; 95% CI, 1.5-4.8). Seventy-five percent of children with FA at 2 years of age had day 2 TEWL in the upper quartile. Even in those without atopic dermatitis (AD), infants with upper-quartile day 2 TEWL were 3.5 times more likely to have FA at 2 years than infants in the lowest quartile (95% CI, 1.3-11.1; $P = .04$).
Conclusion: Neonatal skin barrier dysfunction predicts FA at 2 years of age, supporting the concept of transcutaneous allergen sensitization, even in infants who do not have AD. TEWL could be used for stratifying infants in the first few days of life before development of AD or FA for targeted intervention studies to potentially alter the atopic march. (J Allergy Clin Immunol 2016;137:1111-6.)

From [a]Paediatrics and Child Health and [c]the Vitamin D Research Group, School of Food and Nutritional Sciences, University College Cork; [b]National Children's Research Centre, Dublin; [f]the Irish Centre for Fetal and Neonatal Translational Research, Uni

Key words: *Infant, skin barrier, transepidermal water loss, atopic*

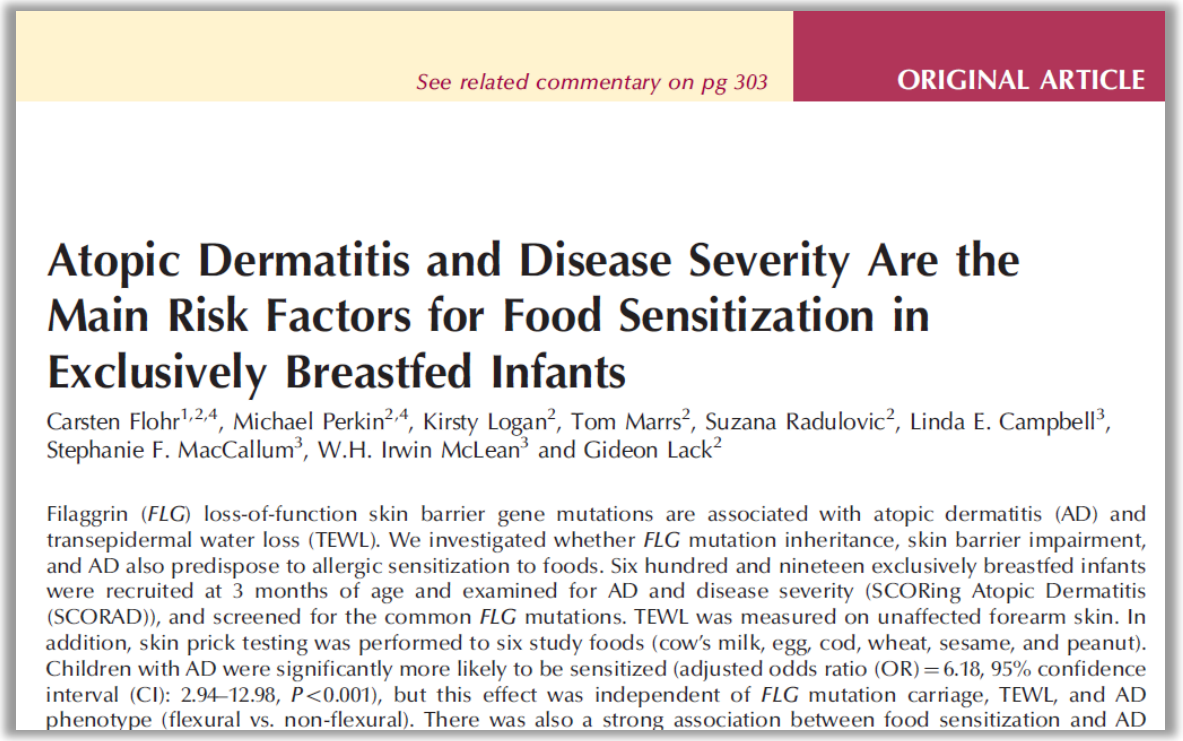
1. Kelleher MM, *et al.* Skin barrier impairment at birth predicts food allergy at 2 years of age. *J Allergy Clin Immunol.* 2016;137(4):1111-1116.e8.
2. Kelleher M, *et al.* Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol.* 2015;135:930-5.

Skin barrier impairment at birth, not AD per se, predicts development of food allergy

Increased risk of transcutaneous sensitization to food is due to impaired skin barrier function, not AD itself[1]

- Transepidermal water loss (TEWL) is a functional marker of impaired skin barrier and is associated with future development of AD[2]
- In children without AD, high TEWL at birth was a strong predictor of food allergy at 2 years of age[1]
    - Infants with in the highest quartile of TEWL were 18 times more likely to have food allergy than those with in the lowest quartile
- Even skin that is not symptomatic or obviously abnormal can have impaired skin barrier function and increased risk of allergy[1]

THE SKIN, NOT THE GUT, DRIVES SENSITIZATION TO FOOD



See related commentary on pg 303

ORIGINAL ARTICLE

Atopic Dermatitis and Disease Severity Are the Main Risk Factors for Food Sensitization in Exclusively Breastfed Infants

Carsten Flohr[1,2,4], Michael Perkin[2,4], Kirsty Logan[2], Tom Marrs[2], Suzana Radulovic[2], Linda E. Campbell[3], Stephanie F. MacCallum[3], W.H. Irwin McLean[3] and Gideon Lack[2]

Filaggrin (*FLG*) loss-of-function skin barrier gene mutations are associated with atopic dermatitis (AD) and transepidermal water loss (TEWL). We investigated whether *FLG* mutation inheritance, skin barrier impairment, and AD also predispose to allergic sensitization to foods. Six hundred and nineteen exclusively breastfed infants were recruited at 3 months of age and examined for AD and disease severity (SCORing Atopic Dermatitis (SCORAD)), and screened for the common *FLG* mutations. TEWL was measured on unaffected forearm skin. In addition, skin prick testing was performed to six study foods (cow's milk, egg, cod, wheat, sesame, and peanut). Children with AD were significantly more likely to be sensitized (adjusted odds ratio (OR) = 6.18, 95% confidence interval (CI): 2.94–12.98, $P<0.001$), but this effect was independent of *FLG* mutation carriage, TEWL, and AD phenotype (flexural vs. non-flexural). There was also a strong association between food sensitization and AD

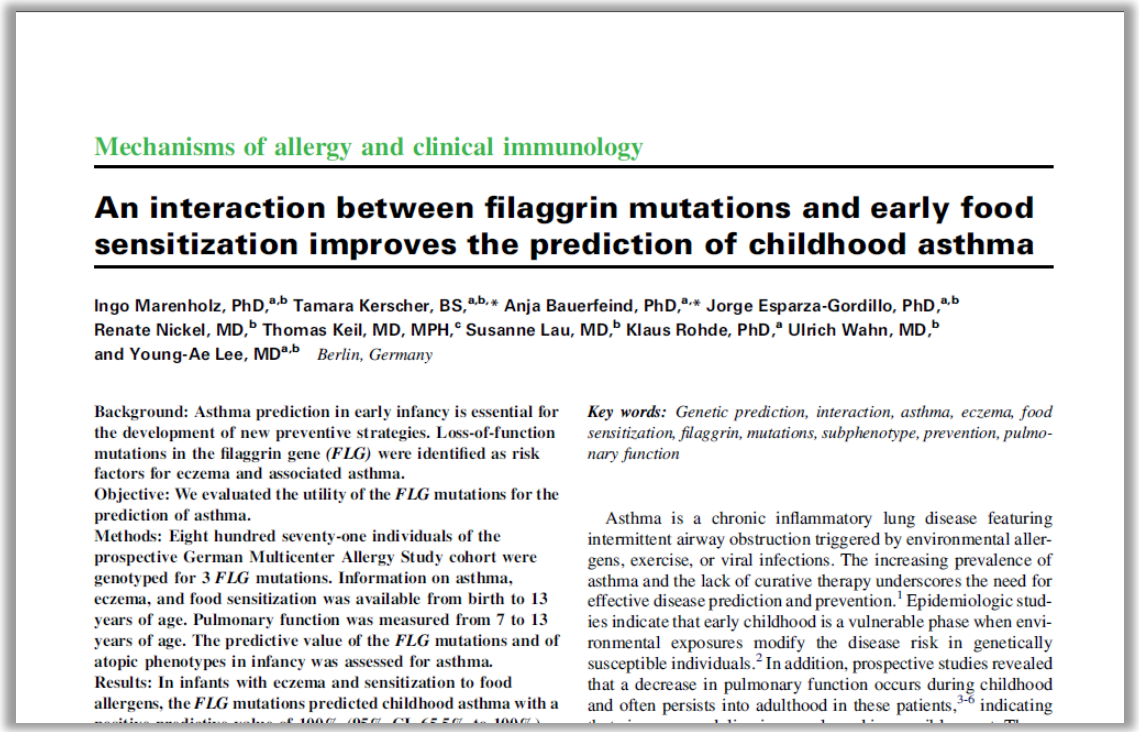
Flohr C, *et al.* Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol.* 2014;134(2):345-350.

Exposure of the gut to food antigens is not necessary for sensitization to foods

Exclusively breastfed infants with impaired skin barrier function have an elevated risk of food sensitization

- Infants who had only over breastfed had a higher risk of sensitization to food if they also showed high transepidermal water loss (TEWL) – a marker of impaired skin barrier function
  - This remained significant when adjusted for FLG mutation status and AD presence
- The fact that these sensitized infants had never ingested food suggests that allergic sensitization to foods can be directly mediated by immune cells in the skin rather than the gut

ASTHMA DEVELOPMENT IS ALSO LINKED TO BARRIER DEFECTS



Mechanisms of allergy and clinical immunology

An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma

Ingo Marenholz, PhD,[a,b] Tamara Kerscher, BS,[a,b,*] Anja Bauerfeind, PhD,[a,*] Jorge Esparza-Gordillo, PhD,[a,b] Renate Nickel, MD,[b] Thomas Keil, MD, MPH,[c] Susanne Lau, MD,[b] Klaus Rohde, PhD,[a] Ulrich Wahn, MD,[b] and Young-Ae Lee, MD[a,b] *Berlin, Germany*

Background: Asthma prediction in early infancy is essential for the development of new preventive strategies. Loss-of-function mutations in the filaggrin gene (*FLG*) were identified as risk factors for eczema and associated asthma.
Objective: We evaluated the utility of the *FLG* mutations for the prediction of asthma.
Methods: Eight hundred seventy-one individuals of the prospective German Multicenter Allergy Study cohort were genotyped for 3 *FLG* mutations. Information on asthma, eczema, and food sensitization was available from birth to 13 years of age. Pulmonary function was measured from 7 to 13 years of age. The predictive value of the *FLG* mutations and of atopic phenotypes in infancy was assessed for asthma.
Results: In infants with eczema and sensitization to food allergens, the *FLG* mutations predicted childhood asthma with a

Key words: *Genetic prediction, interaction, asthma, eczema, food sensitization, filaggrin, mutations, subphenotype, prevention, pulmonary function*

Asthma is a chronic inflammatory lung disease featuring intermittent airway obstruction triggered by environmental allergens, exercise, or viral infections. The increasing prevalence of asthma and the lack of curative therapy underscores the need for effective disease prediction and prevention.[1] Epidemiologic studies indicate that early childhood is a vulnerable phase when environmental exposures modify the disease risk in genetically susceptible individuals.[2] In addition, prospective studies revealed that a decrease in pulmonary function occurs during childhood and often persists into adulthood in these patients,[3-6] indicating

Marenholz I, *et al.* An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol*. 2009;123(4):911-916.

Skin barrier impairment plus food allergy predicts asthma development with 100% accuracy

Atopic march is facilitated by FLG-mutation and food allergy

- In infants with eczema and sensitization to food allergens within the first 3 years of life, the presence of an FLG loss-of-function mutation predicts the future development of asthma with a positive predictive value of 100%

ADULTS CAN ALSO BECOME SENSITIZED VIA THE SKIN

Physician-diagnosed eczema is an independent risk factor for incident mouse skin test sensitization in adults

Torie Grant, M.D.,[1] Jennifer Dantzer, M.D.,[1] Corinne Keet, M.D., Ph.D.,[1] Roger Peng, Ph.D.,[2] Beverly J. Paigen, Ph.D.,[3] Mary Krevans, R.N.,[3] Karol Hagberg, F.N.P.,[3] Jean Curtin-Brosnan, M.A.,[1] Wayne Shreffler, M.D., Ph.D.,[4] and Elizabeth C. Matsui, M.D., M.H.S.[1]

ABSTRACT

Background: *The disrupted skin barrier in eczema has been associated with an increased risk of immunoglobulin E (IgE) sensitization in childhood. However, it is unclear whether eczema, independent of atopy, is a risk factor for the development of allergic sensitization in adulthood.*

Objective: *To determine if skin barrier dysfunction, independent of atopy, is a risk factor for incident sensitization in adult workers at a mouse production and research facility.*

Methods: *New employees at The Jackson Laboratory enrolled in a cohort study and underwent skin-prick testing (SPT) at baseline and every 6 months to mouse and to a panel of aeroallergens (net wheal ≥3 mm indicated a positive SPT result). Mouse allergen exposure was measured every 6 months by using personal air monitors. Physician-diagnosed eczema was defined as self-reported physician-diagnosed eczema. Cox proportional hazard modeling was used to examine the association between baseline physician-diagnosed eczema and incident mouse skin test sensitization and adjusted for potential confounders.*

Results: *The participants (N = 394) were followed up for a median of 24 months. Fifty-four percent were women, 89% were white, and 64% handled mice. At baseline, 7% of the participants reported physician-diagnosed eczema and 9% reported current asthma; 61% had at least one positive skin test result. At 30 months, 36% of those with eczema versus 14% of those without eczema had developed a positive mouse skin test result (p = 0.02, log-rank test). After adjusting for age, race, sex, smoking status (current, former, never), current asthma, hay fever, the number of positive SPT results at baseline, and mouse allergen exposure, physician-diagnosed eczema was an independent risk factor for incident mouse SPT sensitization (hazard ratio 5.6 [95% confidence interval, 2.1–15.2]; p = 0.001).*

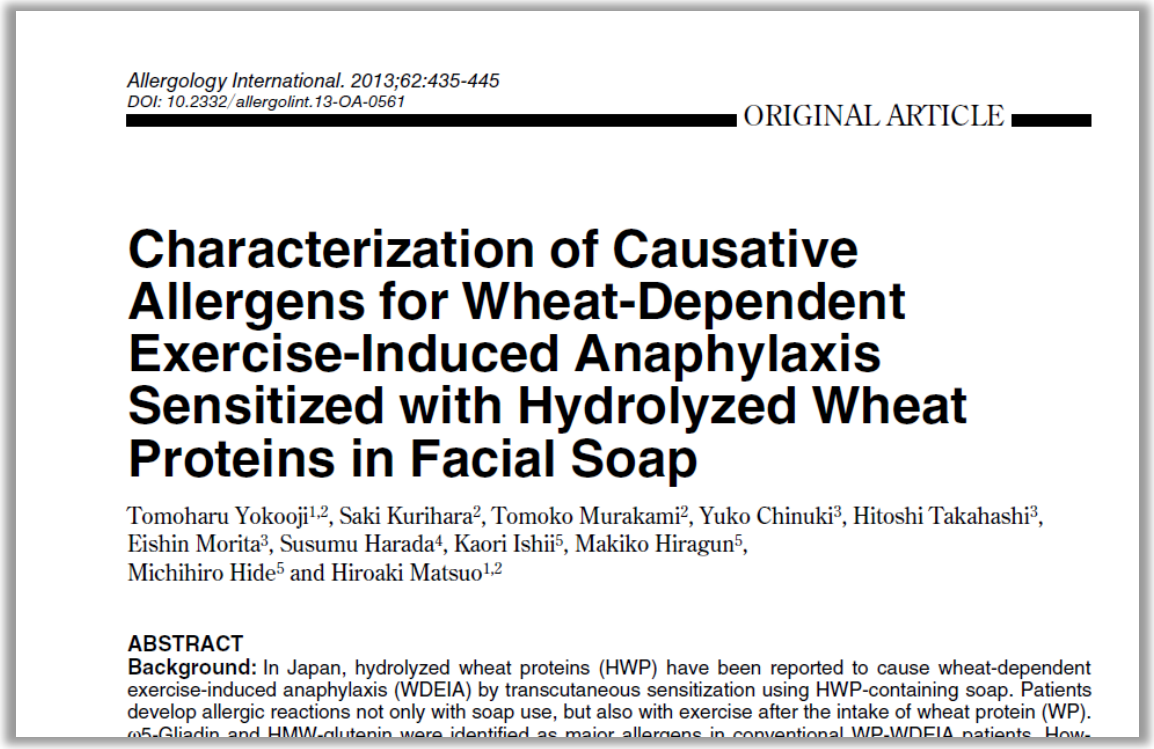
Grant T, *et al.* Physician-diagnosed eczema is an independent risk factor for incident mouse skin test sensitization in adults. *Allergy Asthma Proc.* 2018;39(4):311-315.

New allergy development via the skin can occur throughout life

Eczema increases the risk of developing allergic rhinitis in adults exposed to mice

- New employees at a mouse production and research facility were followed for 30 months
- 36% of adults with eczema versus 14% of those without eczema developed a positive mouse skin test result (p=0.02)
- Eczema increases allergen exposure independent of allergy
    - Eczema was an independent risk factor for incident mouse skin prick test (SPT) sensitization (hazard ratio 5.6, p=0.001) after adjusting for age, race, sex, smoking status, current asthma, hay fever, the number of positive SPT results at baseline and mouse allergen exposure

ADULTS CAN ALSO BECOME SENSITIZED VIA THE SKIN



Allergology International. 2013;62:435-445
DOI: 10.2332/allergolint.13-OA-0561

ORIGINAL ARTICLE

Characterization of Causative Allergens for Wheat-Dependent Exercise-Induced Anaphylaxis Sensitized with Hydrolyzed Wheat Proteins in Facial Soap

Tomoharu Yokooji[1,2], Saki Kurihara[2], Tomoko Murakami[2], Yuko Chinuki[3], Hitoshi Takahashi[3], Eishin Morita[3], Susumu Harada[4], Kaori Ishii[5], Makiko Hiragun[5], Michihiro Hide[5] and Hiroaki Matsuo[1,2]

ABSTRACT
Background: In Japan, hydrolyzed wheat proteins (HWP) have been reported to cause wheat-dependent exercise-induced anaphylaxis (WDEIA) by transcutaneous sensitization using HWP-containing soap. Patients develop allergic reactions not only with soap use, but also with exercise after the intake of wheat protein (WP). ω5-Gliadin and HMW-glutenin were identified as major allergens in conventional WP-WDEIA patients. How-

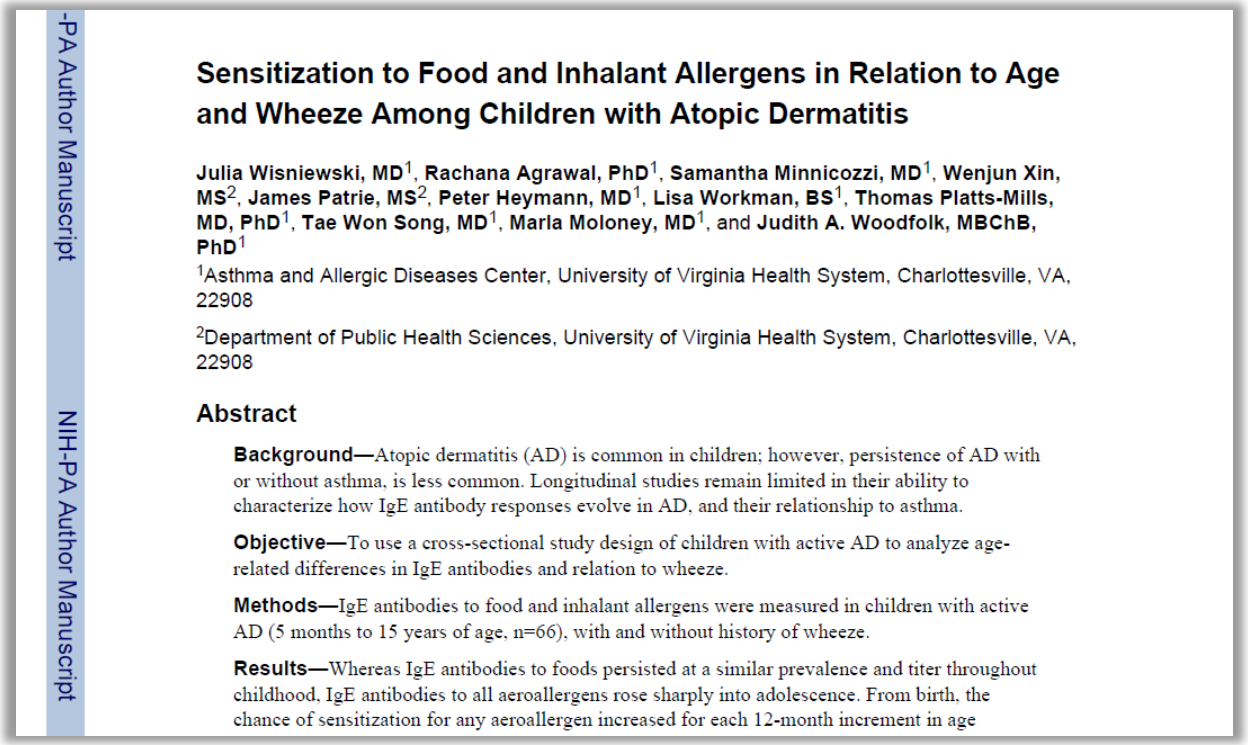
Yokooji T, *et al.* Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. *Allergol Int.* 2013;62(4):435-445.

New allergy development via the skin can occur throughout life

Wheat-containing skin products induce allergy to wheat protein in foods in adults

- Multiple studies have demonstrated transcutaneous sensitization from wheat-containing soap or cosmetics
- Transcutaneously sensitized patients show wheat protein-specific IgE and have immediate allergic reactions to wheat-containing foods

EARLY PREVENTION OF AD MAY PREVENT OTHER ALLERGY



-PA Author Manuscript

NIH-PA Author Manuscript

Sensitization to Food and Inhalant Allergens in Relation to Age and Wheeze Among Children with Atopic Dermatitis

Julia Wisniewski, MD[1], Rachana Agrawal, PhD[1], Samantha Minnicozzi, MD[1], Wenjun Xin, MS[2], James Patrie, MS[2], Peter Heymann, MD[1], Lisa Workman, BS[1], Thomas Platts-Mills, MD, PhD[1], Tae Won Song, MD[1], Marla Moloney, MD[1], and Judith A. Woodfolk, MBChB, PhD[1]

[1]Asthma and Allergic Diseases Center, University of Virginia Health System, Charlottesville, VA, 22908

[2]Department of Public Health Sciences, University of Virginia Health System, Charlottesville, VA, 22908

Abstract

Background—Atopic dermatitis (AD) is common in children; however, persistence of AD with or without asthma, is less common. Longitudinal studies remain limited in their ability to characterize how IgE antibody responses evolve in AD, and their relationship to asthma.

Objective—To use a cross-sectional study design of children with active AD to analyze age-related differences in IgE antibodies and relation to wheeze.

Methods—IgE antibodies to food and inhalant allergens were measured in children with active AD (5 months to 15 years of age, n=66), with and without history of wheeze.

Results—Whereas IgE antibodies to foods persisted at a similar prevalence and titer throughout childhood, IgE antibodies to all aeroallergens rose sharply into adolescence. From birth, the chance of sensitization for any aeroallergen increased for each 12-month increment in age

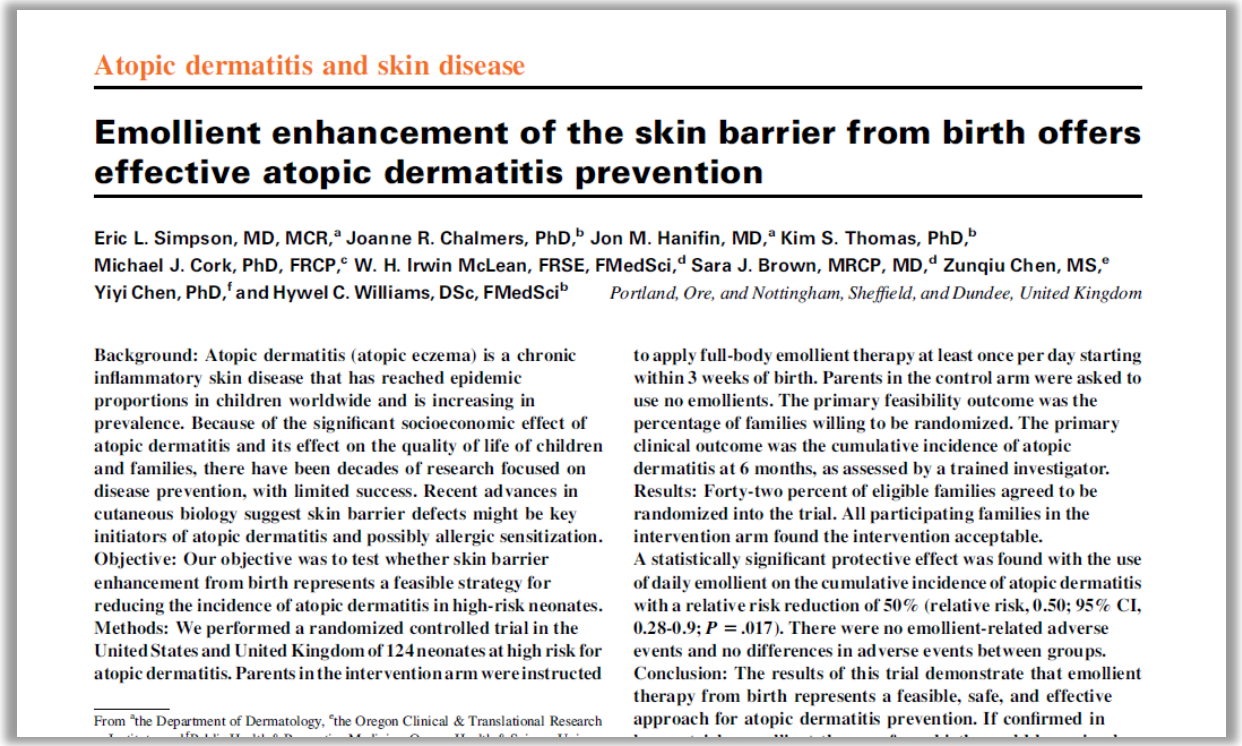
Wisniewski JA, *et al.* Sensitization to food and inhalant allergens in relation to age and wheeze among children with atopic dermatitis. *Clin Exp Allergy*. 2013;43(10):1160-70.

The allergic march is initiated in the skin

Children with AD accumulate sensitivities to different types of allergens as they grow into adolescence

- Development of the "allergic march" starts with AD which then gives way to food and respiratory allergies and asthma
- Children with AD showed an evolution of their sensitivities (as measured by IgE) over time
  - Food sensitivities developed in infancy and remained stable over time
  - Aeroallergen sensitivities showed a strong continuous increase from childhood through adolescence
- These findings argue for early intervention strategies designed to mitigate skin inflammation in children with AD

EMOLLIENT USE CAN PREVENT ATOPIC DERMATITIS



Atopic dermatitis and skin disease

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

Eric L. Simpson, MD, MCR,[a] Joanne R. Chalmers, PhD,[b] Jon M. Hanifin, MD,[a] Kim S. Thomas, PhD,[b] Michael J. Cork, PhD, FRCP,[c] W. H. Irwin McLean, FRSE, FMedSci,[d] Sara J. Brown, MRCP, MD,[d] Zunqiu Chen, MS,[e] Yiyi Chen, PhD,[f] and Hywel C. Williams, DSc, FMedSci[b] *Portland, Ore, and Nottingham, Sheffield, and Dundee, United Kingdom*

Background: Atopic dermatitis (atopic eczema) is a chronic inflammatory skin disease that has reached epidemic proportions in children worldwide and is increasing in prevalence. Because of the significant socioeconomic effect of atopic dermatitis and its effect on the quality of life of children and families, there have been decades of research focused on disease prevention, with limited success. Recent advances in cutaneous biology suggest skin barrier defects might be key initiators of atopic dermatitis and possibly allergic sensitization. Objective: Our objective was to test whether skin barrier enhancement from birth represents a feasible strategy for reducing the incidence of atopic dermatitis in high-risk neonates. Methods: We performed a randomized controlled trial in the United States and United Kingdom of 124 neonates at high risk for atopic dermatitis. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once per day starting within 3 weeks of birth. Parents in the control arm were asked to use no emollients. The primary feasibility outcome was the percentage of families willing to be randomized. The primary clinical outcome was the cumulative incidence of atopic dermatitis at 6 months, as assessed by a trained investigator. Results: Forty-two percent of eligible families agreed to be randomized into the trial. All participating families in the intervention arm found the intervention acceptable. A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of atopic dermatitis with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; $P = .017$). There were no emollient-related adverse events and no differences in adverse events between groups. Conclusion: The results of this trial demonstrate that emollient therapy from birth represents a feasible, safe, and effective approach for atopic dermatitis prevention. If confirmed in

From [a]the Department of Dermatology, [e]the Oregon Clinical & Translational Research

Simpson EL, *et al.* Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

Daily emollient therapy in newborns significantly prevented AD at 6 months of age

- Newborns at high risk for atopic dermatitis received full-body application of an emollient at least once per day starting within 3 weeks of birth
- Emollients prevent skin barrier dysfunction: Treating newborns with daily full-body emollient therapy led to a 50% decrease in AD after 6 months *vs* controls (p=0.017)

AD PREVENTION WITH EMOLLIENTS IS BEING RIGOROUSLY TESTED

Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial

Joanne R. Chalmers[1*], Rachel H. Haines[2], Eleanor J. Mitchell[2], Kim S. Thomas[1], Sara J. Brown[3,4], Matthew Ridd[5], Sandra Lawton[6], Eric L. Simpson[7], Michael J. Cork[8], Tracey H. Sach[9], Lucy E. Bradshaw[2], Alan A. Montgomery[2], Robert J. Boyle[10] and Hywel C. Williams[1]

Abstract

Background: Atopic eczema (AE) is a common skin problem that impairs quality of life and is associated with the development of other atopic diseases including asthma, food allergy and allergic rhinitis. AE treatment is a significant cost burden for health care providers. The purpose of the trial is to investigate whether daily application of emollients for the first year of life can prevent AE developing in high-risk infants (first-degree relative with asthma, AE or allergic rhinitis).

Methods: This is a protocol for a pragmatic, two-arm, randomised controlled, multicentre trial. Up to 1400 term infants at high risk of developing AE will be recruited through the community, primary and secondary care in England. Participating families will be randomised in a 1:1 ratio to receive general infant skin-care advice, or general

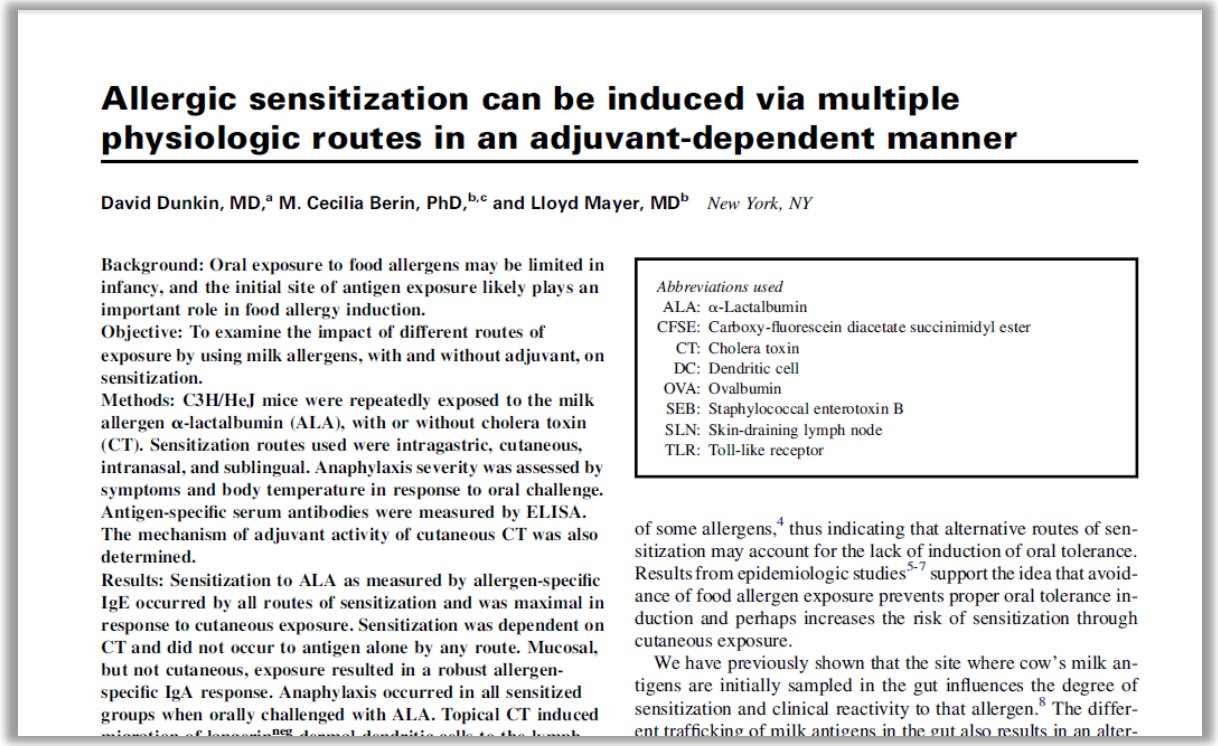
Chalmers JR, *et al.* Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials*. 2017;18(1):343.

The effect of emollients on prevention of AD and allergies is the topic of a major study

A large, independently funded study is being undertaken to test the long-term effect of daily emollient application on AD and allergies

- The BEEP study is a large, rigorous randomized controlled trial to the benefits of daily emollient application in the first year of life on prevention of AD
  - Up to 1400 high-risk infants included
  - AE will be assessed in a blinded manner at Year 2
  - Funded by the National Institute for Health Research (NIHR) in the UK
- The study will show whether emollients are effective, cost-effective, whether their effects persists through 5 years of age and whether emollients reduce the severity of any AD that does develop
- The effect on any other allergic conditions associated with atopic eczema (allergic rhinitis, asthma and food allergy) will also be assessed

THE SKIN IS THE EASIEST ROUTE TO SENSITIZATION



Allergic sensitization can be induced via multiple physiologic routes in an adjuvant-dependent manner

David Dunkin, MD,[a] M. Cecilia Berin, PhD,[b,c] and Lloyd Mayer, MD[b] *New York, NY*

Background: Oral exposure to food allergens may be limited in infancy, and the initial site of antigen exposure likely plays an important role in food allergy induction.
Objective: To examine the impact of different routes of exposure by using milk allergens, with and without adjuvant, on sensitization.
Methods: C3H/HeJ mice were repeatedly exposed to the milk allergen α-lactalbumin (ALA), with or without cholera toxin (CT). Sensitization routes used were intragastric, cutaneous, intranasal, and sublingual. Anaphylaxis severity was assessed by symptoms and body temperature in response to oral challenge. Antigen-specific serum antibodies were measured by ELISA. The mechanism of adjuvant activity of cutaneous CT was also determined.
Results: Sensitization to ALA as measured by allergen-specific IgE occurred by all routes of sensitization and was maximal in response to cutaneous exposure. Sensitization was dependent on CT and did not occur to antigen alone by any route. Mucosal, but not cutaneous, exposure resulted in a robust allergen-specific IgA response. Anaphylaxis occurred in all sensitized groups when orally challenged with ALA. Topical CT induced

Abbreviations used
ALA: α-Lactalbumin
CFSE: Carboxy-fluorescein diacetate succinimidyl ester
CT: Cholera toxin
DC: Dendritic cell
OVA: Ovalbumin
SEB: Staphylococcal enterotoxin B
SLN: Skin-draining lymph node
TLR: Toll-like receptor

of some allergens,[4] thus indicating that alternative routes of sensitization may account for the lack of induction of oral tolerance. Results from epidemiologic studies[5-7] support the idea that avoidance of food allergen exposure prevents proper oral tolerance induction and perhaps increases the risk of sensitization through cutaneous exposure.

We have previously shown that the site where cow's milk antigens are initially sampled in the gut influences the degree of sensitization and clinical reactivity to that allergen.[8] The differ-

Dunkin D, *et al.* Allergic sensitization can be induced via multiple physiologic routes in an adjuvant-dependent manner. *J Allergy Clin Immunol.* 2011;128(6):1251-1258.e2.

While sensitization can occur via all routes of exposure, the skin shows the highest response

In a mouse model for sensitization, cutaneous exposure generated the highest levels of allergen-specific IgE

- The impact of allergen (the milk protein ALA) exposure via the gut, sublingual, nasal or cutaneous routes was tested
- While an IgE response could be induced via all sites, the epicutaneous route showed a significantly higher symptomatic response in the as compared with the oral route
- This suggests that skin is a potent important physiologic route of sensitization, with the sensitization response being initiated in the skin itself

FOOD ALLERGY CAN BE INITIATED BY IMMUNE RESPONSE IN THE SKIN

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Exposure to food allergens through inflamed skin promotes intestinal food allergy via the TSLP-basophil axis

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Noti M, *et al.* Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. *J Allergy Clin Immunol.* 2014;133(5):1390-9, 1399.e1-6.

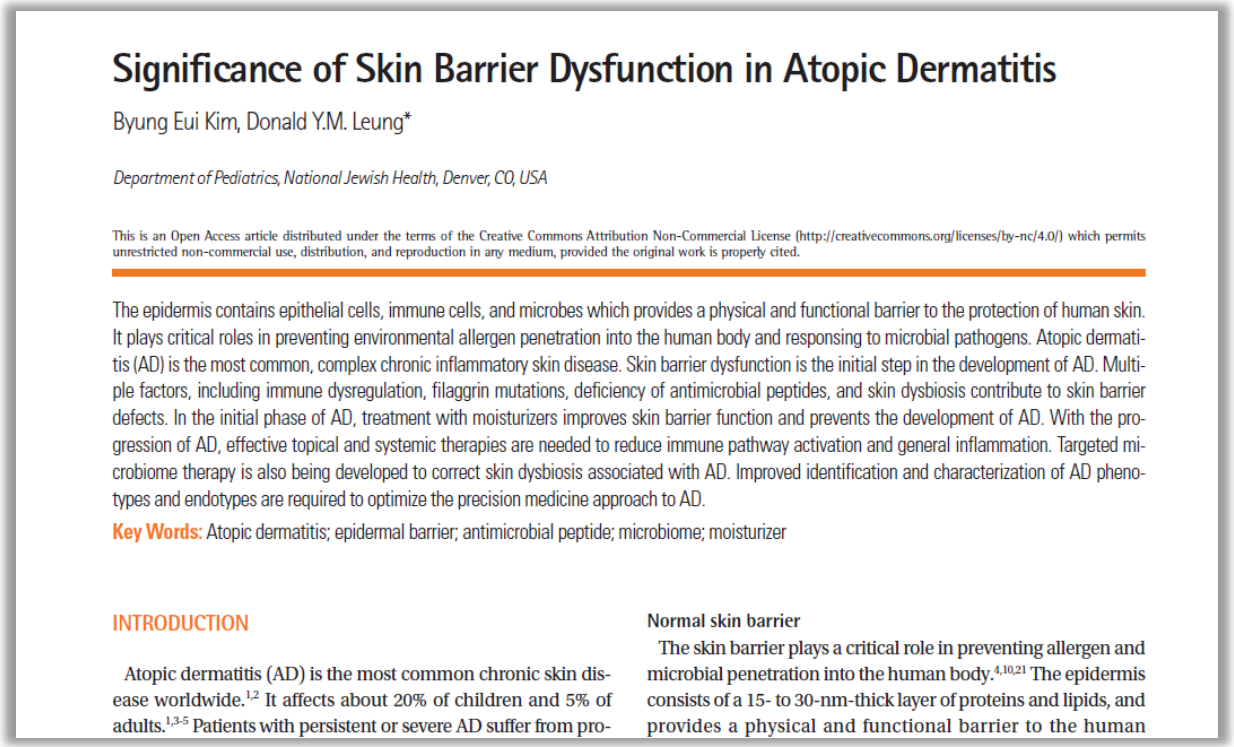
The skin's own immune response initiates food allergy when first exposure occurs via the skin

In a mouse model of allergy based on transcutaneous sensitization, immune response in the skin was necessary for food allergy

- Mice sensitized to the food antigen ovalbumin on a developing AD-like skin lesion showed allergic responses in the gut upon intragastric challenge
- Intestinal food allergy was shown to be dependent on basophils infiltration of the skin, leading to antigen-specific Th2 cytokine responses

REVIEW ARTICLES

SKIN BARRIER FUNCTION IN DEPTH



Significance of Skin Barrier Dysfunction in Atopic Dermatitis

Byung Eui Kim, Donald Y.M. Leung*

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The epidermis contains epithelial cells, immune cells, and microbes which provides a physical and functional barrier to the protection of human skin. It plays critical roles in preventing environmental allergen penetration into the human body and responsing to microbial pathogens. Atopic dermatitis (AD) is the most common, complex chronic inflammatory skin disease. Skin barrier dysfunction is the initial step in the development of AD. Multiple factors, including immune dysregulation, filaggrin mutations, deficiency of antimicrobial peptides, and skin dysbiosis contribute to skin barrier defects. In the initial phase of AD, treatment with moisturizers improves skin barrier function and prevents the development of AD. With the progression of AD, effective topical and systemic therapies are needed to reduce immune pathway activation and general inflammation. Targeted microbiome therapy is also being developed to correct skin dysbiosis associated with AD. Improved identification and characterization of AD phenotypes and endotypes are required to optimize the precision medicine approach to AD.

Key Words: Atopic dermatitis; epidermal barrier; antimicrobial peptide; microbiome; moisturizer

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic skin disease worldwide.[1,2] It affects about 20% of children and 5% of adults.[1,3-5] Patients with persistent or severe AD suffer from pro-

Normal skin barrier

The skin barrier plays a critical role in preventing allergen and microbial penetration into the human body.[4,10,21] The epidermis consists of a 15- to 30-nm-thick layer of proteins and lipids, and provides a physical and functional barrier to the human

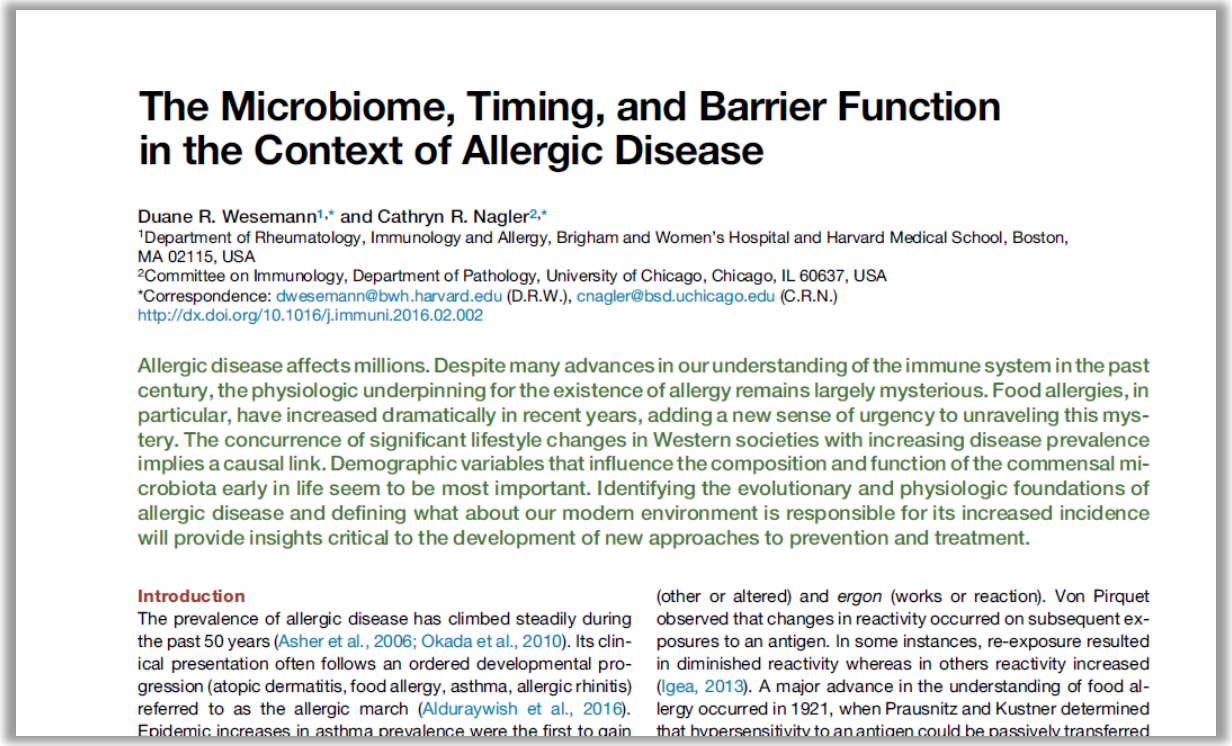
Kim BE, Leung DYM. Significance of skin barrier dysfunction in atopic dermatitis. *Allergy Asthma Immunol Res*. 2018;10(3):207-215.

The epidermis provides both a physical and functional barrier to the skin

Impaired skin barrier enhances allergen penetration and activates the innate immune system

- The epidermis contains epithelial cells, immune cells, and microbes which act as a physical and functional barrier
- AD is not just a local skin disease, but a systemic immune disease
- Recent studies have demonstrated that moisturizers reduce rates of AD development

THE BARRIER REGULATION HYPOTHESIS OF ALLERGY



The Microbiome, Timing, and Barrier Function in the Context of Allergic Disease

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[2]Committee on Immunology, Department of Pathology, University of Chicago, Chicago, IL 60637, USA
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http://dx.doi.org/10.1016/j.immuni.2016.02.002

Allergic disease affects millions. Despite many advances in our understanding of the immune system in the past century, the physiologic underpinning for the existence of allergy remains largely mysterious. Food allergies, in particular, have increased dramatically in recent years, adding a new sense of urgency to unraveling this mystery. The concurrence of significant lifestyle changes in Western societies with increasing disease prevalence implies a causal link. Demographic variables that influence the composition and function of the commensal microbiota early in life seem to be most important. Identifying the evolutionary and physiologic foundations of allergic disease and defining what about our modern environment is responsible for its increased incidence will provide insights critical to the development of new approaches to prevention and treatment.

Introduction

The prevalence of allergic disease has climbed steadily during the past 50 years (Asher et al., 2006; Okada et al., 2010). Its clinical presentation often follows an ordered developmental progression (atopic dermatitis, food allergy, asthma, allergic rhinitis) referred to as the allergic march (Alduraywish et al., 2016). Epidemic increases in asthma prevalence were the first to gain

(other or altered) and *ergon* (works or reaction). Von Pirquet observed that changes in reactivity occurred on subsequent exposures to an antigen. In some instances, re-exposure resulted in diminished reactivity whereas in others reactivity increased (Igea, 2013). A major advance in the understanding of food allergy occurred in 1921, when Prausnitz and Kustner determined that hypersensitivity to an antigen could be passively transferred

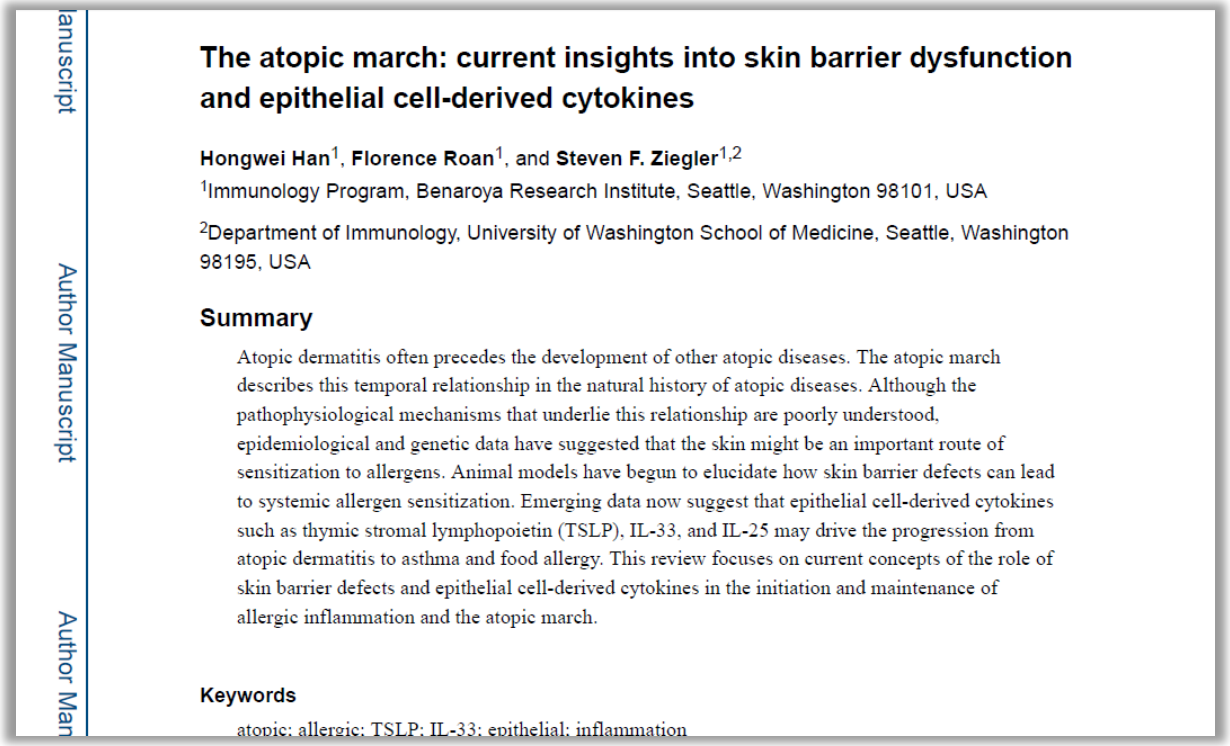
Wesemann DR, Nagler CR. The microbiome, timing, and barrier function in the context of allergic disease. *Immunity*. 2016;44(4):728-38.

Allergy risk could essentially be a function of barrier integrity

Differences in skin barrier function between individuals could explain differences in susceptibility to allergy

- A barrier regulation hypothesis of allergy suggests that diverse barrier mechanisms including allergen exclusion and deactivation might underlie varying allergy risk.
  - In the context of food allergy, non-food-allergic individuals might have relatively more effectual barrier immunity—thus leaving the allergic response untriggered
  - Allergen penetration of barriers might induce perturbations that lead to epithelial stress, which can set the stage for a Th2 cell response

SKIN BARRIER DYSFUNCTION & THE ALLERGIC MARCH



The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines

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Summary

Atopic dermatitis often precedes the development of other atopic diseases. The atopic march describes this temporal relationship in the natural history of atopic diseases. Although the pathophysiological mechanisms that underlie this relationship are poorly understood, epidemiological and genetic data have suggested that the skin might be an important route of sensitization to allergens. Animal models have begun to elucidate how skin barrier defects can lead to systemic allergen sensitization. Emerging data now suggest that epithelial cell-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 may drive the progression from atopic dermatitis to asthma and food allergy. This review focuses on current concepts of the role of skin barrier defects and epithelial cell-derived cytokines in the initiation and maintenance of allergic inflammation and the atopic march.

Keywords

atopic; allergic; TSLP; IL-33; epithelial; inflammation

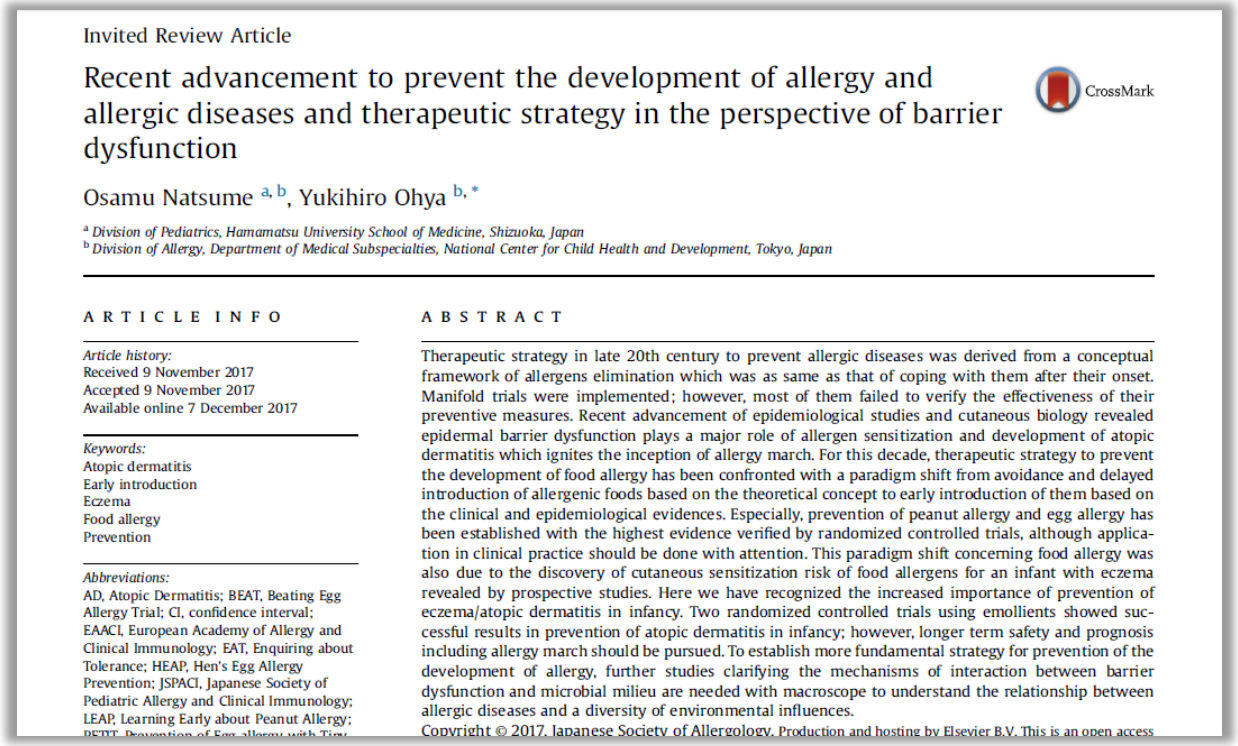
Han H, *et al.* The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev.* 2017;278(1):116-130.

Skin barrier function could help explain progression of the allergic march

The skin barrier and the skin immune system play key roles in the allergic march

- Atopic dermatitis often precedes the development of other allergic diseases
- While this progression is not yet well understood, the skin appears to act as a key route to sensitization to allergens

EMOLLIENT USE SLOWS THE ALLERGIC MARCH



Invited Review Article

Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction

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Keywords:
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Abbreviations:
AD, Atopic Dermatitis; BEAT, Beating Egg Allergy Trial; CI, confidence interval; EAACI, European Academy of Allergy and Clinical Immunology; EAT, Enquiring about Tolerance; HEAP, Hen's Egg Allergy Prevention; JSPACI, Japanese Society of Pediatric Allergy and Clinical Immunology; LEAP, Learning Early about Peanut Allergy;

ABSTRACT

Therapeutic strategy in late 20th century to prevent allergic diseases was derived from a conceptual framework of allergens elimination which was as same as that of coping with them after their onset. Manifold trials were implemented; however, most of them failed to verify the effectiveness of their preventive measures. Recent advancement of epidemiological studies and cutaneous biology revealed epidermal barrier dysfunction plays a major role of allergen sensitization and development of atopic dermatitis which ignites the inception of allergy march. For this decade, therapeutic strategy to prevent the development of food allergy has been confronted with a paradigm shift from avoidance and delayed introduction of allergenic foods based on the theoretical concept to early introduction of them based on the clinical and epidemiological evidences. Especially, prevention of peanut allergy and egg allergy has been established with the highest evidence verified by randomized controlled trials, although application in clinical practice should be done with attention. This paradigm shift concerning food allergy was also due to the discovery of cutaneous sensitization risk of food allergens for an infant with eczema revealed by prospective studies. Here we have recognized the increased importance of prevention of eczema/atopic dermatitis in infancy. Two randomized controlled trials using emollients showed successful results in prevention of atopic dermatitis in infancy; however, longer term safety and prognosis including allergy march should be pursued. To establish more fundamental strategy for prevention of the development of allergy, further studies clarifying the mechanisms of interaction between barrier dysfunction and microbial milieu are needed with macroscope to understand the relationship between allergic diseases and a diversity of environmental influences.

Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction *Allergol Int.* 2018;67(1):24-31.

Early skin protection with emollients could help slow the allergic march

Reinforcing skin barrier function with emollients repairs and prevents damage

- Two randomized controlled trials using emollients showed successful results in prevention of atopic dermatitis in infancy
- In a context where allergy prevention is shifting from allergen avoidance to tolerance, emollients could provide protection from environmental factors