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ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Infant lung function and early skin barrier impairment in the development of asthma at age 3 years

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Abstract

Background: Largely unexplored, we investigated if lower lung function, impaired skin barrier function by transepidermal water loss (TEWL), eczema, and filaggrin (*FLG*) mutations in infancy were associated with asthma in early childhood.

Methods: From the factorially designed randomized controlled intervention study PreventADALL, we evaluated 1337/2394 children from all randomization groups with information on asthma at age 3 years, and at age 3 months either lung function, TEWL, eczema, and/or *FLG* mutations. Lower lung function was defined as the time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) <0.25, and skin barrier impairment as a high TEWL >9.50 g/m^2/h. Eczema was clinically observed, and DNA genotyped for *FLG* mutations. Asthma was defined as asthma-like symptoms (≥3 episodes of bronchial obstruction) between age 2–3 years as well as a history of doctor-diagnosed asthma and/or asthma medication use. Associations were analyzed in logistic regression models, presented with adjusted ORs (aOR) and 95% confidence intervals (CI).

Abbreviations: AD, atopic dermatitis; aOR, adjusted odds ratio; AS, allergic sensitization; CI, confidence interval; *FLG*, filaggrin; g/m^2/h, grams per square meter per hour; GA, gestational age; H&R, Hanifin and Rajka; OR, odds ratio; PreventADALL, Preventing Atopic Dermatitis and ALLergies in children; rBO, recurrent bronchial obstruction; SPT, skin prick test; TEWL, transepidermal water loss; TFV, tidal flow-volume; t_{PTEF}, time to peak tidal expiratory flow; t_{PTEF}/t_E, time to peak tidal expiratory flow to expiratory time; UKWP, United Kingdom Working Party.

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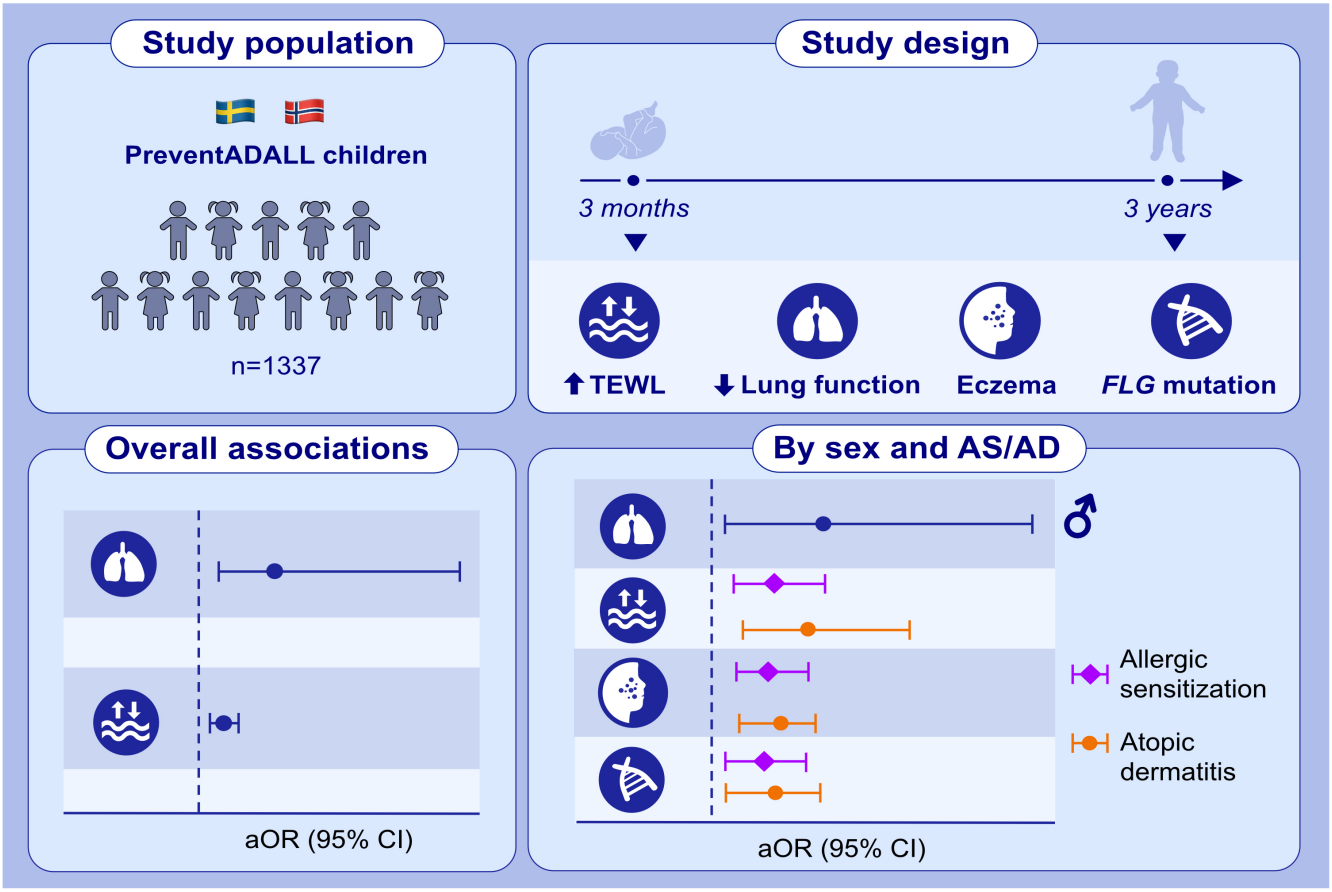
Results: Lower lung function and skin barrier impairment were associated with asthma in general; aOR (95% CI) 5.4 (2.1, 13.7) and 1.6 (1.1, 2.5), while eczema and *FLG* mutations were associated with asthma in children with atopic dermatitis or allergic sensitization only. Stratifying for sex, the risk of asthma was only increased in boys with lower lung function; aOR (95% CI) 7.7 (2.5, 23.6), and in girls with *FLG* mutations; aOR (95% CI) 3.5 (1.5, 8.2).

Conclusion: Lower lung function and impaired skin barrier function in infancy may increase the risk of asthma at age 3 years.

KEYWORDS
asthma, infants, lung function, PreventADALL, skin barrier function



GRAPHICAL ABSTRACT

In a large pediatric population from the factorially designed randomized controlled intervention study PreventADALL, we investigated if lower lung function, impaired skin barrier function by TEWL, eczema at age 3 months and *FLG* mutations were associated with asthma at age 3 years. Lower lung function and skin barrier impairment in infancy increased the risk of asthma in general. Stratifying for sex, the risk of asthma was only increased in boys with lower lung function. Eczema and *FLG* mutations were associated with asthma in children with AD or AS only.

Abbreviations: AD, atopic dermatitis; AS, allergic sensitization; aOR, adjusted odds ratio; CI, confidence interval; *FLG*, filaggrin; PreventADALL, Preventing Atopic Dermatitis and ALLergies in children; TEWL, transepidermal water loss.

1 | INTRODUCTION

Asthma is among the most common respiratory disorders in children affecting 10%–20% worldwide,[1] characterized by airway inflammation, reversible airflow obstruction, and hyperresponsiveness. Typical asthma symptoms of wheeze, shortness of breath, and cough may be triggered by viral infections, physical activity, allergens, and pollutants.[1] Children with wheezy episodes up to school age are often classified in trajectories such as never/infrequent, early transient, late onset, or persistent wheeze.[2] While many outgrow the asthma-like symptoms, others have the first manifestations of persistent asthma in preschool years,[3] pointing to the uncertainty of diagnosing asthma at this age. Nevertheless, a recent Canadian birth cohort study reported a 20–150-fold increased risk of asthma at 5 years in all wheeze trajectories.[4] Treating preschool recurrent wheeze aims to improve control and prevent asthma exacerbations,[5] emphasizing the need for a disease label. *Asthma* in young children as an umbrella term may acknowledge the uncertainty of prognosis yet highlighting the presenting symptoms and signs often requiring pharmacological treatment. While the underlying causes of asthma remain undetermined, the roots likely origin from early life.[4] Atopic dermatitis (AD), a common inflammatory skin disorder in infancy, often precedes asthma development,[6] indicating a possible link between the allergic diseases in early childhood.[7]

Impaired skin barrier function is hypothesized to contribute to the development of inflammatory disorders, including allergic conditions of the skin and the lungs.[8] As the first defense against allergens and irritants that enter through a disrupted epithelial barrier, innate cells of the skin[9] and lungs[10] initiate a cascade of immunological responses, in particular allergic sensitization (AS),[11] involved in both AD and asthma development (Figure 1).[12] The filaggrin (*FLG*) gene is essential for normal epidermal differentiation, with loss-of-function mutations accelerating AD development.[13] An impaired skin barrier function, assessed by transepidermal water loss (TEWL), enables water to passively evaporate from the epidermis.[14] Elevated TEWL in infancy and *FLG* mutations precede the clinical eczematous skin lesions in AD,[14–16] and are both associated with AD[15,16] as well as AS.[11,17]

Lung function in early infancy can be measured with tidal flow-volume (TFV) loops, with a lower ratio of time to reach peak tidal expiratory flow (t_{PTEF}) to expiratory time (t_E) observed in infants with airway obstruction.[18] Lower t_{PTEF}/t_E in infancy increases the risk of developing childhood asthma,[19] and lower lung function was tracked from birth to adolescence in asthmatic children with allergic comorbidities.[20] In addition, infants and children with airway obstruction generally reach t_{PTEF} earlier during expiration.[21–24] Recently, we

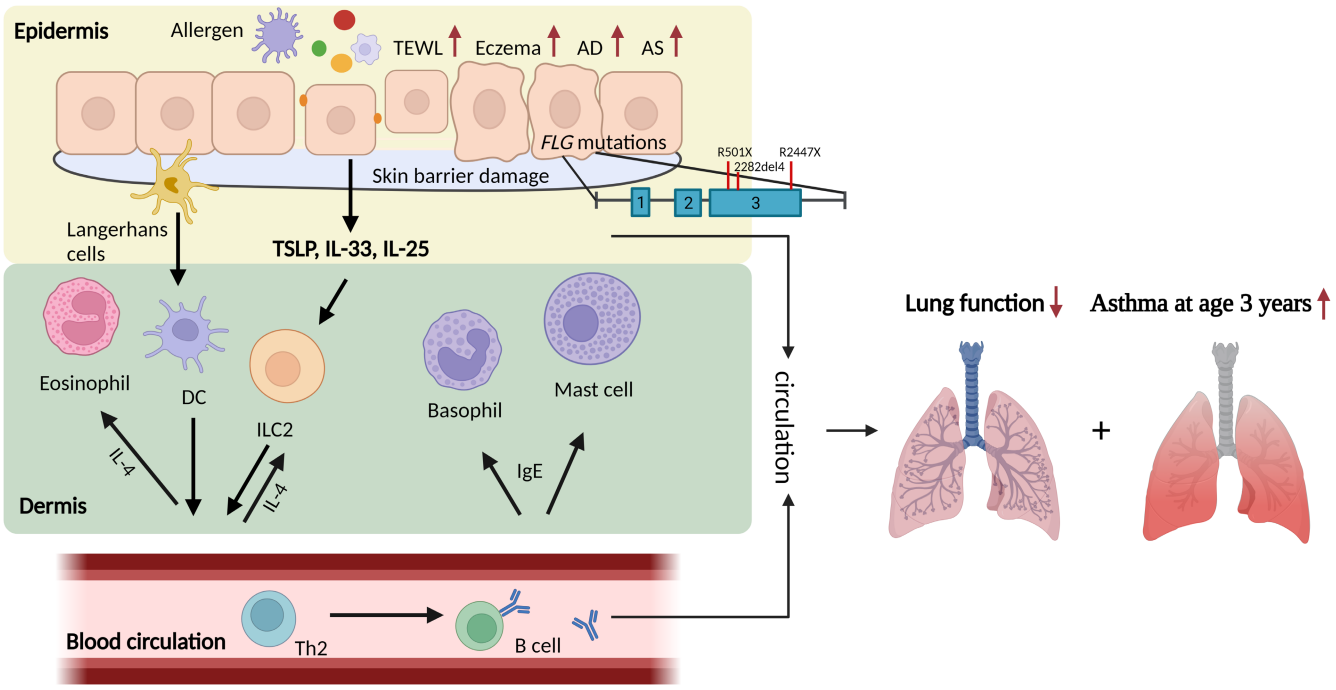


FIGURE 1 Model of the possible contribution of an impaired skin barrier function to the development of inflammatory disorders, including allergic conditions of the skin and the lungs. The first step is the penetration of allergens through an impaired skin barrier due to loss-of-function mutations (R501X, 2282del4, R2447X) in the skin barrier filaggrin (FLG) gene, high transepidermal water loss (TEWL), and/or the presence of eczema. Stimulated by allergens, innate epithelial cells of the skin release cytokines (such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33). In the next step innate immune cells (for instance eosinophils, mast cells, and basophils) are activated, secreting the IL-4 cytokine. Activated innate immune cells create T-helper type 2 (Th2) cells, also producing IL-4, and immunoglobulin E (IgE) in the lymphatic organs. The positive feedback loop of IgE to mast cells and basophils causes the phenotype of atopic dermatitis. TSLP, IgE, Th2 cells, and the interleukins IL-25 and IL-33 are thought to enter the respiratory tract via the blood circulation and hereby lead to the development of asthma. The original figure by Yang et al.[12] was modified for this article. Created with Biorender.com. TEWL, transepidermal water loss; FLG, filaggrin; AD, atopic dermatitis; AS, allergic sensitization; TSLP, thymic stromal lymphopoietin; IL-33, interleukin-33; IL-25, interleukin-25; DC, dendritic cells; ILC2, innate lymphoid cells type 2; IL-4, interleukin-4; Th2, T-helper type 2 cells.

reported a possible link between higher TEWL and lower lung function by t_{PTEF},[18] suggesting that an impaired skin barrier function may play a role in asthma development.

Although both lower lung function and impaired skin barrier have been associated with later asthma, the contribution of the potential risk factors in early infancy remains largely unexplored. Our hypothesis is that both lower lung function and impaired skin barrier function in early life are linked to the development of asthma. Primarily we aimed to investigate if (1) lower lung function, (2) impaired skin barrier function by high TEWL and (3) eczema at 3 months, as well as (4) *FLG* mutations were associated with asthma at age 3 years, secondarily to explore if the possible associations (1–4) differed by sex, or thirdly, by a diagnosis of AD or AS by age 3 years.

2 | METHODS

2.1 | Study design

The present study is based on information prospectively collected from the population-based Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) mother–child birth cohort, a 2×2, factorially designed, cluster-randomized, controlled trial.[25,26] At birth, the infants were randomly assigned (1:1:1:1) to one of the four groups "no intervention," "skin care (0-9 months)," "early food introduction (3-4 months)," and "combined skin and food interventions." Mothers were recruited by inviting pregnant women at the routine ultrasound examination at 18 weeks gestational age (GA) in Norway and Sweden between 2014 and 2016. Their children (n = 2397), born without serious illnesses at GA ≥35 weeks, were enrolled during the first days of life. Consent was withdrawn for three children.

The 3-month follow-up included measurements of lung function and skin barrier function, clinical skin assessments and collection of blood samples (Figure 2).

2.2 | Study population

The study population consisted of 1337/2394 PreventADALL children with information on asthma-like symptoms, diagnosis and/or treatment at age 3 years, as well as either available TFV loop measurements in the awake state, TEWL, eczema at age 3 months, and/or *FLG* mutations.

2.3 | Data collection

2.3.1 | Exposures

Lung function

Infant lung function was determined by TFV loops, using the employed Exhalyzer® D (Eco Medics AG, Duernten, Switzerland) and a face mask covering mouth and nose of calm infants lying in the supine position. All measurements were manually analyzed according to a standard operating procedure.[27] Lower lung function at age 3 months was defined as a t_{PTEF}/t_E <0.25,[19,28–30] and/or a shorter t_{PTEF} <0.17 s (lower 25th percentile).[21–23]

Skin barrier function

Skin barrier function was measured by TEWL (g/m^2/h) using the open chamber DermaLab USB (Cortex, Hadsund, Denmark). Room temperature was between 20 and 25°C, humidity ranged between 6.4% and 72.9% (mean 30.9%), and windows and doors were kept

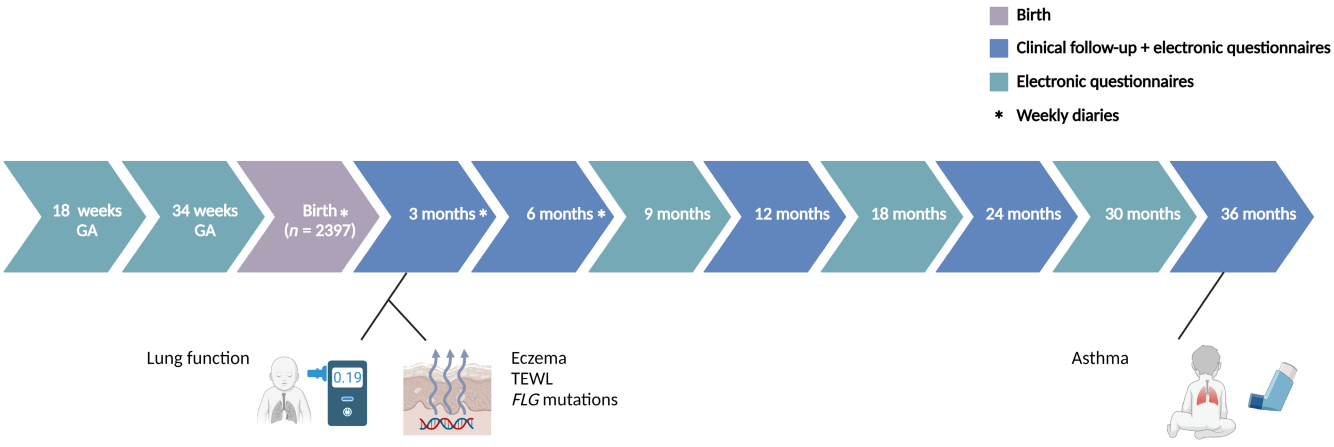


FIGURE 2 Timeline of the PreventADALL birth cohort study. Birth and background characteristics were obtained from electronic questionnaires in pregnancy and from medical records. Follow-up included weekly diaries (Weeks 2–26), electronic questionnaires as well as clinical follow-ups. The current study investigated the association between lung function, TEWL, eczema at 3 months, as well as FLG mutations and asthma at age 3 years. Created with Biorender.com. GA, gestational age, TEWL, transepidermal water loss; FLG, filaggrin.

closed. Measurements were conducted in triplicates on the lateral upper arm of calm infants after 15 min of acclimatization, wearing only diapers. Impaired skin barrier at age 3 months was defined as a TEWL value >9.50 g/m^2/h (upper 75th percentile).[11]

Clinical skin assessments

Examinations were carried out by trained study personnel. Parents were instructed not to bathe the infants with oils or apply skin emollients 24 h before the examinations.

Eczema

Eczema at age 3 months was defined as having clinically observed eczematous skin lesions with the exclusion of common differential diagnosis to AD, such as seborrheic and contact dermatitis, confirmed by physicians.[31]

Atopic dermatitis

Atopic dermatitis by age 3 years was defined as fulfilling the diagnostic criteria for AD at one of the clinical follow-up investigations through either United Kingdom Working Party (UKWP) (3, 6, 12, or 36 months) and/or Hanifin and Rajka (H&R) (12, 24, or 36 months) criteria.[32]

Allergic sensitization

Skin prick tests (SPT) were performed using standard allergen solutions for birch, timothy grass, dog, cat, house dust mite, egg, cow's milk, peanut, wheat, soy, and cod (Soluprick ALK-Albelló, Hørsholm, Denmark). AS by age 3 years was defined as having a positive SPT with a median skin wheal diameter of ≥2 mm at age 6 months and/or ≥3 mm toward at least one allergen at age 1 and/or 3 years.[33]

Filaggrin mutations

DNA was extracted from blood and genotyped for the most common European loss-of-function mutations in the *FLG* gene (R501X, 2282del4 and R2447X), using the TaqMan-based allelic discrimination assay, described by Hoyer et al.[16] Having a *FLG* mutation was defined as being carrier of any of the three mutations.[16]

2.3.2 | Outcomes

Asthma at age 3 years

Episodes of bronchial obstruction and doctor-diagnosed asthma were documented in all questionnaires and at clinical follow-ups after the first year of life. Asthma medication use was recorded in questionnaires. In addition, the children's medical records were screened for the prescription of asthma medication between age 9 months and 3 years to compensate for missing information. Asthma at age 3 years was defined as having ≥3 recurrent bronchial obstruction episodes between age 2 and 3 years, and fulfilling at least one of two criteria: (1) doctor-diagnosed asthma by age 3 years, and/or (2) any use of prescribed asthma medications (bronchodilators, inhaled corticosteroids, or leukotriene-antagonist) between age 9 months and 3 years.[34]

Asthma at age 3 years with a diagnosis of AD by 3 years was defined as fulfilling the UKWP and/or H&R criteria[32] by age 3 years, in addition to fulfilling the criteria for asthma at age 3 years.

Asthma at age 3 years with a diagnosis of AS by 3 years was defined as having a positive SPT to any inhalant or food allergen by age 3 years, in addition to fulfilling the criteria for asthma at age 3 years.

2.4 | Statistical analyses

Comparisons were performed using independent *t*-tests for continuous variables presented with means and standard deviations (SD), and chi-square tests for categorical variables presented with numbers (*n*) and percentages (%). The relationship between lower t_{PTEF}/t_E, shorter t_{PTEF}, high TEWL, eczema, and *FLG* mutations was explored using Spearman's rank correlation, presented with Spearman's rho and 95% confidence intervals (CI). Associations between lower and continuous t_{PTEF}/t_E and shorter and continuous t_{PTEF}, high and continuous TEWL, eczema, *FLG* mutations, and asthma at age 3 years were examined in separate univariate and multivariate logistic regression models, as well as multinominal logistic regression in models including asthma at age 3 years with a diagnosis of either AD or AS by age 3 years. Based on the literature, sex,[35,36] GA,[35,37] tobacco smoke exposure in pregnancy,[38] urban living environment in pregnancy,[39,40] breastfeeding,[41,42] parental atopy,[43] parental education level,[44,45] study center,[46] and the PreventADALL interventions were treated as possible confounders. Models including *FLG* mutations were adjusted for sex.[16,47] Results are presented as odds ratio (OR) and adjusted OR (aOR) with 95% CI. Analyses for possible interactions between t_{PTEF}/t_E, t_{PTEF}, TEWL, eczema and *FLG* mutations, the PreventADALL interventions and asthma at age 3 years were conducted. Statistical analyses were performed using IBM SPSS Statistics 26 software. Statistical significance was set at a *p*-value <.05. Further details are described in Methods S1.

3 | RESULTS

3.1 | Study population

The study population included 1337 children, 635 (47.5%) girls and 702 (52.5%) boys, with a mean ± SD age of 3.1 ± 0.3 months and 3.2 ± 0.3 years at the 3-month and 3-year clinical follow-ups. At age 3 months, lung function was available in 563 infants with a mean t_{PTEF}/t_E of 0.39 ± 0.08 and a t_{PTEF} of 0.20 ± 0.05 s. Lower lung function was observed in 30 (5.3%) infants using t_{PTEF}/t_E and in 139 (24.7%) infants by t_{PTEF}. Skin barrier function was measured in 1173 infants at age 3 months, with a mean TEWL of 8.4 ± 6.1 g/m^2/h and impaired skin barrier function observed in 294 (25.1%) infants. Eczema at age 3 months was seen in 168/1318 infants (12.7%), while 96/1045 (9.2%) carried a *FLG* mutation (Figure S1). At age 3 years, 180/1337 (13.5%)

children had asthma (Table 1). The distribution of lower t_{PTEF}/t_E or shorter t_{PTEF}, as well as high TEWL, eczema, and *FLG* mutations among the children with asthma at age 3 years are shown in Figure S2A,B.

Children with asthma at age 3 years had a higher proportion of any parental atopy compared with children without asthma; 137/167 (82.0%) versus 685/1084 (63.2%) ($p < .001$).

TABLE 1 Birth and background characteristics of the included children with information on lung function, TEWL, eczema at 3 months, FLG mutations as well as asthma at age 3 years ($n = 1337$) compared with the remaining PreventADALL cohort ($n = 1057$).

	Included children ($n = 1337$)		Remaining cohort ($n = 1057$)		
Characteristics	***n* (%) or mean (SD)**	**No.**	***n* (%) or mean (SD)**	**No.**	***p*-value[†]**
Parents					
Nordic origin mother	1155 (91.2)	1266	808 (89.3)	905	.128
Nordic origin father	1141 (91.9)	1241	762 (86.8)	878	**<.001**
High household education ≥4 years	888 (71.9)	1235	567 (64.3)	882	**<.001**
Urban living environment pregnancy	1188 (93.8)	1266	825 (91.2)	905	**.018**
Married/cohabitant mother	1240 (97.7)	1269	883 (97.0)	910	.321
Parity ≥1	517 (38.7)	1336	445 (42.2)	1055	.085
Tobacco smoke in pregnancy	56 (4.2)	1337	48 (4.5)	1057	.674
Parental (any) atopy	822 (65.7)	1251	538 (62.1)	867	.085
Parental asthma	358 (29.5)	1212	249 (30.5)	816	.638
Parental atopic dermatitis	379 (31.8)	1190	236 (29.4)	803	.244
Parental food allergy	264 (22.8)	1157	187 (23.7)	789	.650
Parental allergic rhinitis	523 (45.0)	1163	308 (39.7)	776	**<.021**
Infants (birth)					
Girl	635 (47.5)	1337	504 (47.7)	1057	.927
GA in weeks	40.1 (1.34)	1333	40.0 (1.36)	1055	.816
Caesarian section	217 (16.3)	1330	172 (16.5)	1040	.885
Birth weight in kg	3.56 (0.49)	1331	3.59 (0.48)	1053	.148
Infants (3 months)					
Age in months	3.06 (0.25)	1319	3.09 (0.29)	805	**.018**
Weight in kg	6.23 (0.78)	1320	6.29 (0.78)	806	.115
Breastfed exclusively	823 (67.6)	1217	418 (65.8)	635	.435
Children (3 years)					
Age in months	38.1 (3.92)	1332	40.4 (6.01)	602	**<.001**
Weight in kg	15.2 (1.72)	1192	15.3 (1.63)	436	.185
Lung function (3 months)					
t_{PTEF}/t_E	0.39 (0.08)	563	0.39 (0.08)	336	.494
t_{PTEF} in s	0.20 (0.05)	563	0.21 (0.05)	336	.756
Skin barrier (3 months)					
Mean TEWL in $g/m^2/h$	8.41 (6.12)	1173	8.18 (5.55)	705	.423
Eczema	168 (12.7)	1318	92 (11.6)	794	.432
FLG mutations	96 (9.2)	1045	68 (8.7)	780	.729
Children (3 years)					
Age in months	38.1 (3.92)	1332	40.4 (6.01)	602	**<.001**
Weight in kg	15.2 (1.72)	1192	15.3 (1.63)	436	.185
Asthma	180 (13.5)	1337	2 (16.7)	12	.671
Children (by 3 years)					
Allergic sensitization	253 (19.0)	1334	105 (14.4)	731	**.008**
Atopic dermatitis	374 (28.0)	1337	169 (20.2)	837	**<.001**

Abbreviations: GA, gestational age; $g/m^2/h$, grams per square meter per hour.

[†]Independent *t*-test or chi-square test or Fisher's exact test.

Overall, 524/1337 (39.2%) infants had the lung condition (lower t_{PTEF}/t_E or shorter t_{PTEF}) or either of the three skin conditions (high TEWL, eczema, or *FLG* mutations). None of the 1337 children had all four conditions present in infancy. Associations were observed between high TEWL, eczema, and *FLG* mutations, as well as between t_{PTEF} and high TEWL (Tables S1 and S2).

Boys had higher rates of asthma at age 3 years compared to girls; 122/702 (17.4%) versus 58/635 (9.1%) (*p*-value <.05). The mean t_{PTEF}/t_E and t_{PTEF} were lower in boys compared to girls; 0.38 ± 0.08 versus 0.40 ± 0.08 and 0.20 ± 0.05 versus 0.21 ± 0.05 (*p*-values <.05), whereas the mean TEWL, rates of eczema, and *FLG* mutations were similar between the sexes.

While the distributions of t_{PTEF}/t_E, t_{PTEF}, TEWL, eczema at age 3 months, *FLG* mutations, and asthma at age 3 years were similar between the included children and the remaining cohort, AS and AD by 3 years of age were not. Among the children with asthma at age 3 years, 68/180 (37.8%) and 51/179 (28.5%) also had a diagnosis of AD of AS by age 3 years (Table S3).

Lower lung function was associated with asthma at age 3 years; aOR (95% CI) 5.4 (2.1, 13.7) for lower t_{PTEF}/t_E and 2.7 (1.5, 4.9) for shorter t_{PTEF}. A high TEWL was associated with asthma at age 3 years; aOR (95% CI) 1.6 (1.1, 2.5), while eczema or *FLG* mutations were not (Table 2; Figure 3).

Lower lung function was significantly associated with asthma at age 3 years in boys; aOR (95% CI) 7.7 (2.5, 23.6) for lower t_{PTEF}/t_E and 3.2 (1.5, 6.7), for shorter t_{PTEF}, while high TEWL, eczema, or *FLG* mutations were not. Carrying *FLG* mutations was associated with the development of asthma at age 3 years among girls; aOR (95% CI) 3.5 (1.5, 8.2), whereas none of the other conditions were (Table 3a,b; Figure 3).

Lower lung function was independently associated with asthma at age 3 years, whereas a high TEWL was only associated with asthma at age 3 years in children with a diagnosis of either AD; aOR (95% CI) 3.4 (1.8, 6.4), or AS; 6.8 (3.1, 14.9) by age 3 years. Similarly, eczema and *FLG* mutations were only associated with asthma at age 3 years in children with a diagnosis of either AD (eczema; 3.2 (1.6, 6.1), *FLG* mutations; 2.5 (1.2, 5.2)), or AS (eczema; 3.3 (1.6, 6.8), *FLG* mutations; 2.7 (1.2, 6.1)) by age 3 years (Table S4A,B).

While a shorter t_{PTEF} predicted asthma at age 3 years with 44.6% sensitivity, 78.3% specificity, and a ROC-AUC of 0.62 (95% CI 0.54, 0.69), neither of the three skin conditions did (Table S5).

No interaction effects between the lung and skin conditions, the PreventADALL interventions, and asthma at age 3 years were observed (data not shown).

4 | DISCUSSION

In this population-based study of 1337 children, lower lung function and impaired skin barrier function at age 3 months increased the risk of asthma at age 3 years, whereas *FLG* mutations or eczema at age 3 months did not. Stratifying for sex, the associations between lower infant lung function and asthma at age 3 years remained significant in boys only, whereas *FLG* mutations increased the risk in girls. While neither eczema at age 3 months nor *FLG* mutations alone increased the risk of asthma at age 3 years, their presence as well as skin barrier

TABLE 2 Crude and adjusted logistic regression models for t_{PTEF}/t_E and t_{PTEF}, TEWL, eczema at 3 months, FLG mutations, and asthma at age 3 years in the included children ($n = 1337$).

	Asthma at age 3 years					
Characteristics	**Crude OR (95% CI)**	**No.**	***p*-value**	**Adjusted OR (95% CI)**	**No.**	***p*-value**[†]
Lung function						
Lower t_{PTEF}/t_E[a]	4.32 (1.97, 9.50)	563	**<.001**	5.41 (2.13,13.7)	476	**<.001**
Continuous t_{PTEF}/t_E	0.00 (0.00, 0.06)	563	**<.001**	0.01 (0.00, 0.26)	476	**.007**
Shorter t_{PTEF}[b]	2.91 (1.75, 4.83)	563	**<.001**	2.70 (1.48, 4.93)	476	**.001**
Continuous t_{PTEF}	0.00 (0.00, 0.07)	563	**.005**	0.01 (0.00, 3.07)	476	.109
Skin barrier						
High TEWL[c]	1.45 (1.01, 2.08)	1173	**.045**	1.61 (1.06, 2.46)	957	**.026**
Continuous TEWL	1.03 (1.01, 1.05)	1173	**.016**	1.03 (1.00, 1.06)	957	**.046**
Eczema	1.41 (0.91, 2.18)	1318	.120	1.46 (0.88, 2.42)	1087	.139
FLG mutations	1.64 (0.95, 2.84)	1045	.076	1.57 (0.90, 2.73)	1045	.111

Abbreviations: t_{PTEF}, time to peak tidal expiratory flow; t_{PTEF}/t_E, time to peak tidal expiratory flow to expiratory time; TEWL, transepidermal water loss; FLG, filaggrin; $g/m^2/h$, grams per square meter per hour.

[†]Multivariate logistic regression models adjusted for sex, GA, tobacco smoke exposure in pregnancy, urban living environment in pregnancy, breastfeeding, parental atopy, parental education level, study center, and the PreventADALL interventions (models including *FLG* mutations adjusted for sex).

[a]A lower t_{PTEF}/t_E equals to a value <0.25.

[b]A shorter t_{PTEF} equals to a value <0.17 s (<25th percentile).

[c]A high TEWL equals to a value >9.50 $g/m^2/h$ (>75th percentile).

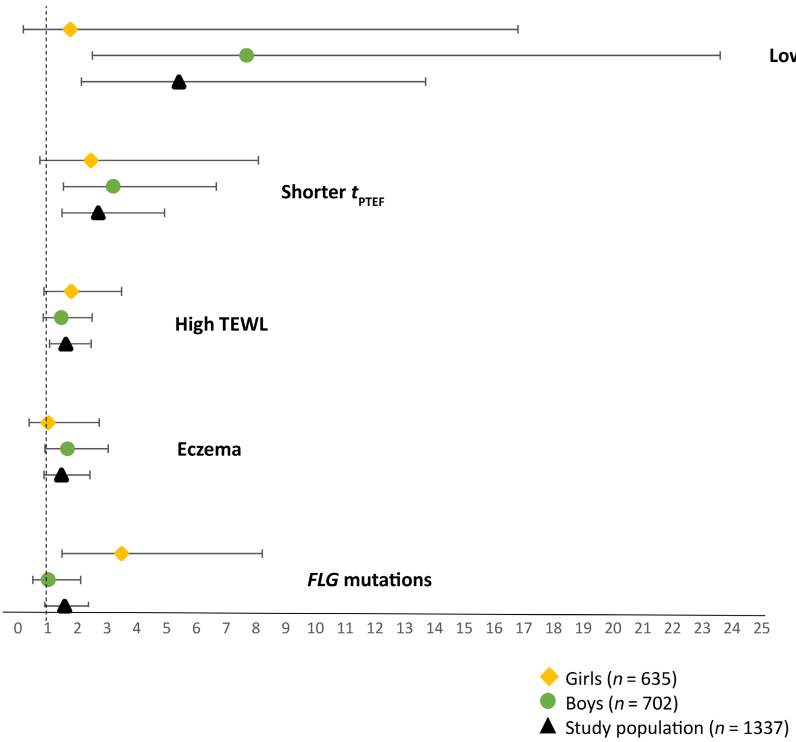


FIGURE 3 Adjusted OR (95% CI) for asthma at age 3 years, according to the presence of lower t_{PTEF}/t_E, shorter t_{PTEF}, high TEWL, eczema at 3 months and FLG mutations. t_{PTEF}/t_E, time to peak tidal expiratory flow to total expiratory time; t_{PTEF}, time to peak tidal expiratory flow; TEWL, transepidermal water loss; FLG, filaggrin.

impairment at age 3 months increased the risk of asthma at age 3 years if diagnosed with either AD or AS by age 3 years.

Lower infant lung function was associated with asthma at age 3 years, in line with previous studies.[19,48] Similarly, a Norwegian study reported associations between lower t_{PTEF}/t_E in infancy and preschool wheeze.[28] We are unaware of others reporting an increased risk of asthma at age 3 years by shorter t_{PTEF} in infancy, but corresponds with previous studies.[21–24]

Our finding that impaired skin barrier function in infancy was associated with asthma at age 3 years is to the best of our knowledge novel. We previously reported an inverse association between impaired skin function and lower lung function by t_{PTEF} among 899 infants at age 3 months.[18] A German study found similar TEWL values using a patch test among 95 subjects with respiratory atopy, AD and controls.[49] Collectively, our finding thus supports that barrier dysfunction may play a role in asthma development.[8,50] No associations between eczema in infancy or *FLG* mutations and asthma at age 3 years were observed in the absence of a diagnosis of either AD or AS by age 3 years, corresponding with previous studies.[51–53] Although a threefold risk of asthma was observed in a study of 3000 Swedish children with itchy eczema,[54] those children were 1–2 years at baseline with asthma follow-up 5 years later.[54] In our cohort, 47.1% of the children with eczema at 3 months had documented AD by age 1 year,[55] which together with younger age at asthma diagnosis may explain some of the differences.[54]

The associations between lower lung function in infancy in boys and *FLG* mutations in girls and asthma at age 3 years, independent of AD or AS, are to the best of our knowledge novel. In line with previous reports,[1] boys more often had lower lung function in infancy and asthma at age 3 years, which partly may explain the observed associations. Dvornyk et al.[47] identified an association between single nucleotide polymorphisms in *FLG* and AD in Caucasian women, but not in men. In conflict with an Australian publication ($n = 620$) reporting infantile eczema being associated with asthma in boys,[56] the presence of eczema, regardless of an AD diagnosis, was not associated with asthma at age 3 years. Nevertheless, we explored eczema at age 3 months, of which many did not develop AD later on.[55]

To our knowledge, we are first to report that the association between impaired skin barrier function in infancy and asthma at age 3 years in children was dependent of a diagnosis of either AD or AS by age 3 years. When itch was absent, a recent study of Japanese infants found no association between parental-reported eczema before age 3 months and the development of asthma at age 3 years,[52] similar to our results. Previous studies found associations between *FLG* mutations and asthma among older children with eczema[51] and AS,[53] in line with our findings.

While lower infant lung function poorly predicted asthma at age 3 years, neither of the skin conditions did. Consequently, our results are likely to be relevant to further understand the role of lung and skin barrier function in early infancy and young children developing asthma, rather than being useful in a clinical setting.

4.1 | Strengths and limitations

The included children were antenatally recruited from the general population and are clinically well-characterized, with detailed information on exposures and outcomes, which is a strength. At the

TABLE 3 Crude and adjusted logistic regression models for t_{PTEF}/t_E and t_{PTEF}, TEWL, eczema at 3 months, FLG mutations, and asthma at age 3 years by boys (a) and girls (b) in the included children ($n = 1337$).

Characteristics	Crude OR (95% CI)	No.	*p*-value	Adjusted OR (95% CI)	No.	*p*-value[†]
(a) Asthma at age 3 years, boys						
Lung function						
Lower t_{PTEF}/t_E[a]	6.14 (2.30, 16.4)	284	**<.001**	7.69 (2.50, 23.6)	240	**<.001**
Continuous t_{PTEF}/t_E	0.00 (0.00, 0.03)	284	**<.001**	0.00 (0.00, 0.07)	240	**.002**
Shorter t_{PTEF}[b]	2.43 (1.33, 4.44)	284	**.004**	3.20 (1.53, 6.67)	240	**.002**
Continuous t_{PTEF}	0.01 (0.00, 4.91)	284	.136	0.02 (0.00, 18.8)	240	.254
Skin barrier						
High TEWL[c]	1.33 (0.84, 2.08)	621	.224	1.46 (0.85, 2.49)	498	.172
Continuous TEWL	1.03 (1.00, 1.06)	621	.081	1.03 (0.99, 1.06)	498	.141
Eczema	1.55 (0.92, 2.61)	690	.103	1.67 (0.91, 3.05)	561	.096
FLG mutations	1.02 (0.50, 2.11)	557	.948	1.02 (0.50, 2.11)	557	.948
(b) Asthma at age 3 years, girls						
Lung function						
Lower t_{PTEF}/t_E[a]	1.26 (0.15, 10.3)	279	.832	1.75 (0.18, 16.8)	236	.630
Continuous t_{PTEF}/t_E	0.22 (0.00, 64.8)	279	.604	0.26 (0.00, 357)	236	.712
Shorter t_{PTEF}[b]	2.47 (0.89, 6.86)	279	.084	2.45 (0.74, 8.08)	236	.141
Continuous t_{PTEF}	0.00 (0.00, 0.96)	279	**.049**	0.00 (0.00, 64.6)	236	.167
Skin barrier						
High TEWL[c]	1.54 (0.83, 2.87)	552	.175	1.79 (0.88, 3.48)	459	.113
Continuous TEWL	1.03 (0.99, 1.07)	552	.146	1.03 (0.99, 1.07)	459	.208
Eczema	1.05 (0.46, 2.41)	628	.912	1.01 (0.38, 2.73)	526	.983
FLG mutations	3.48 (1.48, 8.21)	488	**.004**	3.48 (1.48, 8.21)	488	**.004**

Abbreviations: FLG, filaggrin; g/m^2/h, grams per square meter per hour; t_{PTEF}, time to peak tidal expiratory flow; t_{PTEF}/t_E, time to peak tidal expiratory flow to expiratory time; TEWL, transepidermal water loss.

[†]Multivariate logistic regression models adjusted for sex, GA, tobacco smoke exposure in pregnancy, urban living environment in pregnancy, breastfeeding, parental atopy, parental education level, study center, and the PreventADALL interventions (models including *FLG* mutations adjusted for sex).

[a]A lower t_{PTEF}/t_E equals to a value <0.25.

[b]A shorter t_{PTEF} equals to a value <0.17 s (<25th percentile).

[c]A high TEWL equals to a value >9.50 g/m^2/h (>75th percentile).

3-month and 3-year follow-up, the study achieved a response rate of 89.1% and 81.2%, respectively, and is a further strength. The present study includes 55.8% children from the PreventADALL cohort with information on asthma at age 3 years lung function as well as either eczema, TEWL at age 3 months, and/or *FLG* mutations, which may introduce selection bias that reduces the generalizability of our results. Though all multivariate analyses were adjusted for the PreventADALL interventions, the data were retrieved from a randomized controlled trial and may further limit the generalizability, although neither skin nor food interventions had significant effects on AD,[26] but on food allergy development.[57] The study centers in Norway and Sweden used the same standard operating procedures for all examinations and the health care professionals were jointly trained to increase the inter-observer reliability. The recording of lung function in awake infants is an important asset to this epidemiological study. Choosing eczema instead of AD might be considered as a limitation. However, few 3-month-old infants fulfil the major UKWP AD criteria of itch,[55] and eczema was confirmed by physicians. The 9.2% rate of *FLG* mutation carriers, corresponding with the prevalence in Europeans,[58] is a strength, but the low numbers may underpower the associations including *FLG* mutations wherefore our findings should be considered with caution. Though wheeze is a cardinal symptom of asthma at age 3 years, it is not always related to it, and the diagnosis is mainly based on patterns of symptoms.[1] Therefore, recurrent bronchial obstruction was a mandatory criteria, together with a history of doctor-diagnosed asthma and/or asthma medication use,[34] altogether creating a strict asthma definition. Few children had asthma at age 3 years as well as a diagnosis of either AD or AS by age 3 years, wherefore our findings including asthma phenotypes should be interpreted with caution.

4.2 | Clinical implications for future research

Our findings support the hypothesis that epithelial barrier function may be involved in development of asthma at age 3 years, pointing to a role for both early infant lung function and skin barrier

function. The strongest association between infant lung function and asthma at age 3 years was observed in children with a diagnosis of either AD or AS by age 3 years. Similarly, significant associations between impaired skin barrier function, eczema and *FLG* mutations and asthma at age 3 years were only observed in infants later diagnosed with either AD or AS, likely to represent asthma that may persist in later childhood,[59] and/or suggest that the progression from a reduced skin barrier function to allergic inflammatory conditions are important for the development of asthma. As many preschool children outgrow their asthma-like disease with age,[12] future studies are required to detangle the potential relationship between the lungs and the skin in the development of asthma in older girls and boys, perhaps being more accurate in terms of chronic obstructive airways disease development.

5 | CONCLUSION

In this large general pediatric population, lower lung function and impaired skin barrier function in early infancy were associated with an increased risk of developing asthma at age 3 years. The associations to asthma at age 3 years differed by sex, with lower lung function observed in boys and *FLG* mutations in girls, while none of the other conditions remained significant. Eczema in infancy as well as *FLG* mutations increased the risk of asthma at age 3 years only among children with a diagnosis of either AD or AS by age 3 years. This study suggests that lower infant lung function and early skin barrier impairment may contribute to the development of asthma in early childhood, but further studies are needed.

AUTHOR CONTRIBUTIONS

Martin Färdig contributed to conception and design of the study, data collection, data curation, analysis and interpretation of data, manuscript writing and editing. Angela Hoyer contributed to conception and design of the study, data curation, analysis and interpretation of data, manuscript writing and editing. Catarina Almqvist contributed to conception of the study, and critically revised the manuscript. Karen Eline S. Bains contributed to data collection, data curation and critically revised the manuscript. Karin C. Lødrup Carlsen contributed to conception and design of the study, interpretation of data and manuscript writing and editing. Hrefna Katrín Gudmundsdóttir contributed to data collection, data curation and critically revised the manuscript. Berit Granum contributed to interpretation of data, and critically revised the manuscript. Guttorm Haugen contributed to interpretation of data, and critically revised the manuscript. Gunilla Hedlin contributed to interpretation of data, and critically revised the manuscript. Christine M. Jonassen contributed to interpretation of data, and critically revised the manuscript. Jon R. Konradsen contributed to interpretation of data, and critically revised the manuscript. Anine Lie contributed to data collection, data curation and critically revised the manuscript. Eva Maria Rehbinder contributed to data collection, data curation and critically revised the manuscript. Håvard O. Skjerven contributed to interpretation of data, and critically revised the manuscript. Anne Cathrine Staff contributed to interpretation of data, and critically revised the manuscript. Riyas Vettukattil contributed to data curation, and critically revised the manuscript. Cilla Söderhäll contributed to conception and design of the study, interpretation of data, and critically revised the manuscript. Björn Nordlund contributed to conception and design of the study, interpretation of data, and critically revised the manuscript. All listed authors approved the final version of the manuscript before submission and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Eva Maria Rehbinder has received honoraria for lectures from Sanofi Genzyme, Leo Pharma, Novartis, Norwegian Psoriasis and Eczema Association, Norwegian Asthma and Allergy Association and Karin C. Lødrup Carlsen reports that her institution has received honorarium and travel costs from Thermo Fisher Scientific for international symposium participation. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518), and the Swedish Ethical Review Authority in Sweden (2014/2242-31/4 and 2018/1437-32), registered at https://www.clinicaltrials.gov, NCT02449850 (https://www.clinicaltrials.gov/ct2/show/NCT02449850?term=PreventADALL&draw=2&rank=1, accessed on November 28, 2022). Informed written consent was collected from all mothers at enrolment and from parent(s) at infant inclusion.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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