ORIGINAL ARTICLE

Xerosis is associated with asthma in men independent of atopic dermatitis and filaggrin gene mutations

K.A. Engebretsen,[1,*] A. Linneberg,[2,3,4] B.H. Thuesen,[2] P.B. Szecsi,[5] S. Stender,[5] T. Menné,[1] J.D. Johansen,[1] J.P. Thyssen[1]

[1]National Allergy Research Centre, Department of Dermato-Allergology, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[2]Research Centre for Prevention and Health, the Capital Region of Denmark, Glostrup, Denmark
[3]Department of Clinical Experimental Research, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark
[4]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]Department of Clinical Biochemistry, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
*Correspondence: K.A. Engebretsen. E-mail: kristiane.aasen.engebretsen.02@regionh.dk

Abstract

Background Epidermal filaggrin deficiency due to common filaggrin gene (FLG) mutations causes xerosis and strongly increases the risk of atopic dermatitis and even asthma. However, it is unknown whether xerosis independent of FLG mutations could also increase the risk of asthma.

Objective To evaluate whether generalized xerosis was associated with asthma, independent of atopic dermatitis and common FLG mutations in a cross-sectional study on adult Danes.

Methods A total of 3396 adults from the general population participated in a health examination. Lung function and serum-specific IgE levels to inhalant allergens were measured and information on xerosis and atopic diseases was obtained by means of a questionnaire. Participants were genotypes for the three most common FLG mutations in Northern Europeans: R501X, 2282del4 and R2447X.

Results Fully adjusted logistic regression analyses showed that asthma (either current or at some point in life) was significantly associated with reporting generalized xerosis (OR 1.32; 95% CI 1.02–1.72). The association was stronger in men (OR 1.79; 95% CI 1.13–2.84) when compared to women (OR 1.18; 95% CI 0.86–1.62). Furthermore, a significant association was observed between xerosis and 'allergic asthma' in men (OR 2.13; 95% CI 1.08–4.19).

Conclusion Our findings indicate an association between xerosis and asthma in men independent of atopic dermatitis and FLG mutations. Both facilitated allergen sensitization and secondary degradation of filaggrin following T-helper cell 2 inflammation might be key elements to understanding this relationship.

Received: 7 November 2014; Accepted: 15 January 2015

Conflicts of interest

None declared.

Funding Sources

Jacob P. Thyssen and Kristiane Engebretsen are financially supported by an unrestricted grant from the Lundbeck Foundation. The Health2006 study was financially supported by grants from the Velux Foundation; the Danish Medical Research Council, Danish Agency for Science, Technology and Innovation; the Aase and Ejner Danielsens Foundation; ALK-Abelló A/S (Hørsholm, Denmark), Timber Merchant Vilhelm Bangs Foundation and Research Centre for Prevention and Health, the Capital Region of Denmark.

Prior presentations

The content has not been published previously and is not otherwise submitted for publication.

© 2015 European Academy of Dermatology and Venereology

Introduction

Xerotic skin has reduced water content, often resulting in pruritus, excessive scale formation and even fissures. Xerosis is a common challenge in dermatology, and the prevalence appears to increase with age.[1] Thus, about 55% of the elderly was found to have xerosis in a recent French study, and besides age, risk factors included female gender, and a history of atopic dermatitis (AD).[2] Emollients improve skin hydration and barrier functions, and it has been repeatedly shown that women use significantly more emollients than men.[3–5]

Other physiological causes of xerosis include climatic exposures such as cold, low humidity and UV-irradiation, but also excessive bathing, use of soap, and hormonal changes.[6] Besides inflammatory skin diseases such as psoriasis, non-dermatological conditions including Hodgkin's lymphoma, HIV, thyroiditis, anorexia nervosa, renal dialysis or avitaminosis also associate with xerosis. Even some medications may cause xerosis, e.g. cimetidine, retinoids or statins.

Pertinently, there exists a strong genetic predisposition to xerosis. Thus, loss of function mutations in the filaggrin gene (*FLG*), clinically expressed as ichthyosis vulgaris, reduce the content of filaggrin and its degradation products, resulting in low stratum corneum hydration [5,7] and furthermore an impaired skin barrier integrity, reduced protection against bacterial colonization and UVB photons.[8] Filaggrin deficiency can be either primary due to *FLG* mutations, or secondary due to exogenous factors (e.g. low humidity, UV-irradiation and exposure to skin irritants)[9–11] or cutaneous inflammation.[12,13]

Recently, it was shown that filaggrin-deficient skin not only strongly increases the risk of AD, but also facilitates allergen penetration through the impaired stratum corneum in a mouse model.[14] This may result in IgE sensitization, and therefore *FLG* mutations appear to increase the risk of allergic rhinitis and asthma.[15] While most studies have only shown an increased risk of *FLG* mutations for the development of asthma in the presence of AD,[16] data from Poland and China have suggested that *FLG* mutations could even constitute a single risk factor for allergic asthma.[17] Asthma patients with *FLG* mutations had lower FEV1, were more likely to be prescribed medication (long acting beta2-agonists in addition to inhaled corticosteroids) and use more rescue medications than asthma patients without *FLG* mutations.[18] However, it is unknown whether xerosis beyond common *FLG* mutations could also increase the risk of asthma. In this cross-sectional study, we evaluated whether generalized xerosis was associated with asthma, independent of AD and common *FLG* mutations in adult Danes.

Materials and methods

Study population

Health2006 is a population based cross-sectional cohort and study details have previously been published.[19] Briefly, a randomly drawn sample of Danish adults (with Danish citizenship born in Denmark) aged 19–72 years was invited to participate in a general health examination. A total of 3471 persons were examined and questioned between June 2006 and June 2008. The Health2006 study was approved by the Ethical Committee of Copenhagen (KA-20060011) and the Data Protection Agency. A written informed consent form was obtained prior to inclusion.

Filaggrin genotyping

Regions covering the three most common *FLG* null mutations, R501X, 2282del4 and R2447X were amplified from genomic DNA from 3348 (96.5%) subjects by a multiplexed, allele-specific, asymmetric PCR using tagged primers and analysed by micro-bead-based suspension array.[20] A positive *FLG* mutation status was defined for heterozygote, compound heterozygote or homozygote mutation carriers.

Lung function measurements

Participants underwent spirometry according to international standards.[21] Measures of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were obtained by using the Spiro USB Spirometer (Micro Medical Limited, Rochester, United Kingdom). The fraction of exhaled nitric oxide (FeNO) was measured (Nixo-Mino, Aerocrine, Stockholm, Sweden) as a biomarker of allergic asthma, lower airway inflammation and oxidative stress according to international guidelines.[22–24] Nitric oxide concentrations between 5 and 300 ppb could be detected, and the cut-off was set at 20 ppb.

Measurement of allergen-specific IgE

Blood samples from all participants were analysed for serum-specific IgE, and presence of atopy was defined as at least one positive test result (≥0.35 kU/L) for serum-specific IgE against birch, grass, cat or house dust mite (Dermatophagoides pteronyssinus), being the most clinically important inhalation allergens in Denmark. The samples were analysed using the ADVIA Centaur Specific IgE assay (Siemens, Deerfield, IL, USA).[25]

Definitions of variables from the questionnaire

The participants completed two questionnaires concerning lifestyle factors, general and mental health before the health examination. Questions about xerosis were as follows: (i) 'Have you ever had dry skin all over your body?' (ii) 'If yes, have you during the past 12 months had dry skin all over your body?'. Non-responders were excluded from the study population.

'Atopic dermatitis' was defined by an affirmative answer to the question; (i) 'Has a doctor ever told you that you have atopic dermatitis?'.

Hay fever was defined as an affirmative answer to the question; (i) 'Has a doctor ever told you that you have hay fever?'.

© 2015 European Academy of Dermatology and Venereology

'Asthma current' was defined as an affirmative answer to *at least* one of three questions: (i) 'Have you been woken by an attack of shortness of breath at any time in the past 12 months?', (ii) 'Have you had an attack of asthma in the past 12 months?', (iii) 'Are you currently taking any medication (including inhalers, aerosols, or tablets) for asthma? ', according to the criteria of Sunyer *et al.*[26]

'Asthma ever' was defined as an affirmative answer to the question: (i) 'Has a doctor ever told you that you have asthma?'.

'Persistent asthma' was defined when participants were categorized as having 'asthma ever', and answered affirmative to *all* of the following; 'asthma attack within the past 12 months', 'use of asthma medication' and 'an attack of dyspnoea within the past 12 months'.

'Allergic asthma' was defined as either 'asthma ever' or 'asthma current' together with at least one positive test result (≥0.35 kU/L) for serum-specific IgE, or a positive response to question about physician diagnosed hay fever.

'Non-allergic asthma' were all those with asthma who did not fulfil the criteria for allergic asthma.

Smoking status was reported as daily, occasional, former or never smoking.

Statistical analysis

Characteristics of the study population were compared by using the χ^2 test. Logistic regression analyses were then performed to adjust for possible confounding effects of gender, age, AD and *FLG* mutation status on the association between xerosis and asthma. When analysing asthma-associated parameters such as FEV1, FEV1/FVC and FeNO, the analyses were also adjusted for smoking status. Effect modification of xerosis by gender was evaluated by assessing the *P* values of the interaction terms (xerosis*gender) in the regression models. The Statistical Products and Service Solution package (SPSS Inc., Chicago, IL, USA) for Windows (release 19) were used for data analysis. Odds ratio (OR) and 95% confidence intervals (CI) were given. *P*-values of likelihood ratio tests were used to test for statistical significance in all regression analyses. All *P*-values were two-tailed and statistical significance was defined as $P < 0.05$.

Results

Among adult Danes from the general population, 'asthma current' was reported by 11.3% (380/3365) and 'asthma ever' by 10.3% (359/3363). Paradoxically, more reported 'asthma current' than 'asthma ever', but this is due to the definitions of these variables. Among participants with 'asthma ever', 56.8% (204/359) were also defined as having 'asthma current'.

The overall prevalence of self-reported generalized xerosis at 'some point in life' and 'within the past 12 months' was 15.0% (511/3396) and 10.3% (347/3370) respectively. Study population characteristics stratified by xerosis are shown in Table 1. Notably, the prevalence of 'xerosis ever' and 'xerosis within the past 12 months' was 20.3% (73/359) and 14.0% (50/356), respectively, in participants with 'asthma ever' and 20.3% (77/380) and 14.4% (54/374), respectively, in participants with 'asthma current'. Data analyses showed that 'xerosis ever' and 'xerosis within the past 12 months' were significantly associated with AD, *FLG* mutations, asthma ever, asthma current, persistent asthma, allergic asthma and hay fever (Table 1). The strongest association with 'xerosis ever' was found for AD and homozygous carrier status of *FLG* mutations, the crude ORs being 5.33 (95% CI 3.88–7.34) and 96.69 (95% CI 12.26–762.50) respectively.

Table 2 shows characteristics of participants who fulfilled the criteria for 'asthma ever' and 'asthma current' thereby supporting the validity of the categories. Data analysis adjusted for age and sex showed that 'asthma ever' and 'asthma current' were significantly associated with FEV1 < 80%, FEV1/FVC<70%, FeNO>20 ppb, positive-specific IgE, dyspnoea within the past 12 months due to contact with furry animals, pollen or cleaning/stay in bed as well as AD.

We then performed several logistic regression analyses with xerosis (ever or current) as the dependent variable and with different categories of asthma as the explanatory variables and adjusted for gender, age, AD and *FLG* mutations. Having any of the two types of asthma (either 'asthma current' or 'asthma ever') was significantly associated with 'xerosis ever' after adjustment (OR 1.32; 95% CI 1.02–1.72). The association was stronger in men (OR 1.79; 95% CI 1.13–2.84) than women (OR 1.18; 95% CI 0.86–1.62) (the interaction term was *P* 0.14).When analysing the two forms of asthma separately, the association between 'xerosis ever' and 'asthma ever' was, however, not significant (OR 1.11; 95% CI 0.81–1.52). Similar, non-significant associations were observed between 'xerosis within the past 12 months' and 'asthma current' (OR 1.35; 95% CI 0.96–1.91) as well as between 'xerosis ever' and 'allergic asthma' (OR 1.33; 95% CI 0.94–1.88). Again, when restricting the analyses to men, the association between 'xerosis within the past 12 months' and 'asthma current' became significant as well as the association between 'xerosis ever' and 'allergic asthma', the ORs being 1.90 (95% CI 1.05–3.44) and 2.19 (95% CI 1.23–3.89) respectively. No association was observed between 'persistent asthma' and 'xerosis ever' after adjustment (OR 1.94; 95% CI 0.85–4.44).The same applied for 'xerosis ever' and hay fever (OR 1.27; 95% CI 0.98–1.64).

Fully adjusted logistic regression analyses further adjusted for smoking showed that other variables which significantly associated with 'xerosis ever'included: 'FEV1 < 80' (OR 1.63; 95% CI 1.20–2.21), 'FEV1/FVC<70' (OR 1.43; 95% CI 1.06–1.93), 'dyspnoea within the past 12 months because of contact with at least one out of three sources of allergens' (fur animals, pollen or stay in/cleaning of bed) (OR 1.46; 95% CI 1.08–1.97) and 'attack of dyspnoea within the past 12 months' (OR 1.80; 95% CI 1.23–2.63).Furthermore, allergic asthma was significantly associated with FeNO>20 ppb (OR 1.78; 95% CI 1.36–2.33).

© 2015 European Academy of Dermatology and Venereology

Table 1 The prevalence of generalized xerosis ever and within the past 12 months, stratified by population characteristics and asthma subgroups

	Total % (*n*/*n*total)	Generalized xerosis ever % (*n*/*n*total)	OR§§ (95% CI)	Generalized xerosis within past the 12 months % (*n*/*n*total)	OR§§ (95% CI)
Sex					
Men	44.8 (1522/3396)	9.5 (145/1522)	1 (ref)	6.3 (95/1514)	1 (ref)
Women	55.2 (1874/3396)	19.5 (366/1874)	2.31 (1.88–2.84)	13.6 (252/1856)	2.36 (1.84–3.02)
Age at examination					
19–35	16.5 (562/3396)	15.5 (87/562)	1 (ref)	11.1 (62/561)	1 (ref)
36–55	47.9 (1626/3396)	14.8 (241/1626)	0.98 (0.75–1.28)	9.7 (157/1614)	0.89 (0.65–1.22)
56–72	35.6 (1208/3396)	15.1 (183/1208)	1.04 (0.79–1.38)	10.7 (128/1195)	1.03 (0.75–1.43)
Atopic dermatitis*					
No	94.6 (3142/3323)	13.2 (414/3142)	1 (ref)	9.3 (289/3120)	1 (ref)
Yes	5.4 (181/3323)	45.3 (82/181)	5.33 (3.88–7.34)	26.8 (48/179)	3.44 (2.40–4.94)
Filaggrin gene mutation (FLG)†					
Wild type	90.9 (2980/3277)	12.9 (385/2980)	1 (ref)	8.5 (253/2962)	1 (ref)
Heterozygote	8.7 (285/3277)	33.0 (94/285)	3.41 (2.59–4.48)	26.4 (74/280)	3.95 (2.92–5.33)
Homozygote	0.4 (12/3277)	91.7 (11/12)	96.69 (12.26–762.50)	72.7 (8/11)	37.43 (9.60–146.02)
Asthma ever‡					
No	89.3 (3004/3363)	14.4 (433/3004)	1 (ref)	9.8 (293/2982)	1 (ref)
Yes	10.7 (359/3363)	20.3 (73/359)	1.40 (1.06–1.85)	14.0 (50/356)	1.38 (1.00–1.92)
Asthma current§					
No	88.7 (2985/3365)	14.4 (430/2985)	1 (ref)	9.8 (291/2965)	1 (ref)
Yes	11.3 (380/3365)	20.3 (77/380)	1.46 (1.11–1.92)	14.4 (54/374)	1.50 (1.09–2.05)
Persistent asthma¶					
No	98.9 (3296/3331)	14.8 (488/3296)	1 (ref)	10.2(333/3273)	1 (ref)
Yes	1.1 (35/3331)	37.1 (13/35)	2.94 (1.46–5.93)	21.2 (7/33)	1.98 (0.85–4.64)
Allergic and non-allergic asthma					
No asthma	84.2 (2804/3329)	14.1 (394/2804)	1 (ref)	9.6 (266/2785)	1 (ref)
Non-allergic asthma‖	7.3 (242/3329)	18.2 (44/242)	1.28 (0.91–1.81)	12.6 (30/239)	1.27 (0.84–1.90)
Allergic asthma**	8.5 (283/3329)	21.9 (62/283)	1.67 (1.23–2.26)	15.7 (44/280)	1.72 (1.21–2.44)
Specific IgE/Atopy††					
No	76.9 (2592/3369)	15.4 (399/2592)	1 (ref)	10.2 (263/2572)	1 (ref)
Yes	23.1 (777/3369)	13.6 (106/777)	0.94 (0.75–1.19)	10.4 (80/772)	1.11 (0.85–1.46)
Hay fever‡‡					
No	82.2 (2759/3356)	14.0 (387/2759)	1 (ref)	9.4 (257/2739)	1 (ref)
Yes	17.8 (597/3356)	19.3 (115/597)	1.45 (1.15–1.83)	14.2 (84/593)	1.59 (1.22–2.08)

OR, odds ratio; CI, confidence interval.

*An affirmative answer to the question 'Has a doctor ever told you that you have atopic dermatitis?'

†Mutations R501X, 2282del4 and R2447X.

‡An affirmative answer to the question 'Has a doctor ever told you that you have asthma?'

§Asthma was defined according to the European Community Respiratory Health Study as an affirmative answer to at least one of the three following questions; (i) Have you been woken by an attack of shortness of breath at any time in the past 12 months? (ii) Have you had an attack of asthma in the past 12 months? (iii) Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?

¶Persistent asthma was defined as asthma ever + asthma attack within the past 12 months + use of asthma medication + attack of dyspnoea within the past 12 months.

‖Asthma ever or asthma current who did not fulfil the criteria of allergic asthma.

**Allergic asthma was defined as participants having asthma (ever or current), and a positive test result (≥0.35 kU/L) for serum-specific IgE against birch, grass, cat or house dust mite (Dermatophagoides pteronyssinus) or an affirmative answer to the question 'Has a doctor ever told you that you have hay fever?'

††Atopy was defined as at least one positive test result (≥0.35 kU/L) for serum-specific IgE against birch, grass, cat or house dust mite (Dermatophagoides pteronyssinus).

‡‡An affirmative answer to the question 'Has a doctor ever told you that you have hay fever?'

§§Adjusted for age and sex.

© 2015 European Academy of Dermatology and Venereology

Table 2 The prevalence of asthma ever and asthma current stratified by population characteristics

	Asthma ever* % (*n*/*n*total)	OR‖ (95% CI)	Asthma current† % (*n*/*n*total)	OR‖ (95% CI)
Sex				
Men	8.2 (123/1505)	1 (ref)	10.2 (154/1510)	1 (ref)
Women	12.7 (236/1858)	1.60 (1.27–2.02)	12.2 (226/1855)	1.23 (0.99–1.53)
Age at examination				
19–35	14.5 (81/557)	1 (ref)	10.2 (57/558)	1 (ref)
36–55	10.8 (175/1616)	0.72 (0.55–0.96)	11.2 (181/1612)	1.12 (0.82–1.54)
56–72	8.7 (103/1190)	0.58 (0.42–0.79)	11.9 (142/1195)	1.21 (0.87–1.67)
FEV1 ≤ 80%				
No	9.3 (276/2970)	1 (ref)	9.4 (278/2973)	1 (ref)
Yes	21.6 (79/365)	3.14 (2.35–4.18)	26.2 (96/366)	3.55 (2.72–4.65)
FEV1/FVC ≤ 70%				
No	9.5 (281/2971)	1 (ref)	9.5 (281/2973)	1 (ref)
Yes	20.4 (77/377)	2.80 (2.10–3.73)	25.6 (97/379)	3.32 (2.55–4.33)
FENO >20 ppb				
No	9.6 (203/2118)	1 (ref)	10.5 (222/2123)	1 (ref)
Yes	13.5 (129/955)	1.75 (1.37–2.24)	13.1 (125/952)	1.37 (1.08–1.74)
Specific IgE/Atopy‡				
No	7.5 (193/2563)	1 (ref)	9.3 (238/2566)	1 (ref)
Yes	21.2 (164/774)	3.45 (2.74–4.35)	17.9 (138/772)	2.28 (1.81–2.87)
Dyspnoea provoked by fur animals last 12 months				
No	8.9 (285/3216)	1 (ref)	9.7 (314/3221)	1 (ref)
Yes	53.3 (73/137)	11.04 (7.70–15.82)	47.8 (64/134)	8.60 (6.00–12.35)
Dyspnoea provoked by pollen last 12 months				
No	8.5 (267/3132)	1 (ref)	9.2 (288/3134)	1 (ref)
Yes	41.2 (91/221)	7.67 (5.68–10.34)	40.1 (89/222)	6.63 (4.94–8.91)
Dyspnoea provoked by cleaning or staying in bed last 12 months				
No	8.5 (272/3182)	1 (ref)	9.2 (293/3189)	1 (ref)
Yes	50.3 (84/167)	10.65 (7.64–14.84)	51.2 (85/166)	10.40 (7.48–14.45)
Attack of asthma last 12 months				
No	7.8 (251/3232)	1 (ref)		
Yes	90.4 (104/115)	5.09 (3.68–7.05)		
Current use of asthma medications				
No	6.1 (192/3135)	1 (ref)		
Yes	77.7 (167/215)	59.64 (41.34–86.03)		
Smoking status				
Never	10.0 (140/1394)	1 (ref)	9.5 (133/1402)	1 (ref)
Former	12.5 (135/1081)	1.37 (1.06–1.77)	13.2 (143/1084)	1.44 (1.12–1.85)
Occasional	11.7 (13/111)	1.12 (0.61–2.05)	11.9 (13/109)	1.33 (0.72–2.45)
Daily	9.3 (71/765)	0.93 (0.69–1.26)	12.0 (91/759)	1.29 (0.97–1.71)
Filaggrin gene mutation (FLG)§				
Wild type	10.5 (310/2953)	1 (ref)	10.7 (316/2951)	1 (ref)
Heterozygote	12.9 (36/280)	1.24 (0.86–1.80)	15.5 (44/283)	1.54 (1.09–2.17)
Homozygote	25.0 (3/12)	3.14 (0.83–11.82)	25.0 (3/12)	2.81 (0.75–10.45)
Atopic dermatitis¶				
No	9.2 (288/3128)	1 (ref)	10.6 (331/3119)	1 (ref)
Yes	32.8 (59/180)	4.35 (3.10–6.10)	21.3 (38/178)	2.34 (1.60–3.42)

OR, odds ratio; CI, confidence interval.

*An affirmative answer to the question 'Has a doctor ever told you that you have asthma?'

†Asthma was defined according to the European Community Respiratory Health Study as an affirmative answer to at least one of the three following questions; (i) Have you been woken by an attack of shortness of breath at any time in the past 12 months? (ii) Have you had an attack of asthma in the past 12 months? (iii) Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?

‡Atopy was defined as at least one positive test result (≥0.35 kU/L) for serum-specific IgE against birch, grass, cat or house dust mite (Dermatophagoides pteronyssinus).

§Mutations R501X, 2282del4 and R2447X.

¶An affirmative answer to the question 'Has a doctor ever told you that you have atopic dermatitis?'

‖Adjusted for age and sex.

© 2015 European Academy of Dermatology and Venereology

Table 3 Logistic regression analyses showing the association between AD, xerosis, FLG mutations and different categories of asthma

Logistic regression	Total			Men			Women		
	Asthma ever* OR‖ (95% CI)	Asthma current† OR‖ (95% CI)	Allergic asthma‡ OR‖ (95% CI)	Asthma ever* OR** (95% CI)	Asthma current† OR** (95% CI)	Allergic asthma‡ OR** (95% CI)	Asthma ever* OR** (95% CI)	Asthma current† OR** (95% CI)	Allergic asthma‡ OR** (95% CI)
AD§, xerosis and *FLG* mutation¶									
No AD, no xerosis, no FLG mutation	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No AD, xerosis, no FLG mutation	1.03 (0.70–1.53)	1.29 (0.90–1.85)	1.22 (0.79–1.87)	0.90 (0.38–2.12)	1.82 (1.00–3.34)	2.13 (1.08–4.19)	1.06 (0.68–1.66)	1.09 (0.70–1.69)	0.91 (0.52–1.57)
No AD, xerosis, FLG mutation	1.54 (0.80–2.98)	1.95 (1.07–3.54)	1.53 (0.72–3.24)	3.01 (0.99–9.13)	3.92 (1.50–10.25)	3.74 (1.22–11.47)	1.19 (0.53–2.68)	1.39 (0.64–3.02)	0.94 (0.33–2.67)
AD, xerosis and FLG mutation	5.50 (2.38–12.70)	5.74 (2.47–13.31)	8.81 (3.84–20.21)	7.92 (2.25–27.90)	7.10 (1.96–25.68)	9.96 (2.71–36.58)	4.30 (1.42–13.06)	5.09 (1.66–15.57)	8.47 (2.86–25.03)

AD, atopic dermatitis; OR, Odds ratio; CI, confidence interval.

*An affirmative answer to the question 'Has a doctor ever told you that you have asthma?'

†Asthma was defined according to the European Community Respiratory Health Study as an affirmative answer to at least one of the three following questions; (i) Have you been woken by an attack of shortness of breath at any time in the past 12 months? (ii) Have you had an attack of asthma in the past 12 months? (iii) Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?

‡Allergic asthma was defined as participants having asthma (ever or current), and a positive test result (≥0.35 kU/L) for serum-specific IgE against birch, grass, cat or house dust mite (Dermatophagoides pteronyssinus) or an affirmative answer to the question 'Has a doctor ever told you that you have hay fever?'

§An affirmative answer to the question 'Has a doctor ever told you that you have atopic dermatitis?'

¶Mutations R501X, 2282del4 and R2447X.

‖Adjusted for age and sex.

**Adjusted for age.

© 2015 European Academy of Dermatology and Venereology

Finally, we divided the study population into four groups according to the presence of AD, 'xerosis ever' and *FLG* mutations and evaluated the association with different categories of asthma (Table 3). As expected, the strongest association with 'asthma ever', 'asthma current' and 'allergic asthma' was found when AD, xerosis and *FLG* mutations were all present together. No significant association was found between only xerosis and the different categories of asthma in the overall population. However, when restricting the analyses to men, the association between xerosis and allergic asthma became significant, the ORs being 2.04_{crude} (95% CI 1.04–4.00) and $2.13_{adjusted}$ (95% CI 1.08–4.19). No significant association was found in women before and after adjustment for age (OR_{crude} 0.90; 95% CI 0.52–1.56 and $OR_{adjusted}$ 0.91; 95% CI 0.52–1.56).

Discussion

This cross-sectional general population study in adult Danes indicate that asthma (ever or current) was significantly associated with generalized xerosis, independent of gender, age, AD and *FLG* mutations. The association appeared to be driven by male participants, as only the adjusted analyses restricted to men showed significant associations. It is our clear impression that women are much better than men to take care of their skin and use moisturizers to prevent xerosis. Indeed, a study on dermatological healthcare resources revealed that 65% of all prescribed emollients were dispensed to women.[3] In another study on xerosis in young adults and the elderly, women were also significantly more likely than men to consider their skin as dry (39% vs. 11%) and to use body moisturizers regularly (43% vs. 7%).[5] It has been shown that long-term treatment with the right moisturizer improves skin barrier function and makes the skin more resistant to skin irritants.[27] These observations may explain why we mainly identified an association between xerosis and asthma in male participants. Thus, the frequent application of moisturizers in women may tend to reduce the effect of xerosis on morbidity.

Allergic, but not non-allergic asthma was associated with generalized xerosis in men, independent of *FLG* mutations. Although our definition of 'allergic asthma' allows for misclassification, we hypothesize that xerosis could indeed be an independent, but weak risk factor for developing allergic asthma. As for *FLG* mutations, the barrier abnormality in xerotic skin might act as one important starting point in the etiopathogenesis of asthma. Hence, allergens could penetrate the impaired xerotic skin barrier and then cause allergen sensitization. Following secondary airway exposure to the same allergens, asthma could then develop. Others have studied the possible connection between the skin and airways. Thus, an experimental study on mice with very xerotic skin due to filaggrin deficiency showed increased sensitization (specific antibody response and inflammation) after topical allergen application.[14] Likewise, human studies have suggested a possible connection between occupational skin exposure to chemicals such as isocyanates, insufficient use of protective gloves and secondary asthma.[28,29] A Japanese study on AD, asthma and *FLG* mutations found that serum IgE levels were extremely high in AD patients with asthma, compared to the total group of asthma patients, and the authors proposed extrinsic allergic sensitization as a possible explanation.[30] However, in a murine study where mice with AD-like skin disease were sensitized with intraperitoneal ovalbumin injections and later exposed to ovalbumin intranasally, they achieved a much stronger and more pronounced pulmonary hyper-responsiveness than wild-type mice.[31] As no epicutaneous sensitization took place, the authors proposed that the inflammation in AD itself caused and aggravated lung inflammation, and that TSLP (thymic stromal lymphopoietin) most likely was the systemic cytokine that provided the signal from the inflamed skin barrier to the lungs thereby driving the allergic inflammation.[31] This notion suggests that xerotic skin with inflammation is more likely to result in allergic sensitization and airway disease, than xerotic skin without inflammation.

As we applied a cross-sectional design, it is impossible to evaluate whether xerosis preceded asthma, or vice-versa. It has been shown that epidermal filaggrin expression is down-regulated by, e.g. Th2 and Th17 cytokines, and even independently of *FLG* mutations in both lesional and non-lesional AD skin.[12,13,32] Xerosis in asthmatic patients could therefore, at least in theory, be a result of secondary filaggrin degradation following the downstream effects of systemic Th2 inflammation.[8] Interestingly, a Japanese study on seasonal allergic rhinitis in patients *without* AD, to some degree supports that Th2 inflammation potentially could influence skin barrier functions. Thus, the authors found decreased levels of skin hydration and amino acids in the stratum corneum in patients with rhinitis during the allergic season when compared to healthy control subject in the same period.[33]

The so-called 'atopic march' describes the progression from AD in infancy or early childhood, often concomitant with food allergy, to asthma and allergic rhinitis in later childhood.[34] A Danish cohort study showed a *FLG*-associated pattern of atopic diseases characterized by the early onset of asthma symptoms and eczema and with secondary development of sensitization.[35] A study of two large European populations, including 1092 children with eczema, found a strong association between *FLG* mutations, AD and other allergic phenotypes such as allergic rhinitis, asthma and elevated IgE levels.[36] However, the association between *FLG* mutations and the other allergic phenotypes was only significant in the presence of AD. The authors therefore suggested that the *FLG* mutation is not an independent risk factor, but rather a requirement for the subsequent development of allergic sensitization and allergic airway disease due to an abnormal skin barrier function and increased allergen penetration.[36] Due to the recent findings, the 'atopic march' hypothesis has been challenged. Thus, not all children follow the classic progression from AD to airway disease and in a prospective study

© 2015 European Academy of Dermatology and Venereology

on children with asthma only at baseline, 20% developed AD later in life.[34,37] It has therefore been proposed that the atopic diseases could represent one systemic disease with different clinical manifestations in affected patients, and that the presence of one of the clinical diseases might be a forerunner to developing the others.[37] If so, secondary prevention in form of optimal treatment of the first atopic disease could be essential to avoid further progression of the systemic disease and arrest of the 'atopic march'. A pilot study on neonates with high risk of developing AD, frequent application of emollients reduced the incidence of AD.[38] The results suggest a novel and feasible approach to prevention of AD and possibly a way to arrest the atopic march.

As expected, our study confirmed a positive and significant association between xerosis and, respectively, AD and *FLG* mutations. Moreover, the self-reported asthma categories appeared to be valid when correlations were performed with objective asthma parameters as well as self-reported complaints from the airways. Allergic asthma was also significantly associated with FeNO>20 ppb. It is a study limitation that xerosis and AD were not assessed by clinical examination, but by questionnaire. We therefore cannot exclude that residual confounding and misclassification could have affected our results and, we acknowledge that we did not perform genotyping for all existing *FLG* mutations, also allowing for misclassification. Furthermore, AD was defined as an affirmative answer to the question 'Has a doctor ever told you that you have atopic dermatitis?', and not according to the validated UK Working Party's criteria where generalized xerosis is one of the minor criteria.[39] Some participants might therefore have had AD without us being able to register it in our study.

Conclusion

This cross-sectional study indicates an association between xerosis and asthma, primarily in men, independent of AD and *FLG* mutations. Previous research suggests that key elements to understanding this potential relationship involve both increased allergen sensitization through an impaired skin barrier as well as secondary degradation of filaggrin due to systemic Th2 inflammation. While we could not evaluate the causal relationship between the two conditions, it opens up for future studies that can further explore this.

References

1 Norman RA. Xerosis and pruritus in the elderly: recognition and management. *Dermatol Ther* 2003; **16**: 254–259.

2 Paul C, Maumus-Robert S, Mazereeuw-Hautier J, Guyen CN, Saudez X, Schmitt AM. Prevalence and risk factors for xerosis in the elderly: a cross-sectional epidemiological study in primary care. *Dermatology* 2011; **223**: 260–265.

3 Nyberg F, Osika I, Evengård B. 'The Laundry Bag Project'– unequal distribution of dermatological healthcare resources for male and female psoriatic patients in Sweden. *Int J Dermatol* 2008; **47**: 144–149.

4 Weber TM, Kausch M, Rippke F, Schoelermann AM, Filbry AW. Treatment of xerosis with a topical formulation containing glyceryl glucoside, natural moisturizing factors, and ceramide. *J Clin Aesthet Dermatol* 2012; **5**: 29–39.

5 Sergeant A, Campbell LE, Hull PR, Porter M, Palmer CN, Smith FJ, *et al.* Heterozygous null alleles in filaggrin contribute to clinical dry skin in young adults and the elderly. *J Invest Dermatol* 2009; **129**: 1042–1045.

6 Pons-Guiraud A. Dry skin in dermatology: a complex physiopathology. *J Eur Acad Dermatol Venereol* 2007; **21**: 1–4.

7 Thyssen JP, Godoy-Gijon E, Elias PM. Ichthyosis vulgaris: the filaggrin mutation disease. *Br J Dermatol* 2013; **168**: 1155–1166.

8 Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 2014; **134**: 792–799.

9 Katagiri C, Sato J, Nomura J, Denda M. Changes in environmental humidity affect the water-holding property of the stratum corneum and its free amino acid content, and the expression of filaggrin in the epidermis of hairless mice. *J Dermatol Sci* 2003; **31**: 29–35.

10 Del Bino S, Vioux C, Rossio-Pasquier P, Jomard A, Demarchez M, Asselineau D, *et al.* Ultraviolet B induces hyperproliferation and modification of epidermal differentiation in normal human skin grafted on to nude mice. *Br J Dermatol* 2004; **150**: 658–667.

11 Angelova-Fischer I, Dapic I, Hoek AK, Jakasa I, Fischer TW, Zillikens D, *et al.* Skin barrier integrity and natural moisturising factor levels after cumulative dermal exposure to alkaline agents in atopic dermatitis. *Acta Derm Venereol* 2014; **94**: 640–644.

12 Pellerin L, Henry J, Hsu CY, Balica S, Jean-Decoster C, Mechin MC, *et al.* Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol* 2013; **131**: 1094–1102.

13 Howell MD, Kim BE, Boguniewicz M, Leung DYM. Modulation of filaggrin by Th2 cytokines in the skin of Atopic Dermatitis (AD). *J Allergy Clin Immunol* 2007; **119**: S283.

14 Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, *et al.* A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. *Nat Genet* 2009; **41**: 602–608.

15 van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; **339**: b2433.

16 Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, *et al.* Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009; **123**: 1361–1370 e1367.

17 Poninska J, Samolinski B, Tomaszewska A, Raciborski F, Samel-Kowalik P, Walkiewicz A, *et al.* Filaggrin gene defects are independent risk factors for atopic asthma in a Polish population: a study in ECAP cohort. *PLoS ONE* 2011; **6**: e16933.

18 Palmer CNA, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, *et al.* Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007; **120**: 64–68.

19 Thuesen BH, Cerqueira C, Aadahl M, Ebstrup JF, Toft U, Thyssen JP, *et al.* Cohort Profile: the health 2006 cohort, research centre for prevention and health. *Int J Epidemiol* 2013; **43**: 568–575.

20 Meldgaard M, Szecsi PB, Carlsen BC, Thyssen JP, Johansen JD, Menné T, *et al.* A novel multiplex analysis of filaggrin polymorphisms: A universally applicable method for genotyping. *Clin Chim Acta* 2012; **413**: 1488–1492.

21 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; **26**: 319–338.

22 ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and NasalNitric Oxide, 2005; American Thoracic Society Documents Nasal nitric oxide: longitudinal reproducibility and the effects of a nasal allergen challenge in patients with allergic rhinitis. *Chest* 2004;**126**; 1013–1014.

23 Deykin A. Targeting biologic markers in asthma – is exhaled nitric oxide the bull's-eye? *N Engl J Med* 2005; **352**: 2233–2235.

 © 2015 European Academy of Dermatology and Venereology

24 Dalsgard OJ, Vestbo J. Oxidativt stress og genetiske polymorfismer ved KOL. *Ugeskr Laeger* 2002; **164**: 4056–4061.
25 Petersen AB, Gudmann P, Milvang-Gronager P, Morkeberg R, Bogestrand S, Linneberg A, *et al.* Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin Biochem* 2004; **37**: 882–892.
26 Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, *et al.* Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* 2004; **114**: 1033–1039.
27 Buraczewska I, Berne B, Lindberg M, Torma H, Loden M. Changes in skin barrier function following long-term treatment with moisturizers, a randomized controlled trial. *Br J Dermatol* 2007; **156**: 492–498.
28 Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 2000; **118**: 1183–1193.
29 Shahzad K, Akhtar S, Mahmud S. Prevalence and determinants of asthma in adult male leather tannery workers in Karachi, Pakistan: a cross sectional study. *BMC Public Health* 2006; **6**: 292.
30 Osawa R, Konno S, Akiyama M, Nemoto-Hasebe I, Nomura T, Nomura Y, *et al.* Japanese-specific filaggrin gene mutations in japanese patients suffering from atopic eczema and asthma. *J Invest Dermatol* 2010; **130**: 2834–2836.
31 Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol* 2009; **7**: e1000067.
32 Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, *et al.* Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2009; **124**: R7–R12.
33 Tanaka M, Okada M, Zhen YX, Inamura N, Kitano T, Shirai S, *et al.* Decreased hydration state of the stratum corneum and reduced amino acid content of the skin surface in patients with seasonal allergic rhinitis. *Br J Dermatol* 1998; **139**: 618–621.
34 Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014; **69**: 17–27.
35 Bonnelykke K, Pipper CB, Tavendale R, Palmer CN, Bisgaard H. Filaggrin gene variants and atopic diseases in early childhood assessed longitudinally from birth. *Pediatr Allergy Immunol* 2010; **21**: 954–961.
36 Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, *et al.* Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006; **118**: 866–871.
37 Barberio G, Pajno GB, Vita D, Caminiti L, Canonica GW, Passalacqua G. Does a 'reverse' atopic march exist? *Allergy* 2008; **63**: 1630–1632.
38 Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010; **63**: 587–593.
39 Williams H, Burney P, Hay R, Archer C, Shipley M, Hunter J, *et al.* The UK working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminator for atopic dermatitis. *Br J Dermatol* 1994; **131**: 383–396.

© 2015 European Academy of Dermatology and Venereology