

Hand eczema, atopic dermatitis and filaggrin mutations in adult Danes: a registry-based study assessing risk of disability pension

Nina G. Heede¹ , Betina H. Thuesen², Jacob P. Thyssen¹, Allan Linneberg^{2,3,4}, Pal B. Szecsi⁵, Steen Stender⁵, Torkil Menné¹ and Jeanne D. Johansen¹

¹Department of Dermatology and Allergy, The National Allergy Research Centre, Copenhagen University Hospital Herlev-Gentofte, 2900 Hellerup, Denmark,

²Research Centre for Prevention and Health, the Capital Region of Denmark, 2600 Glostrup, Denmark, ³Department of Clinical Experimental Research, Rigshospitalet, 2600 Glostrup, Denmark, ⁴Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, 2200 Copenhagen, Denmark, and ⁵Department of Clinical Biochemistry, Copenhagen University Hospital Herlev-Gentofte, 2900 Hellerup, Denmark

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Summary

Background. Atopic dermatitis and hand eczema often impair the ability of people to work. Only a few studies have investigated whether individuals with loss-of-function filaggrin gene (*FLG*) mutations, who often have severe and early onset of dermatitis, experience occupational consequences.

Objective. To investigate the personal consequences of having atopic dermatitis and/or hand eczema and *FLG* mutations.

Method. Adult Danes from the general population ($n = 3247$) and patients with atopic dermatitis and/or hand eczema ($n = 496$) were genotyped for common *FLG* mutations, and completed a questionnaire about skin symptoms and hand eczema. Socioeconomic variables, including disability pension, and information on work in risk occupations were retrieved from national registries. The reasons for granting disability pension were unknown.

Results. Disability pension was associated with hand eczema in the general population, especially among individuals with a history of atopic dermatitis. Moreover, self-reported hand eczema and atopic dermatitis were associated with particularly high risk of disability pension among *FLG* mutation carriers [odds ratio (OR) 4.02 and 95% confidence interval (CI): 1.15–14.11; and OR 6.01 and 95%CI: 2.37–15.34, respectively]. Furthermore, 60% of the *FLG* mutation carriers with atopic dermatitis who developed hand eczema had experienced symptoms before adulthood.

Conclusion. In the general population, self-reported hand eczema and atopic dermatitis, particularly in individuals with a genetically impaired skin barrier, were associated with disability pension, suggesting that *FLG* mutations carriers with a history of atopic dermatitis and hand eczema could benefit from early attention with respect to choice of occupation.

Key words: atopic dermatitis; disability pension; filaggrin null mutations; hand eczema; risk occupation.

Correspondence: Nina G. Heede, Department of Dermato-Allergology, The National Allergy Research Centre, Copenhagen University Hospital Herlev-Gentofte, Kildegårdsvej 28, Opgang 20A, 1. Sal, 2900 Hellerup, Denmark. Tel: +45 38 67 73 08; Fax: +45 39 77 71 18. E-mail: nina.glasser.heede@regionh.dk

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Dermatitis is the most common skin disease; the term covers several disease entities, of which atopic dermatitis and hand eczema are among the most prevalent in the general population, with estimated 1-year prevalence rates in adults of 2–15% and 10%, respectively (1–3). Hand eczema is also the most frequently recognized occupational skin disease in Denmark (4). Because individuals with atopic dermatitis are at particular risk of developing

hand eczema later in life, early occupational counselling and preventive strategies are encouraged (5–8).

The personal and societal consequences of both atopic dermatitis and hand eczema are substantial, and include reduced quality of life (9–11), increased healthcare costs (12–14), increased sick leave, reduced work productivity, and even job change, rehabilitation benefits, and/or disability pension (8, 15–20). Changes in the average total number of disability pensions granted because of skin diseases in Denmark have been reported in the last decades: 79 per year during 1970–1976, 115.7 per year during 1999–2002, and 95.8 per year during 2003–2008; the changes have been suggested to reflect societal changes in terms of granting disability pensions, changes in environmental exposure, and advances in treatment (18, 19, 21).

FLG mutations are found in 8% of the general population in northern European countries (22, 23), and are associated with an increased risk of, often severe, atopic dermatitis (24–26). Notably, *FLG* mutations have also been found to increase the risk of early-onset and persistent hand eczema in individuals with atopic dermatitis (27). In relation to occupation, it has previously been suggested that a combination of atopy and *FLG* mutations in patients with occupational irritant contact dermatitis of the hands is associated with an increased risk of abandoning the profession (28).

In this study, we investigated the personal consequences of having both *FLG* mutations and atopic dermatitis and/or hand eczema. We investigated socioeconomic variables, including disability pension, and a history of working in risk occupations, to evaluate whether occupational counselling and preventive strategies should be focused not only on individuals with atopic dermatitis, but also on individuals with *FLG* mutations.

Methods

In this study, we used data from two populations: (i) a cross-sectional study including adult dermatological patients; and (ii) a cross-sectional study of the adult general Danish population.

The patient population

We included 515 patients (aged ≥ 18 years) diagnosed with atopic dermatitis and/or hand eczema at the Dermatology Department at Gentofte Hospital during 2006–2012 (participation: 46.5%). All patients received a written invitation, and interested patients received oral information about the study. Genomic DNA was collected by a buccal swap (Isohelix, Harrietsham, UK) and stored

at -80°C until extraction was performed with a JetQuick kit (Genomed, Löhne, Germany), according to the manufacturer's instructions. *FLG* genotyping was performed as previously described (29) for three of the most common *FLG* mutations, namely R501X, 2282del4, and R2447X, which together constitute 83% of the total risk alleles associated with atopic dermatitis (24, 30, 31). A positive test result was defined as a heterozygote, homozygote or compound heterozygote mutation. Patients were diagnosed with atopic dermatitis and/or hand eczema by a dermatologist at our Dermatological Department, as previously described in detail (32). In the clinic, a history of atopic dermatitis was investigated as a lifetime prevalence, whereas hand eczema was investigated as a point prevalence. All patients also filled in a questionnaire about hand eczema. In this study, the self-reported patient data on hand eczema were used. Overall, 85.3% ($n = 193$) of the patients with atopic dermatitis reported hand eczema in their lifetime.

The general population

We included 3471 participants (aged ≥ 18 years) from a cross-sectional study, the 'Health2006 study', performed in the south-western part of Copenhagen (participation: 44.7%). The population was selected as a random sample of the general population by use of the Danish Central Personal Registry, and the inclusion period started in 2006. Detailed information about the study has previously been published (33). Participants were subjected to a general health examination, which did not include a skin examination, and completed a questionnaire regarding lifestyle factors and chronic diseases, including skin disorders and symptoms. A history of atopic dermatitis was estimated according to a slightly modified version of the UK Working Party's diagnostic criteria as a history of an itchy skin condition plus a minimum of two of four minor criteria (34). The major criterion was an itchy skin condition, and the minor criteria were: (i) a history of involvement of the skin creases, (ii) a history of asthma or hay fever, (iii) a history of generally dry skin, and (iv) onset before the age of 2 years (34). *FLG* genotyping was based on blood samples and performed as described above (29). Overall, 50.6% ($n = 169$) of the participants with a history of atopic dermatitis reported hand eczema in their lifetime.

Questions about history of self-reported hand eczema

The questions about hand eczema in both populations were introduced by the following description of eczema: 'Eczema is an itchy skin disorder showing redness, dryness, and possibly vesicles and exudation. Eczema

remains on the same area of the body for some time'. Participants were asked: 'Have you ever had hand eczema?' Participants who gave an affirmative answer were further asked 'At what age did you have hand eczema on the first occurrence?' (<6 years, 6–14 years, 15–18 years or >18 years).

Linkage to registry data

Data from both populations were transferred to Statistics Denmark and linked to information from different nationwide registries on an individual level. Socioeconomic data were retrieved from the general population in 2006 and from the patient population in 2013. Occupational status, including disability pension, was obtained from the National Registry of Personal Income. However, the reasons for granting disability were unknown. A dichotomous variable for disability pension was created. Participants receiving disability pension formed one group, and individuals who were either 'working', 'unemployed' or 'on leave or sick leave' formed another group 'not receiving disability pension'. Retired participants ($n = 429$) were set to 'missing' because they represent a group outside the workforce and cannot be considered as candidates for disability pension. Because of the low number of individuals with more than one *FLG* mutation and the privacy rules of Statistics Denmark, it was not possible to investigate whether the proportion of individuals receiving disability pension differed between homozygous/compound heterozygous *FLG* mutation carriers and heterozygous *FLG* mutation carriers. A retrospective linkage of both populations during 1994–2013 investigating 'work in a risk occupation' was performed for all individuals in the work-active period (16–64 years) by use of the Danish Registers on Labour Market Affiliation, which record occupational classification based on DISCO codes (35). We used published literature to define risk occupations (36–38).

Ethics and statistics

Written informed consent was obtained for all participants, in both populations, prior to inclusion. The patient study was approved by the Ethics Committee of Copenhagen County (H-1-2013-127), and so was the general population study (KA-20060011). The study was also approved by the Danish Data Protection Agency.

We included 3247 (93.5%) of the participants from the general population and 496 (96.3%) of the patients from the patient population in the present analyses; the remaining participants were omitted because of missing data on *FLG* genotype, on atopic dermatitis (only in the general population), or on the hand eczema questions.

Thereby, we analysed only complete cases to enable stratification on atopic dermatitis and/or hand eczema and *FLG* genotype. A few people were registered as 'missing cases' in the different registries, causing small variations in the total n values presented in the tables. Statistical analyses for dichotomous variables were performed with the χ^2 test or Fisher's exact test. Non-parametric variables were tested for group differences with the Kruskal–Wallis test. The level of significance was set to $p < 0.05$. Continuous variables were presented as median scores with 25th and 75th percentiles. Multiple logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed with SAS software (Version 9.3 for Windows; SAS Institute, Cary, NC, USA), and the figure was created with GRAPHPAD PRISM version 6.07 for Windows (GraphPad Software, La Jolla, CA, USA).

Results

Atopic dermatitis and/or hand eczema is reflected by occupational status in the general population

Table 1 shows the characteristics of the two populations stratified by atopic dermatitis and/or hand eczema as well as *FLG* genotype. In the general population, significant group differences were found for age, sex, occupational status, and income (Table 1A). In addition to the statistical results presented in Table 1, participants with atopic dermatitis (with or without hand eczema) were significantly younger than those with hand eczema but without a history of atopic dermatitis, and had a predominance of females as compared with the latter group ($p < 0.001$). In relation to occupational status, the proportion of individuals receiving disability pension was increased among participants with a history of dermatitis, atopic dermatitis with or without hand eczema (6.6%) and hand eczema only (5.0%) as compared with participants without dermatitis (2.3%) ($p < 0.001$; Table 1A). When only *FLG* genotype was taken into account and dermatitis was not considered, a significant difference between occupational status and *FLG* mutations was observed. In general, the lowest level of income was found among individuals with atopic dermatitis and/or hand eczema. Moreover, *FLG* mutation carriers overall had a lower level of income than individuals without the mutation ($p = 0.044$; Table 1A).

In contrast to the general population, no sex difference was found among the patients with or without atopic dermatitis. However, the patients with atopic dermatitis were significantly younger than patients with hand eczema but without atopic dermatitis, and the proportion of patients in education was significantly higher ($p < 0.001$; Table 1B). It is of note that the proportion

Table 1. Demographics of the populations, including: age, sex, education, family status, occupational status, and income. Table 1A shows data from the general adult population (N = 3247) and Table 1B shows data from adult dermatitis patients (N = 496).

A	The general adult population								
	Total N = 3247	No dermatitis		Hand eczema (no atopic dermatitis)		Atopic dermatitis ± hand eczema		p-Value (1)	p-Value (2)
		FLG _{wt} (n = 2187)	FLG _{mut} (n = 195)	FLG _{wt} (n = 493)	FLG _{mut} (n = 36)	FLG _{wt} (n = 276)	FLG _{mut} (n = 60)		
Explanatory variables (n _{group})									
Age (years) (n = 3247), median (25–75 percentiles)	50 (40–60)	51 (41–61)	52 (42–61)	50 (41–60)	47 (39–60)	47 (37–57)	46 (35–54)	<0.001	0.74
Sex (n = 3247), % female	55.0	51.2	50.3	61.1	66.7	74.3	65.0	<0.001	0.83
Education (n = 3223) (%) ^a									
In education	5.4	5.3	3.1	4.9	5.6	8.8	3.3	0.11	0.23
Vocational education or lower	67.4	66.3	73.2	70.9	66.7	63.6	63.3		
Family status (n = 3246), % living alone with or without children	22.3	21.6	25.1	21.3	27.8	25.5	30.0	0.31	0.077
Occupational status ^d (n = 3201) (%)									
Working	80.9		81.2		78.4		Not shown ^b	<0.001	<0.001
Unemployed (receiving social benefit)	1.9		1.5		3.3		2.4		
Leave, maternity leave or sick leave	0.6		0.5		1.2		Not shown ^b		
Disability pension	3.2		2.3		5.0		6.6		
Retired	13.4		14.4		12.2		8.1		
Annual gross income (n = 3247), mean in Danish kroner	316 719	324 522	298 596	307 955	296 617	291 096	293 141	0.001	0.044

B	Adult dermatitis patients						
	Total N = 496	Hand eczema (no atopic dermatitis)		Atopic dermatitis ± hand eczema		p-Value (1)	p-Value (2)
		FLG _{wt} (n = 245)	FLG _{mut} (n = 25)	FLG _{wt} (n = 165)	FLG _{mut} (n = 61)		
Age (years) (n = 496), median (25–75 percentiles)	48.5 (36–58)	50 (42–59)	52 (47–57)	42 (30–53)	42 (27–55)	<0.001	0.27
Sex (n = 496), % female	74.6	70.2	80.0	80.6	73.8	0.11	0.74
Education (n = 487) (%) ^a							
In education	11.5	5.7	12.5	15.2	25.5	<0.001	0.008
Vocational education or lower	55.2	63.5	75.0	44.5	41.8		
Family status (n = 496) % living alone with or without children	28.4	24.5	28.0	30.9	37.7	0.18	0.14
Occupational status ^d (n = 487) (%)							
Working	79.1		76.2		82.4	0.32	0.68 ^c
Unemployed (receiving social benefit)	4.5		4.5		4.5		
Leave, maternity leave or sick leave	2.1		1.9		2.2		
Disability pension	3.7		4.9		2.3		
Retired	10.7		12.5		8.6		
Annual gross income (n = 496), mean in Danish kroner	353 449	341 439	312 529	389 841	320 019	0.39	0.18

The general population was linked to the registries in 2006, and patients were linked in 2013. *p*-Value (1) = all group difference between the six groups according to the Chi² test (Kruskal–Wallis test for age and income). *p*-Value (2) = overall difference in relation to filaggrin genotype: wild-type versus mutation carriers according to the chi² test (Kruskal–Wallis test for age and income). *Education* (highest education attained) was available from the Attainment Registry, *family status* was available from the National Danish Registry of Population Statistics, and *occupational status* and *income* were available from the National Registry of Personal Income.

^aHighest obtained education. A vocational education is defined as 1 or 2 years of education after high school (e.g. nursing assistants or cooks).

^bNot shown because of privacy restrictions.

^cFisher's exact test. Bold values indicate significant differences (*p* < 0.05).

^dOccupational status is not stratified by FLG genotype, because many cells contained numbers smaller than 3, and are therefore deleted in agreement with discretion policy. However, the overall *p*-value is shown

of patients with a vocational education was highest among patients with hand eczema and no history of atopic dermatitis, irrespective of *FLG* genotype (hand eczema + *FLG*_{wt}: 63.5%, hand eczema + *FLG*_{mut}: 75.0%, atopic dermatitis + *FLG*_{wt}: 44.5%, and atopic dermatitis + *FLG*_{mut}: 41.8%) ($p < 0.001$). In addition to the data presented in Table 1B, 18% of the patients were aged ≤ 30 years. Notably, the proportion of *FLG* mutation carriers was higher among patients ≤ 30 years when compared with the proportion among patients older than 30 years, which may have influenced the educational level (24.2% and 15.8%, respectively; $p = 0.057$).

The proportion of individuals receiving disability pension in the general population was higher among participants reporting hand eczema, especially in individuals with a history of atopic dermatitis

To further investigate the difference in occupational status among participants with and without atopic dermatitis and/or hand eczema in the general population, we performed logistic regression analyses with 'disability pension' as the dependent variable (Table 2). Self-reported hand eczema was found to be associated with receiving disability pension, irrespective of atopic dermatitis (adjusted OR 2.30; 95%CI: 1.50–3.54). In addition, a history of atopic dermatitis was associated with receiving disability pension, although the association became weaker after adjustment for hand eczema, sex, and age group (crude OR 2.29 and 95%CI: 1.41–3.73; and adjusted OR 1.89; 95%CI: 1.11–3.21). When we considered both atopic dermatitis and hand eczema, we found that atopic dermatitis alone was not associated with disability pension in individuals without self-reported hand eczema as compared with individuals without any dermatitis (adjusted OR 1.18; 95%CI: 0.42–3.35). However, individuals with a history of atopic dermatitis who also reported hand eczema had a highest risk of being granted disability pension (11.7%) than individuals without dermatitis (adjusted OR 4.80; 95%CI: 2.69–8.57).

In addition, the proportion of individuals receiving disability pension was increased among *FLG* mutation carriers (6.40%) as compared with non-mutation carriers (3.45%). However, the association between *FLG* mutations and disability pension lost its significance after adjustment for both atopic dermatitis and hand eczema (crude OR 1.91 and 95%CI: 1.10–3.32; and adjusted OR 1.77 and 95%CI: 0.996–3.13), as *FLG* mutations themselves cannot predispose to disability pension, but may result in symptoms leading to disability pension. To address this further, we performed a regression analysis taking both dermatitis and *FLG* genotype into account. Individuals without dermatitis and *FLG* wild type were

used as references. Notably, self-reported hand eczema and/or atopic dermatitis were associated with a particularly high risk of disability pension among *FLG* mutation carriers (OR 4.02 and 95%CI: 1.15–14.11; and OR 6.01 and 95%CI: 2.37–15.34, respectively), although interactions did not reach statistical significance. Overall, 3.2% of the general population had been granted disability pension in 2006. A similar proportion of 3.7% was identified among the patient population in 2013. However, no statistical difference in relation to disability pension was found among the patients (hand eczema only, 5.6%; atopic dermatitis only, 0%; and both atopic dermatitis and hand eczema, 2.9%; Fisher's exact test, $p = 0.28$). Moreover, no statistical difference was seen according to *FLG* genotype (Fisher's exact test, $p = 0.75$).

The patterns of onset of hand eczema in the general population and among patients are very similar

Among the individuals reporting hand eczema, Figure 1 shows the onset of hand eczema symptoms by atopic dermatitis and *FLG* genotype for the general population (Fig. 1a) and for patients (Fig. 1b). The trend was very similar for the two populations, and confirms that *FLG* mutations increase the risk of early onset of hand eczema symptoms in individuals with atopic dermatitis. In detail, 40% of the *FLG* mutations carriers with atopic dermatitis developed symptoms of hand eczema before the age of 6 years, and 60% before adulthood (age 18 years). Notably, *FLG* mutations did not predispose for early symptoms of hand eczema in individuals without a history of atopic dermatitis. The majority of the participants developing hand eczema, but without a history of atopic dermatitis, developed hand eczema in adulthood presumably as a consequence of environmental exposure to allergens and/or irritants.

History of work in a high-risk occupation

We investigated employment in high-risk dermatitis occupations by retrospective linkage to Statistics Denmark during 1994–2013 (Table 3). Almost one-third of the individuals in the general population had been employed in a risk occupation at some time. In contrast, almost half of the patients had been occupied in a risk occupation. For both populations, the most common occupation was cleaning, followed by nursing assistants and nurses, which together represented more than half of the participants working in a risk occupation (Table 3A).

After stratification by dermatitis and *FLG* genotype, the prevalence of having worked in a risk occupation was increased among participants who reported hand eczema and/or atopic dermatitis in the general population

Table 2. Logistic regression analyses with 'disability pension' as dependent variable and filaggrin genotype, hand eczema (HE) or atopic dermatitis (AD) as explanatory variables for participants in the general population

Explanatory variables (n _{group})	Receiving disability pension (n = 103), % (n)	Crude OR (95%CI)	Adjusted OR (95%CI)
Age group (years)			
18–40 (n = 809)	0.74 (6)	Not calculated ^a	Not calculated ^a
41–55 (n = 1221)	3.52 (43)		
>56 (n = 742)	7.28 (54)		
Sex			
Male (n = 1245)	2.73 (34)	1 (reference)	1 (reference)
Female (n = 1527)	4.52 (69)	1.69 (1.11–2.56)	1.87 (1.23–2.86) ^b
Filaggrin genotype			
Wild type (n = 2522)	3.45 (87)	1 (reference)	1 (reference)
Mutation carrier (n = 250)	6.40 (16)	1.91 (1.10–3.32)	1.77 (0.996–3.13) ^c
Hand eczema (HE)			
Never (n = 2157)	2.74 (59)	1 (reference)	1 (reference)
Lifetime prevalence (n = 613)	7.18 (44)	2.75 (1.84–4.11)	2.30 (1.50–3.54) ^d
Atopic dermatitis (AD)			
No (n = 2467)	3.28 (81)	1 (reference)	1 (reference)
Lifetime prevalence (n = 305)	7.21 (22)	2.29 (1.41–3.73)	1.89 (1.11–3.21) ^e
AD and HE			
No dermatitis (n = 2008)	2.7 (55)	1 (reference)	1 (reference) ^f
HE (no AD) (n = 459)	5.7 (26)	2.13 (1.32–3.44)	2.04 (1.26–3.32)
AD (no HE) (n = 149)	2.7 (4)	0.98 (0.35–2.74)	1.18 (0.42–3.35)
AD and HE (n = 154)	11.7 (18)	4.70 (2.69–8.23)	4.80 (2.69–8.57)
Dermatitis and filaggrin status			
No dermatitis (<i>FLG</i> _{wt}) (n = 1846)	2.60 (48)	1 (reference)	1 (reference) ^f
No dermatitis (<i>FLG</i> _{mut}) (n = 162)	4.32 (7)	1.69 (0.75–3.80)	1.60 (0.71–3.64)
HE (no AD) (<i>FLG</i> _{wt}) (n = 427)	5.39 (23)	2.13 (1.28–3.55)	2.02 (1.21–3.83)
HE (no AD) (<i>FLG</i> _{mut}) (n = 32)	9.38 (3)	3.88 (1.14–13.16)	4.02 (1.15–14.11)
AD (±HE) (<i>FLG</i> _{wt}) (n = 249)	6.43 (16)	2.57 (1.44–4.60)	2.74 (1.51–4.99)
AD (±HE) (<i>FLG</i> _{mut}) (n = 56)	10.71 (6)	4.50 (1.84–11.00)	6.01 (2.37–15.24)

CI, confidence interval; *FLG*_{mut}, filaggrin mutation carrier; *FLG*_{wt}, filaggrin wild type; OR, odds ratio.

A dichotomous variable for disability pension was created. Participants who were working, unemployed or on 'leave or sick leave' were considered to be 'not receiving disability pension', and retired participants (n = 429) were set to be 'missing' because they were outside the workforce. Students were also considered to be working. The reasons for granting disability pension to the 103 individuals are unknown. The analyses for each explanatory variable were performed separately. n = 2772.

^aDisability pension is primarily granted to individuals between aged 50–59 years.

^bAdjusted for age group (18–40, 41–55 and >56 years).

^cAdjusted for age group, sex, hand eczema (HE) and atopic dermatitis.

^dAdjusted for age group, sex and atopic dermatitis.

^eAdjusted for age group, sex, and HE.

^fAdjusted for age group and sex.

($p < 0.001$) (Table 3B). In addition to the data in Table 3B, no differences in the proportion of *FLG* mutation carriers were found between risk occupations and non-risk occupations among individuals in the general population or among patients ($p = 0.97$ and $p = 0.12$, respectively).

Finally, we also investigated the lifetime prevalence of being granted rehabilitation benefits by retrospective linkage to Statistics Denmark in the period 1994–2013 based on information from the National Danish Registry of Personal Income. In total, 2.3% (n = 77) of the individuals in the general population had, at some point, been granted rehabilitation benefits, in contrast to 5.5% (n = 27) of the patients ($p < 0.001$). Furthermore, we found that the proportion of individuals ever having been granted rehabilitation benefits in the general population

differed in relation to self-reported dermatitis; no dermatitis, 1.8%; hand eczema (no atopic dermatitis), 2.6%; and atopic dermatitis (with or without hand eczema), 5.7%. Notably, the grounds for granting rehabilitation benefits were unknown.

Discussion

We showed that the proportion of individuals receiving disability pension in the general population was increased among participants reporting hand eczema, especially among those with a history of atopic dermatitis. Moreover, the association between self-reported hand eczema and/or atopic dermatitis and disability pension was found particularly in individuals with a genetically determined

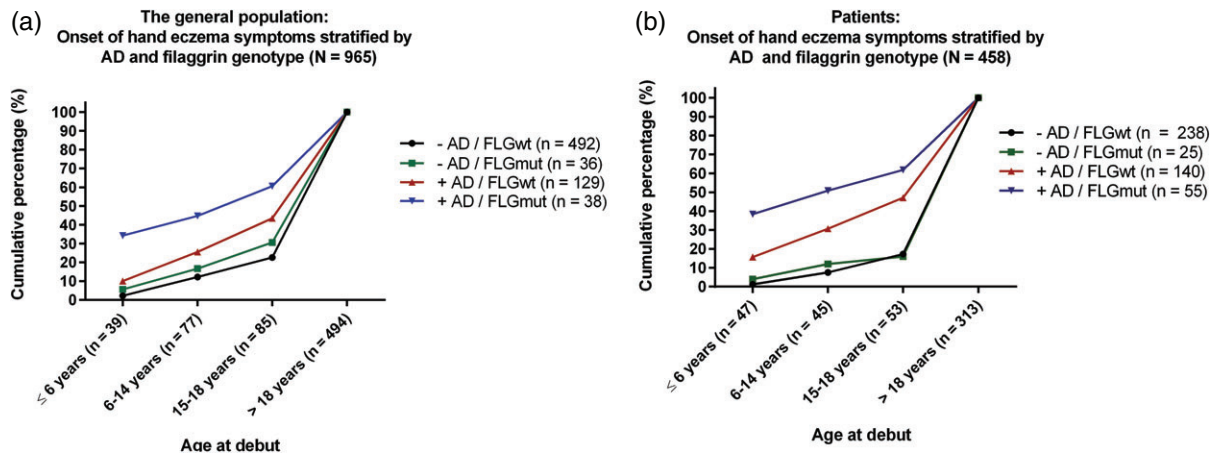


Fig. 1. Age at onset of self-reported hand eczema symptoms stratified by history of atopic dermatitis (AD) and filaggrin gene (*FLG*) mutations in the general population (a) and in patients (b). *FLG*_{mut}, filaggrin mutation carrier; *FLG*_{wt}, filaggrin wild type.

impaired skin barrier, in this context manifested by presence of *FLG* mutations. *FLG* mutations themselves evidently cannot predispose to disability pension, but may result in skin symptoms leading to disability pension.

The grounds for granting disability pension were unknown in this study, which is why new studies designed to further investigate our findings are needed. However, the association between disability pension and self-reported dermatitis suggests that individuals receiving disability pension stand out in relation to reporting skin symptoms. Although the number of disability pensions granted because of skin diseases is low, previous publications have repeatedly shown associations between disability pension and both hand eczema and atopic dermatitis (17, 18, 39). In our analyses, atopic dermatitis alone was not associated with disability pension, but, when it was combined with self-reported hand eczema, the association was strong. In total, 11.7% of the participants with a history of atopic dermatitis and hand eczema had been granted disability pension. An investigation of disability pensions granted because of skin diseases in Denmark identified contact dermatitis as the dominant diagnosis in the 1970s (18), whereas, during 2003–2008, the number of disability pensions granted because of contact dermatitis was halved (19).

Today, the biological interplay between contact dermatitis, *FLG* mutations and atopic dermatitis remains to be elucidated. Recently, *FLG* mutations were associated with contact dermatitis in construction workers, most strongly in individuals with an atopic predisposition (40). Accordingly, Landeck et al. reported in 2012 that patients with irritant contact dermatitis who had both atopy and *FLG* mutations had a worse clinical course and a higher risk of leaving their profession after 3 years than patients

with irritant contact dermatitis but without atopy or *FLG* mutations (28). Moreover, a Swedish study from 2016 showed that 36% of disability pensions granted because of skin diseases were granted because of eczema. Of those granted disability pensions, painters, cement workers and plumbers formed the major group (20). In our setup, it was not possible to link disability pension and occupation. In future studies, it could, however, be relevant to investigate whether *FLG* mutation carriers working in risk occupations, such as construction workers, have an increased risk of receiving disability pension, or rehabilitation benefits, as compared with wild-type carriers.

In the general population, we found that participants with atopic dermatitis and/or hand eczema had a lower income, which could be a result of occupational status. Another explanation could be that individuals with hand eczema more often work in low-income occupations with more skin hazards, such as wet work, than those without dermatitis. However, differences in age and sex should be taken into account. Accordingly, in the group of individuals with atopic dermatitis and/or hand eczema, there are more females, who tend to have a lower income than men. Although the incidence of atopic dermatitis in Scandinavian children is now stable (41), it is well known that the incidence of atopic dermatitis has increased over time (42–44). It is of note that the number of disability pensions granted per year with atopic dermatitis as the primary diagnosis has increased from the 1970s to the 2000s (18, 19). In our study, the prevalence of atopic dermatitis in the general population was found to decrease with increasing age: 13.7% (18–40 years), 10.9% (41–55 years), and 7.5% (>56 years). It could therefore be hypothesized that more individuals who are prone to developing hand eczema will hence enter the

Table 3. Lifetime prevalence of employment in risk occupations (A). Prevalence of employment in a risk occupation stratified by dermatitis and filaggrin genotype (B)

(A) Risk occupations	The general adult population ($n_{\text{total}} = 3245$), % (n)	Adult dermatitis patients ($n_{\text{total}} = 490$), % (n)
Hairdressers and beauticians	0.68 (22)	4.49 (22)
Bakers	0.34 (11)	1.02 (5)
Cooks	1.85 (60)	4.49 (22)
Butcher	0.15 (5)	–
Painters	0.77 (25)	1.02 (5)
Mechanics	1.97 (64)	2.45 (12)
Machine workers	1.05 (34)	–
Cleaners	6.56 (213)	8.78 (43)
Electricians	1.73 (56)	1.02 (5)
Plumbers	0.92 (30)	–
Blacksmith/locksmith	1.23 (40)	0.82 (4)
Nurses	2.50 (81)	6.94 (34)
Nursing assistants	7.61 (247)	12.65 (62)
Physicians	0.31 (10)	2.24 (11)
Dentists and dental surgery assistants	0.12 (4)	1.02 (5)
Laboratory technicians	1.33 (43)	2.04 (10)
Total: History of work in a risk occupation	29.12 (945)	49.18 (241)
Total: No history of work in a risk occupation	70.88 (2300)	50.82 (249)

(B) Stratification by dermatitis and filaggrin genotype	Prevalence of individuals in risk occupation N = 945	Prevalence of individuals in risk occupation N = 241
No dermatitis (FLG_{wt})	26.84 (587)	–
No dermatitis (FLG_{mut})	28.72 (56)	–
HE (no AD) (FLG_{wt})	35.50 (175)	57.72 (142)
HE (no AD) (FLG_{mut})	30.56 (11)	44.00 (11)
AD ($\pm$ HE) (FLG_{wt})	35.77 (98)	40.24 (66)
AD ($\pm$ HE) (FLG_{mut})	30.00 (18) ^a	40.00 (22) ^b

AD, atopic dermatitis; FLG_{mut} , filaggrin mutation carrier; FLG_{wt} , filaggrin wild type; HE, hand eczema.

Data were obtained by linkage to the Danish Registry on Labor Market Affiliation in the period 1994–2013. Only complete cases with a filaggrin genotype, history of AD and HE are included. Cells with a number of participants smaller than three are deleted because of discretion policies, causing the difference in total n. Risk occupations were selected on the basis of the literature, and represent occupations with high exposure to allergens and irritants, such as wet work (36–38).

^a $p < 0.001$ (overall group difference, χ^2 test).

^b $p = 0.002$ (overall group difference, χ^2 test).

workforce in the years to come, when the younger generations with more atopic dermatitis become older, as a history of atopic dermatitis is the most pronounced predictive factor for hand eczema (6, 45, 46). This encourages effective preventive measures and early detection of skin symptoms.

Similar proportions of individuals being granted disability pensions were identified among the general population and the patient population (3.2% and 3.7%, respectively). Among the 18 patients who were granted disability pensions in 2013, all reported hand eczema and 27.9% had a history of atopic dermatitis. The finding that self-reported atopic dermatitis and hand eczema in the general population was associated with receiving disability pension, primarily among FLG mutation carriers, was not reproduced in patients, and there could be several explanations for this. First, fewer FLG mutation carriers

were found among patients included with hand eczema only, who were the group with the highest proportion of individuals being granted disability pensions (5.6%). In total, 8.9% of the patients with hand eczema but without atopic dermatitis were FLG mutation carriers, in contrast to 26.8% of the patients with atopic dermatitis ($p < 0.001$). Second, disability pension is mainly granted to older individuals. In the patient population, the patients with atopic dermatitis (representing 71.3% of the FLG mutation carriers) were significantly younger than the patients with hand eczema but without a history of atopic dermatitis. Finally, it is possible that the patients with FLG mutations obtained early information about prevention and career advice because their dermatitis commenced early in life.

In line with this, rehabilitation is a social benefit from Danish society aimed at helping individuals with reduced

work ability to stay employed, or to get into the labour market by receiving retraining (47). We found that the overall lifetime prevalence of being granted rehabilitation benefit was almost twice as high among patients as among the general population (5.5% and 2.3%, respectively), whereas similar proportions of individuals being granted disability pensions were found in the two populations (3.7% and 3.2%, respectively). Although differences in inclusion time for the two populations exist, and we do not have any information regarding age, sex, time of granting of the social benefits, or whether it is the same individuals being granted rehabilitation and disability pension, our results might indicate that rehabilitation among dermatological patients works, because the proportion of patients receiving disability pension is not higher. This stresses the importance of providing patients with proper diagnoses and early occupational guidance.

Furthermore, we found that the patterns of onset of symptoms of hand eczema in the general population and among patients were very similar after stratification by *FLG* genotype and atopic dermatitis. The trend in the patient population can thereby be interpreted as a control for the trend seen in the general population. It could be hypothesized that, because 60% of the individuals with *FLG* mutations and concomitant atopic dermatitis, and 40% of the non-mutation carriers with atopic dermatitis who develop hand eczema, will have onset of symptoms before adulthood, individuals with atopic dermatitis might have 'an advantage' in terms of choosing a future career with a low risk of exposure to irritants and allergens or in terms of using preventive measures. In line with this, it has been suggested that *FLG* mutation carriers, with onset of hand eczema in childhood, avoid professional exposure to irritants (48). However, previous publications have shown that a history of atopic dermatitis does not influence the choice of occupation (49–52). Nevertheless, Wei et al. report that having received occupational counselling was associated with greater use of preventive measures, which encourages continued occupational counselling (49). In contrast, patients with hand eczema but without atopic dermatitis were characterized by onset of hand eczema in adulthood, vocational education, and an increased prevalence of history in a risk occupation, which suggests

a different pattern in the development of hand eczema symptoms than that in patients with atopic dermatitis.

The strength of this study is the combination of cross-sectional data from two populations combined with registry data. However, there is always a risk of misclassification and/or recall bias when questionnaire data are used, and this can influence the sensitivity and specificity of both self-reported hand eczema and atopic dermatitis (defined according to the UK criteria). Nevertheless, the greatest limitation of this study is that, because we used registry-based data, we have no information on the primary diagnoses leading to the local authority granting disability pension. The grounds for disability pension can therefore be physical, psychological, or social, or a combination of these. Finally, we did not have any information on clinical severity in the patient population.

In conclusion, our results indicate that self-reported hand eczema, particularly in persons with a history of atopic dermatitis and a genetically determined impaired skin barrier (*FLG* mutation), was associated with receiving disability pension in the general population. Although the grounds for receiving disability pension were unknown, a focus on the early detection of skin symptoms is suggested. Moreover, our data indicate that an economic burden on society might be expected as the younger generations with a higher rate of atopic dermatitis and thus hand eczema risk age, unless appropriate actions are taken to prevent this, such as medical counselling on early change of occupation and optimized treatment.

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