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Allergic contact dermatitis in children

PhD dissertation

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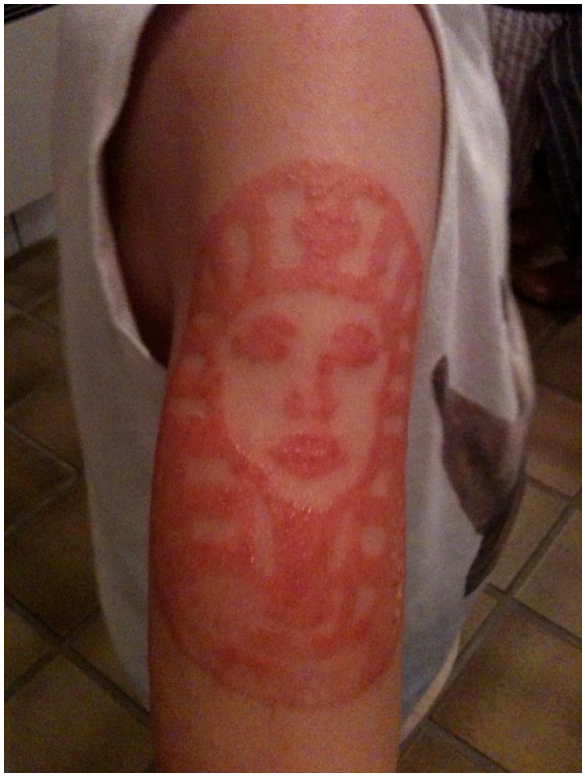

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This PhD is a product of scientific cooperation between

1) Department of Dermatology and Venereology
Aarhus University Hospital,

2) National Allergy Research Centre, Department of dermatology and Allergy,
Copenhagen University Hospital, Herlev-Gentofte

and

3) Department of Dermatology and Allergy Centre, Odense University Hospital

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I. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M: Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multi-centre study. Contact dermatitis. 2014 Feb; 70(2): 104-111.

II. Simonsen AB, Sommerlund M, Deleuran M, Mortz CG, Johansen JD: Course of skin symptoms and quality of life in children referred for patch testing – a long-term follow-up study. Acta Dermato-Venereologica. 2015 Feb; 95(2): 206-10.

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Anne Birgitte Simonsen, December 2017.

Abbreviations:

The abbreviations are listed alphabetically.

CDLQI	Children's Dermatology Life Quality Index
DLQI	Dermatology Life Quality Index
DNCB	Dinitrochlorobenzene
HRQoL	Health-related quality of life
IPPD	N-isopropyl-N'-phenyl-paraphenylenediamine
PPD	Para-phenylenediamine
QoL	Quality of Life
SCORAD	Scoring Atopic Dermatitis
SL-mix	Sesquiterpene lactone-mix
TRUE test	Thin-layer Rapid Use Epicutaneous Test

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1. Introduction

1.1 Contact allergy and allergic contact dermatitis

In our daily life, we encounter countless natural and synthetic chemicals. Contact allergy is an acquired immunological response to contact with such chemicals and the underlying pathomechanism of allergic contact dermatitis. It involves two phases – the sensitization phase and the elicitation phase. Certain substances, known as haptens, are reactive chemicals, usually with a molecular weight of < 500 Da, exceptionally in the range of 500-1000 Da (1). Because of their small size and polarity, they are able to penetrate the stratum corneum of the epidermis. Haptens are generally not antigenic in themselves. However, upon penetration, they either covalently bind to or, in the case of metal ions, react with endogenous proteins and form immunologically relevant allergen-carrier complexes (2) , which are crucial for the activation of the innate immune system. To provide simplicity, the word *allergen* will cover both hapten and the antigenic allergen-carrier complex for the remaining part of this work. The entrance of the haptens through the epidermis activates keratinocytes to release inflammatory cytokines and chemokines, which induce the recruitment, migration and maturation of cutaneous dendritic cells (3). An important feature of the dendritic cells is the ability to present exogenous antigens to other cells of the immune system. They take up the allergen-carrier complex and present it on their cellular surface. Depending on the allergen, this presentation will either be in the context of major histocompatibility complex (MHC) class I or II. Through the afferent lymph vessels the dendritic cells migrate to the regional lymph nodes. They home to the T-cell-rich paracortical areas of the lymph node where local conditions are optimal for encountering naïve T cells. Upon recognition of the allergen-MHC molecule complexes, the T-cells become activated and start to proliferate and thereby generating allergen-specific effector- and memory T cells. This process, defined as "sensitization" lasts 10–15 days (3). The person now has an acquired contact allergy to the specific allergen and in immunological terms, the person is now sensitized to that particular allergen. This is not necessarily a problem if the person throughout life is able to avoid the particular allergen. However, if the skin is ever re-exposed to the same (or a cross reacting) allergen in a sufficient amount, surpassing the individual threshold, a secondary immune response will occur. This is known as the elicitation phase. Re-exposure to the contact

allergen triggers the release of cytokines and chemokines from keratinocytes and dendritic cells, which attracts the allergen-specific T-cells. The skin-infiltrating T-cells release cytokines, which drives the attraction and subsequent activation of T-cells, natural killer cells, macrophages, mast cells and/or eosinophils to the site of allergen exposure (2). The massive release of inflammatory mediators causes vasodilatation, oedema, spongiosis, and vesiculation. In the skin, this reaction will manifest itself as allergic contact dermatitis in the exposed skin or sometimes even outside the initial area of contact (4).
Once it is developed, a contact allergy is lasting and the patient must in principle throughout life avoid the allergen in order to prevent recurrent outbreaks of dermatitis (5). However, with time, the reactivity may diminish if the allergen is avoided.

1.2 Patch testing

1.2.1 The patch test procedure

Epicutaneous patch testing is the gold standard method of diagnosing contact allergy and allergic contact dermatitis. It is used in patients with a history of dermatitis to determine if the patient has a contact allergy and is followed by an evaluation of the relation between the dermatitis and exposure to the contact allergen. The history and clinical examination of the patient will usually provide clues to the possible sensitizers and should guide the choice of patch test materials. As unsuspected allergens frequently turn out to be relevant, it is recommended to patch test with a "baseline series" of the most frequent allergens in the given population, supplemented with specific allergens or series of allergens according to the history and clinical picture (4, 6).
The patch test involves the application of various test substances to the skin. Usually, one of two systems is used: the original system where allergens, patches and tapes are supplied separately, or the so-called "ready-to-use" system, where only a covering material has to be removed before the test is applied. After patch test application at day 0 and allergen exposure for 2 days, the test substances are removed. Evaluation of the exposed skin is optimally performed at the day of removal (day 2), day 3-4, and day 7. The patch test reading is based on inspection and palpation of the skin reaction and is classified as "+1", "+2", "+3", "+?", "IR", or "negative" according to the globally acknowledged criteria of the International Contact Dermatitis Research Group (6, 7). For a patch test reaction to be considered positive, homogeneous infiltration and erythema of the entire test area is required for a weak positive

reaction (+ 1), with additional vesicles defining a strong positive (+2) and coalescing vesicles an extreme positive (+3) reaction. No reaction is classified as a negative reaction, faint erythema only as a doubtful reaction (+?), and various unspecific morphologies (e.g. bulla, necrosis, soap effect) is classified as an irritant reaction (IR).

A positive patch test reaction to a substance is a sign of contact allergy, i.e. sensitization to the specific allergen has occurred. For each positive reaction, the clinical relevance of the reaction in relation to the skin symptoms has to be determined. In other words, it has to be determined whether the patient has been exposed to the allergen in question and whether the patient has or ever had concurrent skin symptoms that could be explained by this exposure. Thus, a positive patch test reaction can be of current and/or past relevance, of unknown relevance, or of no relevance to the current skin symptoms. If a clinical relevance is found in a person with established contact allergy, the diagnosis of allergic contact dermatitis can be made. If the clinical relevance is unknown, the conclusion of the patch test is that the patient has a contact allergy (is sensitized) to the specific allergen, but the criteria for the diagnosis of allergic contact dermatitis have not been met. However, it is important to be aware that this patient is at risk of developing allergic contact dermatitis, if he or she is ever exposed to the same allergen in the future (6).

Although the patch testing procedure is well established and has been globally used for more than a century (8), it is important to bear in mind, that it is a biological assay. As with any other biological measurements, there will be inherent variability as well as pitfalls in performance and interpretation. The patch test procedure may appear simple but one should not be fooled – it is in fact a highly sophisticated and complicated procedure that takes years of training and experience to fully master (9).

1.2.2 Patch testing in children

The patch test procedure in children is frequently a subject of discussion. Although children are not merely smaller versions of adults, most authors agree that patch testing children is safe and that children tolerate the same allergen concentrations as adults (10-14). It is, however, a recurrent topic of discussion whether especially young children have a lowered irritancy threshold as compared to adults. As a strong irritant reaction can be difficult to distinguish from a weak positive reaction (15), this would imply a higher risk of false positive reactions in children (16). Furthermore, some authors have proposed that positive reactions

in young children are of low clinical relevance and rarely reproducible. Johnke et al. (17) patch tested 543 healthy infants without skin symptoms up to 5 times during the first 18 months of life with nickel sulphate and fragrance mix patches. Among the 304 children who were patch tested more than once, 8.6% of the positive patch tests to nickel sulphate were reproducible, indicating true sensitization. However, 111 of the positive reactions to nickel sulfate were transient, suggesting irritant reactions and making the authors advocate that children should be patch tested with a lower concentration of nickel sulfate than what is tolerated by adults. Using the same cohort, Mortz et al. (18) re-tested 24 of the 26 nickel-sensitized children at 3 years and found that the patch test reaction to nickel could only be reproduced in 7 cases, suggesting that reactions in infancy are likely irritant or non-specific of nature. Nonetheless, the current general consensus is that allergic contact dermatitis occurs in all ages, even in infants (19-24).

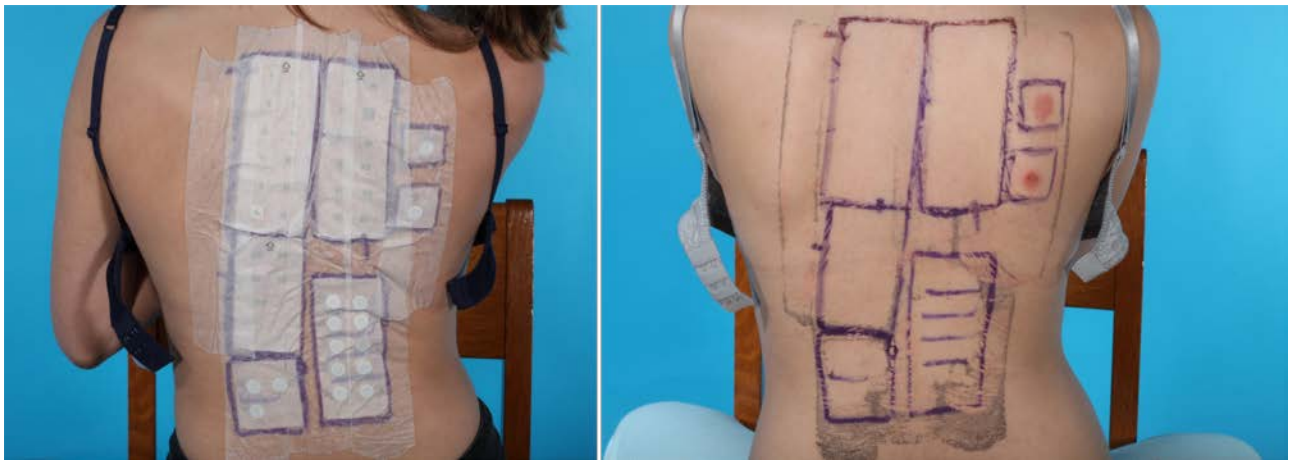

Figure 1. A child with the patch test applied (left) and at the patch test reading day 7 (right).

Patch testing of children may involve some practical challenges. The patch testing technique is exactly the same as in adults, but certain factors should be taken into account, such as the smaller test area on the back and the greater mobility of younger children, which may require the use of a stronger adhesive tape. Because of the space limitations, it may be impossible to apply the full baseline series at once. In this case the investigator must carefully choose the most relevant selection of allergens. In some countries special pediatric baseline series are used.

1.2.3 The impact of patch testing

Patch testing is fundamental to the correct diagnosis of allergic contact dermatitis. Early identification of the causative allergen and subsequent allergen avoidance is crucial in order to reduce the duration and durability of the disease and its progression (25). Few authors have assessed how positive or negative findings influence the course of skin symptoms. Results of studies on adult patients indicate a significant risk of allergic contact dermatitis resulting in ongoing disease and disability (26-28). In a recent Danish study, 89% of adult patients with occupational contact dermatitis still suffered from active eczema at 2-year follow-up (29). For the patch test to be beneficial in cases with a positive result, the patients have to adopt sufficient avoidance behaviour. Some allergens are easily excluded, whereas others may be difficult to avoid. In a study by Lewis et al. (30) 72% of patch tested patients believed that patch testing helped in the management of their skin disease, but only half of patients with allergic contact dermatitis were able to avoid the causative allergen. In the Danish study by Clemmensen et al. (29) only 31% of patients were able to avoid the relevant allergen exposure.

Diagnosis of allergic contact dermatitis by patch testing has been shown to improve patients' quality of life (31, 32). In adult patients, Thomson et al. (27) reported quality of life improvement only in patients with positive patch tests, whereas Woo et al. (26) observed improvement of quality of life in all patch-tested patients at 6 weeks follow-up, suggesting that all patients benefit from general advice about skin management and protection.

1.3 Allergic contact dermatitis in children

1.3.1 History

A.F. Coca and W.C. Spain were the first to address the issue of contact sensitization in children. Back in 1922 the possibilities within experimental studies were different. In studies on what was then termed "hypersensitiveness", the authors applied patches with extract from poison ivy to study participants of all ages and both observed "a considerable difference in susceptibility" to poison ivy between adults and children under the age of 5 years (33, 34). Spain (34) noted that out of 19 infants, none reacted to poison ivy. Whether this was an evidence of an altered sensitization potential in infants was further investigated by H.W. Straus in 1931(35). Extract from poison ivy was applied to 1-4 days old infants. Of the 48 infants, who 2-4 weeks later were retested, 72.9% showed a positive skin reaction. Although

Straus proved that even infants were able to produce a delayed-type hypersensitivity response, for many decades, the problem of contact allergy and allergic contact dermatitis was considered very rare in children. It was the general belief that children were less exposed to potential allergens and eczematous skin symptoms were mostly explained as endogenous skin disease.

In 1956 McCleary and Kierland (36) called attention to the importance of considering contact allergy in children, having observed that "*their natural inquisitiveness exposes children to many chemicals and plants, and their dislike of cleanliness often permits prolonged exposure. These characteristics, coupled with their predilection for collecting various oddities and storing them in their pockets, in their mouths, and about their persons, bring them into contact with many unusual substances*". Despite this, through the 1960s and 70s, contact allergy in children was still considered uncommon and they were rarely patch tested (20, 37-40). In 1980 Levy et al. (41) reiterated the importance of patch testing children and described 87 children with positive patch test reactions. Two years later, the Danish dermatologists Veien et al. (42) reported the results of patch testing 168 children. These two studies seemed to launch an increased interest in the area and in the subsequent years, several studies were published (10, 11, 43-46). Since then, the interest has been increasing, reflecting the importance of the matter, and allergic contact dermatitis is now recognized as a common skin disease in children.

1.3.2 Epidemiology

Children referred for patch testing

The majority of existing articles are retrospective analyses reporting the results of patch testing children with skin symptoms suggestive of allergic contact dermatitis. With their systematic review in 1999 Mortz and Andersen (47) provided the first overview of the literature. In the 17 studies published from 1982-1998 the reported sensitization rates in children and adolescents referred for patch testing ranged from 14.5-70.7% with a weighted average of 37.1%. In a similar review article from 2011 based on 20 studies published since 1999, we found reported prevalences of contact allergy between 26.6-95.6% and a weighted average of 49.2% (48). Thus, the prevalence of contact allergy in children referred for patch testing seemed to increase through the 80s, 90s and 00s. Since 2011 further 21 studies have been published reporting prevalences between 25.1-78% (21, 49-68).

Unselected children

Studies on asymptomatic children are valuable but may imply challenges with regard to design and execution, and only a limited number exist. Even though experimental studies on sensitization in asymptomatic children had been carried out earlier, Röckl et al. in 1966 (69) were the first to report the results of patch testing otherwise healthy children. The authors patch tested 357 children with potassium dichromate, mercury bichloride, formalin, nickel sulfate, turpentine, and benzocaine and noted a high rate of toxic reactions, concluding that the concentrations used were "not suitable for the detection of epidermal hypersensitiveness in children". The first study comparable with the research of today was published 20 years later by Weston et al. (45). In this study, 314 asymptomatic children were patch tested with a broad screening panel of allergens and at least one positive patch test reaction was seen in 20% of the participants. Similar frequencies of positive patch test reactions among school children were reported by Barros (70) and Dotterud (71). The largest study so far is the study by Mortz et al. (72). Among 1146 schoolchildren aged 12-16 years, 15.2% were sensitized to at least one allergen. The prevalence of allergic contact dermatitis was 7.2%. In the latest study on unselected children, Machovcova (73) found a sensitization rate of 30.7% among 236 Czech children aged 6-16 years.

1.4 Contact allergy in children with atopic dermatitis

1.4.1 Atopic dermatitis

Atopic dermatitis is the most common inflammatory skin disease in childhood. It has a common phenotypic expression, characterized by dry and itchy skin with chronic or recurrent episodes of dermatitis at typical anatomical sites (74). The prevalence has increased dramatically over the last three decades and now affects 15-30% of all children in Western countries (75-77).

The pathogenesis is complex and multifactorial. Although it remains incompletely understood, it is clear, that both a strong genetic predisposition as well as environmental triggers play a role. Immunologically, atopic dermatitis is dominated by the Th2 phenotype in the acute phase, with Th1, Th17, and Th22 cells contributing to the inflammatory response in chronic atopic dermatitis lesions (78). It was traditionally considered an immune-mediated condition with the primary defect residing solely in the immune system, causing excessive IgE sensitization, inflammation, and a dysfunctional skin barrier secondarily to this. This so-called

"inside-outside" theory has recently been challenged by the "outside-inside" theory, proposing that the primary defect in fact resides in the skin barrier, causing increased allergen and pathogen penetration, which then leads to secondary increased IgE sensitization and inflammation (77, 78).

One of the major hallmarks of atopic dermatitis is a dysfunctional skin barrier with increased water loss and a defect in terminal keratinocyte differentiation leading to reduced levels of ceramides and antimicrobial peptides (79) and favouring enhanced percutaneous penetration of bacteria, viruses, allergens, and chemicals in both lesional and non-lesional skin (77, 80). Filaggrin is a critical epidermal protein and has been shown to play an important role in the pathogenesis of atopic dermatitis (81). It derives from its larger precursor pro-filaggrin, which is present in keratinocytes in stratum granulosum. Pro-filaggrin is constituted by a central region of filaggrin-repeat units. During the differentiation of keratinocytes from granular to cornified cells, pro-filaggrin is released, proteolytically cleaved, and then dephosphorylated into filaggrin monomers (82, 83). The filaggrin monomers aggregate keratin filaments into tight bundles, resulting in collapse and flattening of corneocytes, and furthermore, filaggrin degradation products affect multiple functions that are crucial for the maintenance of epidermal homeostasis (83). Loss-of-function mutations in one or both alleles of filaggrin result in reduced levels or complete lack of epidermal filaggrin and consequently a compromised skin barrier. It has been shown to strongly increase the risk of atopic dermatitis and affects between 25-50% of patients with atopic dermatitis in certain Northern European populations (84).

1.4.2 Contact allergy in patients with atopic dermatitis

The relationship between atopic dermatitis and contact allergy has been discussed for decades. Although Epstein and Mohajerin (85) in 1964 stressed the importance of considering contact allergy in patients with atopic dermatitis, it was traditionally believed to be a rare occurrence. Patients with atopic dermatitis were thought to have a reduced ability to produce a type IV immunologic response owing to suppressed Th1-mediated cellular immunity (86, 87). This belief was primarily based on the results of clinical and experimental studies in which patients with atopic dermatitis were found to have reduced sensitivity to rhus and to be less responsive to sensitization to dinitrochlorobenzene (DNCB) (86-90). Uehara and Sawai (90), showed that the reduced sensitization potential depended on disease severity and

that it was primarily present in patients with severe atopic dermatitis. In their experimental study from 1989, 100% of patients with mild atopic dermatitis, 95% of patients with moderate atopic dermatitis, and 33% of patients with severe atopic dermatitis could be sensitized to DNCB. Patients with mild atopic dermatitis were also found to be significantly less responsive to DNCB as compared to nonatopic controls (89). In a 15-year prospective study, Rystedt et al. (91) found that patients with severe atopic dermatitis had a lower prevalence of contact allergy than patients with moderate disease and similarly, Thyssen et al. (92) reported an inverse association between severe atopic dermatitis and contact allergy. The apparent inverse correlation between atopic dermatitis and contact allergy has mainly been explained by mutually antagonistic influences of Th1 and Th2 cells. A delayed type hypersensitivity response is primarily dominated by Th1 cells (93), whereas the atopic dermatitis is mainly driven by Th2 inflammation. Thus, the prevalent theory has been that the Th1 response in atopic dermatitis individuals is repressed, making the sensitization to contact allergens less effective and/or requiring higher concentrations of allergens for sensitization (94).

Recently, new insights in the pathogenesis of atopic dermatitis have reignited the discussion and authors have suggested that cutaneous exposure to haptens may play a greater role in atopic dermatitis than previously expected. It has even been proposed that the cutaneous exposure to allergens could in fact lead to the immunological and clinical abnormities characterizing atopic dermatitis (95). As early as 1956, Calnan (96) noted that systemic contact dermatitis could actually mimic atopic dermatitis: Of 400 women with nickel contact allergy, 75% developed a clinical picture reminiscent of atopic dermatitis with widespread eczema affecting elbow flexures, eyelids, sides of neck and face, and inner aspects of thighs. It is now well known that contact allergy to several airborne allergens may mimic atopic dermatitis (97-99) and Thyssen et al. (100) proposed that the increase of atopic dermatitis in Western countries might to some degree be influenced by exposure to chemicals including contact allergens.

Even so, it is clear that multiple factors play a role and interact, and as neither experimental nor epidemiological studies can adjust for all of these, the relationship between atopic dermatitis and contact allergy remains incompletely understood (94).

In a clinical perspective, the important question is whether contact allergy is a relevant diagnosis to consider in patients with atopic dermatitis. Theoretically, the impaired skin

barrier in atopic dermatitis facilitates the penetration of potential allergens (80). Indeed, children with atopic dermatitis are exposed to topical agents and emollients from an early age (101) and the prolonged use of these agents could in theory increase the risk of contact sensitization to both ingredients and vehicles. Although several authors have highlighted the risk of underestimating and overlooking allergic contact dermatitis in patients with atopic dermatitis (64, 65, 102, 103), children with atopic dermatitis are not routinely patch tested. From reviewing the literature on patch test results in both selected and unselected children with atopic dermatitis, it seems that contact allergy is not uncommon in this patient group and children with atopic dermatitis may be at greater risk of sensitization to certain allergens, especially components of skin care products (104).

1.5 Quality of life in children with contact allergy and allergic contact dermatitis

It is well known that skin disease have a large impact on patients' quality of life (105), but few authors have assessed the impact of contact allergy and allergic contact dermatitis on life quality. In a study by Kadyk et al. (31), 149 adult patients with allergic contact dermatitis answered a questionnaire regarding life quality. All experienced impaired life quality and this was especially pronounced if the patient had dermatitis located to the face or hands. In studies by Thomson et al. (27) and Woo et al. (26) adult patients with allergic contact dermatitis experienced a moderate effect on life quality that improved after patch testing. Heisterberg et al. (106) compared 550 patients with fragrance allergy to 1100 controls who all suffered from eczema. The impact on life quality was similar in the two groups indicating that the important factor was having eczema.

In children, Beattie et al. (107) showed that the life quality impairment from having chronic skin disease was at least equal to that experienced by children with many other chronic diseases of childhood. The negative impact on quality of life has been demonstrated in children with atopic dermatitis (108, 109), psoriasis (110), and vitiligo (111), but so far no one has addressed the quality of life in children with contact allergy and allergic contact dermatitis.

1.6 Quality of life assessment in dermatology

Quality of Life (QoL) is a broad multidimensional concept that refers to the general well-being of a person or society, defined in terms of health and happiness, rather than wealth (112). In

health care the term Health-related quality of life (HRQoL) refers to patients' perception of the influence of disease and treatment on their physical, psychological, and social function and well-being (113). QoL instruments are used to measure either changes in HRQoL or differences in HRQoL between patients at any point in time (113). In dermatology, HRQoL can be assessed with generic instruments, which measure the quality of life outside of a clinical context allowing for comparison between diseases, dermatology-specific instruments that are applicable in all skin diseases, and disease-specific instruments, which are used to study a precise disease (114, 115). Disease specific outcome measures have been developed for several skin disorders including psoriasis (116), atopic dermatitis (117), acne (118), vitiligo (119), non-melanoma skin cancer (120), and hand eczema (121). The most commonly used generic and dermatology-specific outcome measures in the field of dermatology are The Dermatology Life Quality Index (DLQI), Short Form 36 (SF36), Skindex -16, -17, -29, Dermatology Quality of Life Scales (DQoLS), and The Dermatology-Specific Quality of Life (DSQL) (122). Allergic contact dermatitis-specific instruments are limited, and include only the Fragrance Quality of Life Index (123) and the Contact Dermatitis Specific Questionnaire (124). Despite the availability and variety of instruments, there is no consensus as to which HRQoL instruments are preferred in dermatology and in particular in the research field of allergic contact dermatitis. Thus, authors of the existing studies reporting HRQoL measurement among allergic contact dermatitis patients have used different generic or dermatology specific questionnaires (32).

2. Objectives of the PhD thesis

The overall objective of this PhD thesis was 1) to estimate the prevalence of contact allergy and allergic contact dermatitis in Danish children and adolescents referred for patch testing, 2) to investigate the course of skin symptoms and impact of contact allergy and allergic contact dermatitis on the children's quality of life, and 3) to assess the prevalence of contact allergy in children with atopic dermatitis.

The specific aims of the individual studies were as follows:

Study I: Contact allergy and allergic contact dermatitis in children referred for patch testing.

- To describe the demographic characteristics of the study population of Danish children referred for patch testing in 2003-2011.
- To determine the prevalence of contact allergy and allergic contact dermatitis.
- To identify risk factors for allergic contact dermatitis.
- To determine the most common allergens.

Study II: Course of skin symptoms and quality of life in children referred for patch testing.

- To uncover the course of skin symptoms in pediatric patients referred for patch testing.
- To evaluate the impact of skin symptoms on quality of life.

Study III: Contact allergy in children with atopic dermatitis.

- To determine the prevalence of contact allergy in Danish children with atopic dermatitis.
- To explore if unacknowledged contact allergies could maintain or aggravate skin symptoms in children with atopic dermatitis.

3. Methods

3.1 Study I

3.1.1 Data and study population

This was a retrospective register study based on the Danish Database of Contact Allergy. The database contains information on all patients patch tested in 12 different dermatology clinics throughout Denmark (Danish Group for Contact Dermatitis), which are estimated to cover approximately one-fifth of patients patch tested in Denmark. Patients below the age of 18 have been included since 2003. From 2003-2011, information on 2594 children was entered in the database. Of these, 49 were patch tested twice and two were patch tested three times during the study period. We included only the primary patch test results in this study.
The children all suffered from recalcitrant eczema or had a suspected diagnosis of allergic contact dermatitis. Information according to the MOAHLFA index (**M**ale, **O**ccupational dermatitis, **A**topic dermatitis, **H**and dermatitis, **L**eg dermatitis, **F**ace dermatitis, **A**ge >40 years) was registered by the dermatologist who initially ordered the patch test. The diagnosis of atopic dermatitis was ticked if the child had a history of atopic dermatitis or met the Hanifin & Rajka criteria.

3.1.2 Patch testing

The children were tested with either the European Baseline Series (allergens retrieved from either Chemotechnique Diagnostics, Malmö, Sweden, or from Almirall Hermal, Reinbek, Germany) or with TRUE test (SmartPractice Denmark, Hilleroed, Denmark) supplemented with the allergens from the European Baseline Series that are not included in the TRUE test. Patch tests were removed on day 2. Readings were performed according to the ICDRG guidelines (7) on minimum day 3 or day 4, and often also day 2 and day 7. The patch test reading was classified as "+1", "+2", "+3", "+?", "IR", or "negative". Homogeneous infiltration and erythema of the entire test area was required for a weak positive reaction (+ 1), with additional vesicles defining a strong positive (+2) and coalescing vesicles an extreme positive (+3) reaction. No reaction was classified as a negative reaction, faint erythema only and follicular reactions as a doubtful reaction (+?), and various unspecific morphologies (e.g. bulla, necrosis, soap effect) were classified as irritant reactions (IR).

Relevance of the positive reactions was evaluated according to national guidelines (125) based on patient history, product labels, spot tests etc. For the purpose of this study, reactions of past or current relevance were combined and all reactions were designated either relevant or not.

3.1.3 Statistics

To compare subgroups, we divided the patients into 4 different age categories (1-4 years, 5-8 years, 9-12 years, 13-17 years).

The data analysis was done using the statistical software program STATA 12.0. Comparison of sensitization rates was made using χ^2 test and employing a 5% significance level. Linear regression analysis was used to compare sensitization rates in multiple age groups. An F-test was used to test whether age coefficients from the regression were jointly equal.

3.2 Study II

3.2.1 Data and study population

This was a retrospective follow-up cohort study, using the cohort from study I consisting of children and adolescents patch tested during 2003-2011. The study was initiated in the spring of 2013. Of the 2594 patients in the database, 2591 were registered in the Danish Civil Registration System, and 2567 had a valid address in Denmark. Since 307 did not wish to be contacted for research purposes, the questionnaire-based follow-up was conducted on the remaining 2260. After one reminder, 1039 questionnaires were returned, giving a response rate of 46%.

3.2.2 The questionnaire

As this was the first study of its kind, a new questionnaire was constructed aiming to describe the skin status of the cohort and to uncover persisting skin symptoms. At the time of follow-up, patients were between 4-24 years of age. Thus, in some cases the patient's parents answered the questionnaires, whereas adolescents and young adults answered the questionnaires themselves. To investigate how well the outcome of the patch test was remembered by the patients and/or their parents, they were asked if they had contact allergy to metals, fragrances, preservatives, leather, plants or rubber. If the allergen to which they had reacted did not fit in any of the major categories, the patients were asked to write the

name of the allergen. To study the current skin status of the patients, they were asked "how often do you/your child have eczema?" with the response options "never", "all the time/every day", "every week", "1-3 times every month", "4-6 times every year", and "1-3 times every year". To investigate the quality of life of those with persisting skin symptoms, the Children's Dermatology Life Quality Index (CLDQI) questionnaire (126) was used for patients aged 16 or younger. For patients aged 17 and above, the Dermatology Life Quality Index (DLQI) questionnaire (127) was used. The CDLQI and DLQI each consist of 10 questions that focus on the effects of skin disease on activities of daily life during the preceding week. Since this was a follow-up study, the temporal parameter was expanded to the preceding year. Each question addresses to what degree the patient felt that the skin symptoms affected different activities of daily life and gives 5 different options for the answer of each question. Each answer is scored from 0-3 as follows: "very much" = 3, "a lot" = 2, "a little" = 1, "not at all" = 0, and "not relevant" = 0.

3.2.3 Validation of the baseline questionnaire

We used validated questions when possible. To validate the complete questionnaire, a pilot study was conducted. The parents of 10 children aged 1-12 years with no skin disease, 10 adolescents aged 13-27 years with no skin disease, the parents of 10 children aged 1-12 years with atopic dermatitis, and 10 adolescents aged 13-27 years with atopic dermatitis, answered the questionnaire. This was followed by telephone interviews to confirm the validity of their interpretation of each question and any concerns regarding the wording, response categories etc. were discussed. The questionnaire was then revised after which the final version was constructed.

3.2.4 Definitions of outcome variables

To classify the severity of skin symptoms at follow-up and identify the patients that were severely affected, we defined the variables "persistent eczema" as eczema all the time/every day or at least once every week, "frequent eczema" as eczema 1-3 times each month, and "rarely eczema" as episodes of eczema less than 6 times each year.

The CDLQI/DLQI is calculated by summing the score for each question, which result in a minimum score of 0 and a maximum score of 30. The scoring and interpretation was done with permission from the author, professor A. Y. Finlay, Cardiff University School of Medicine,

United Kingdom, and according to official instructions (126, 128). We defined "severely affected life quality" as a CDLQI score ≥13 or DLQI score ≥11 ("very large" or "extremely large" effect on patient's life).

3.3 Study III

3.3.1 Design

To assess the prevalence of contact allergy among children with atopic dermatitis, we conducted a clinical cross-sectional study. Prior to initiation of the study, approval was obtained by the National Committee on Health Research Ethics (1-10-72-267-13) and the Danish Data Protection Agency (1-16-02-396-13).

The study was conducted at Department of Dermatology and Venereology, Aarhus University Hospital, Department of Dermatology and Allergy Centre, Odense University Hospital, and Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen.

3.3.2 Study population

Consecutive patients visiting one of the three departments as part of their regular follow-up were invited to participate. Inclusion criteria were age 5-17 years and a diagnosis of atopic dermatitis according to the Hanifin & Rajka criteria. Patients receiving systemic immunosuppressive treatment and patients with severe generalized dermatitis were excluded from the study.

3.3.3 Assessment of the severity of atopic dermatitis

At the time of inclusion, the severity of atopic dermatitis was assessed according to the SCORAD (SCORing Atopic Dermatitis) index (129). This is a clinical tool used to assess the extent and severity of atopic dermatitis. To determine extent, the affected body sites are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body: Head and neck 9%, upper limbs 9% each, lower limbs 18% each, anterior trunk 18%, back 18%, and genitals 1%. The score for each area is added up giving a total score of "A", which has a possible maximum of 100.

Intensity of the dermatitis in assessed by selecting a representative area with dermatitis. In this area, the intensity of redness, swelling, oozing/crusts, scratch marks, lichenification, and

dryness of the skin is assessed as none (0), mild (1), moderate (2) or severe (3). The intensity scores are added together to give ”B”, which has a possible maximum of 18.
Subjective symptoms, i.e. itching and loss of sleep, are scored by the patient by using a visual analogue scale where 0 is no itch or no loss of sleep and 10 is the worst imaginable itch or loss of sleep. These scores are added to give ”C” which has a maximum of 20.
The final SCORAD score is then calculated as A/5 + 7B/2 + C.
To ensure consistency in the assessment of severity, the dermatologists used the same scoring sheet created for this study with an accessible scoring guide. The dermatologists who examined the patients then filled out the sheet with information on “B” and “C”. For the assessment of “A” they marked the involved body surface area on a drawing of a child. The final SCORAD score of all 100 participants was calculated by the same person.

3.3.4 Patch testing

For the purpose of this study, we constructed a pediatric series of 31 allergens (table 1). Allergens were chosen based on the results of study I that provided us with information on the most common allergens in Danish children. Because we hypothesized that children with atopic dermatitis are at greater risk of having contact allergy to ingredients in emollients, skin care products, and prescribed products for the treatment of their skin symptoms, the allergen series also included selected preservatives used in topical products. The selection was based on a literature search using PubMed and the search items (("preservatives" OR "topical products" OR "cosmetics" OR "ingredients") AND ("contact allergy" OR "allergic contact dermatitis" OR "sensitization")) (130-145) combined with the clinical experience and knowledge of the supervisors.

Allergen	Test concentration	
Nickel sulfate	5% pet.	200 µg/cm²
Cobalt chloride	1% pet.	20 µg/cm²
Potassium dichromate	0.5% pet.	25 µg/cm²
Fragrance mix I	8% pet.	450 µg/cm²
Fragrance mix II	14% pet.	14% pet.
Balsam of Peru	25% pet.	800 µg/cm²
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5% pet.	5% pet.
Carba mix	3% pet.	250 µg/cm²
Black rubber mix	0.6% pet.	75 µg/cm²
Mercaptobenzothiazole	2% pet.	75 µg/cm²
Mercapto mix	1% pet.	75 µg/cm²
Thiuram mix	1% pet.	25 µg/cm²
Paraben mix	16% pet.	1000 µg/cm²
Formaldehyde	1% aq.	180 µg/cm²
Diazolidinyl urea	2% pet.	550 µg/cm²
Imidazolidinyl urea	25 aq.	600 µg/cm²
Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)	0.01% aq.	4 µg/cm²
Methylisothiazolinone	0.2% aq.	0.2% aq.
Quaternium 15	1% pet.	100 µg/cm²
P-tert butylphenol formaldehyd resin	1% pet.	40 µg/cm²
Colophonium	20% pet.	1500 µg/cm²
Lanolin alcohol	30% pet.	1000 µg/cm²
Sesquiterpene lactone mix	0.1% pet.	0.1% pet.
Tixocortol pivalate	0.1% pet.	3 µg/cm²
Hydrocortison 17 butyrat	1% eth.	20 µg/cm²
Budesonid	0.1% pet.	1 µg/cm²
Ethylene diamine	1% pet.	50 µg/cm²
Benzyl alcohol	1% pet.	1% pet.
Benzyl benzoate	1% pet.	1% pet.
Triethanolamine	2.5% pet.	2.5% pet.
Phenoxyethanol	1% pet.	1% pet.

Table 1. Pediatric series of allergens.

The pediatric series was supplemented by additional allergens as indicated by the child's history. After patch test application at day 0 and allergen exposure for 2 days, readings were performed on day 3-4 and day 7. In one department patch tests were also evaluated on the day of removal (day 2). Patch test reactions were classified as "+1", "+2", "+3", "+?", "IR", or "negative" according to the ESCD criteria (6, 7). For a patch test reaction to be considered positive, homogeneous infiltration and erythema of the entire test area was required for a weak positive reaction (+1), with additional vesicles defining a strong positive (+2) reaction, and coalescing vesicles an extreme positive (+3) reaction. Relevance of the positive reactions was evaluated according to national guidelines (125) based on patient history, product labels, spot tests or product analyses.

4. Manuscripts

Manuscript I:

Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M:

Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multi-centre study.

Contact dermatitis. 2014 Feb; 70(2): 104-111.

Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multicentre study

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Summary

Background. Although contact allergy among children was previously considered to be rare, data from the past decade have shown that it is common among children and that the prevalence may be increasing.

Objectives. To describe the demographics of all children referred for patch testing in Denmark during 2003–2011, to examine the frequency and relevance of positive patch test reactions, and to assess the most common allergens.

Methods. A retrospective analysis of the patch test data from the Danish National Database of Contact Allergy was performed.

Results. Of 2594 children and adolescents aged 1–17 years, 25.1% had one or more positive patch test reactions. The associated relevance was 66.4%. The most common sensitizers were metals, fragrances, and hair dyes. The frequency of positive patch test reactions and allergic contact dermatitis was significantly higher among girls.

Conclusions. Allergic contact dermatitis in children is a significant clinical problem. Contact allergy should always be considered when children with recalcitrant eczema are encountered, and special attention should be paid to girls. Patch testing is important, and children may be tested with the same patch test concentrations as adults.

Key words: allergic contact dermatitis; children; contact allergy; patch testing

Allergic contact dermatitis acquired in childhood has important consequences for the individual, as it may affect the quality of life (1, 2). It may interfere with play, sports activities, and school (2), and affect decisions regarding future occupation. The morbidity from allergic contact dermatitis depends on the ability to avoid exposure to the contact allergen, and the patient may experience chronic or recurrent episodes of dermatitis if the source is not identified as early as possible by patch testing (3).

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Traditionally, allergic contact dermatitis was considered to be uncommon in the paediatric population (4, 5). Children were thought to be less exposed to allergens, and the immune system of children was considered to be less susceptible to contact allergens (5, 6). Data from the past decade have shown that contact allergy is common among children, and suggest that the prevalence may be increasing (7, 8). Several patch test studies from different parts of the world on symptomatic children have been published. We previously reviewed the existing literature on the prevalence of contact allergy and allergic contact dermatitis, and found reported sensitization rates of 26.6–95.6% in selected groups of children who were referred for patch testing. The associated relevance was 51.7–100% (8).

The apparent increase in allergic contact dermatitis among children is thought to be the result of increased exposure to allergens at a younger age, new trends in body piercing, the use of cosmetic products, and participation in sports and hobbies, in addition to improved recognition of allergic contact dermatitis and more frequent patch testing of children (9).

Allergen exposure varies throughout the world, and is determined by different factors, such as climate, cultural habits, and legislation (10). Furthermore, the frequency of positive patch test results may vary with referral patterns, criteria for patch testing, selection of patch test series, and patch test methodology (8, 11).

The aim of this study was to describe the demographics of a sample of children referred for patch testing in Denmark during 2003–2011, to examine the frequency and relevance of positive patch test reactions, and to assess the most common allergens. This is the first study on the prevalence of contact allergy and allergic contact dermatitis in Danish children referred for patch testing since 1982, when Veien et al. (5) found a sensitization rate of 45.8% and a prevalence of allergic contact dermatitis of 36.9% among 168 children.

Materials and Methods

Our retrospective analysis was based on data from the Danish National Database for Contact Allergy. From 1 January 2003 to 31 December 2011, a total of 2594 patients aged 1–17 years were patch tested in 12 dermatology clinics throughout Denmark (Danish Group for Contact Dermatitis), which is estimated to cover approximately one-fifth of patients patch tested in Denmark. Of the 2594 children, 49 were patch tested twice and 2 were patch tested three times during the study period. We included only the primary patch test results in this study.

All patients either suffered from recalcitrant eczema or had a suspected diagnosis of allergic contact dermatitis. Characteristics according to the MOAHLFA index (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Age >40 years) were registered. Atopic dermatitis was evaluated according to the Hanifin and Rajka criteria (12). The children were tested with either the European baseline series (allergens obtained from either Chemotechnique Diagnostics, Vellinge, Sweden, or from Almirall Hermal, Reinbek, Germany) or with TRUE Test™ (SmartPractice Denmark, Hilleroed, Denmark) supplemented with the allergens from the European baseline series that are not included in the TRUE Test™. In a few cases, the patient had an already known contact allergy and was therefore not tested with the specific allergen.

Patch tests were removed on D2. Readings were performed according to the International Contact Dermatitis Research Group guideline on D3 or D4, and often also on D2 and D7. Reactions designated as either 1+, 2+ or 3+ were regarded as positive. Skin reactions characterized by dry skin, scaling, pustules, shiny skin and a silk or cigarette paper-like surface were regarded as irritant reactions. The relevance of the positive reactions was evaluated according to national guidelines (13), on the basis of patient history, product labels, spot tests, etc. For the purpose of this study, reactions of past or current relevance were combined, and all reactions were designated as either relevant or not.

Data analysis was performed with the statistical software program STATA™ 12.0. Comparison of sensitization rates was performed with the χ^2-test, employing a 5% significance level. Linear regression analysis was used to compare sensitization rates in multiple age groups. An F-test was used to test whether age coefficients from the regression were jointly equal.

Results

A total of 2495 children and adolescents aged 1–17 years were patch tested. The characteristics summarized by the MOAHLFA index were as follows: 34.1% were male, 2.7% had an allergy that was related to occupation, 44.8% had atopic dermatitis, 28.0% had hand dermatitis, 1.5% had leg dermatitis, and 19.2% had facial dermatitis.

A positive reaction to at least one allergen was seen in 25.1% of the children, and 66.4% of these were considered to be of current or past relevance. The number of children annually referred for patch testing increased steadily during the study period (Fig. 1). The pronounced increase from 2008 was attributable to the addition of more clinics reporting to the database. There could be a trend for an increase in sensitization rates, which calls for further investigation (Fig. 2).

We divided the patients into four different age groups. Table 1 shows the positive and relevant reactions by age group and sex. Overall, more girls than boys were patch tested. The female dominance was evident from the age of 5 years, and the sex difference with regard to frequency of patch testing increased with age. Overall, girls were significantly more likely to have a positive patch test reaction (26.7% versus 22.1%, $p < 0.05$). This sex difference became apparent after the age of 13 years.

There were no significant differences in sensitization rates or relevance between age groups (Table 1).

Metals were the most frequent sensitizers (12.2%), followed by fragrances (4.7%) and hair dyes/*p*-phenylenediamine (PPD) (3.5%). Table 2 shows all

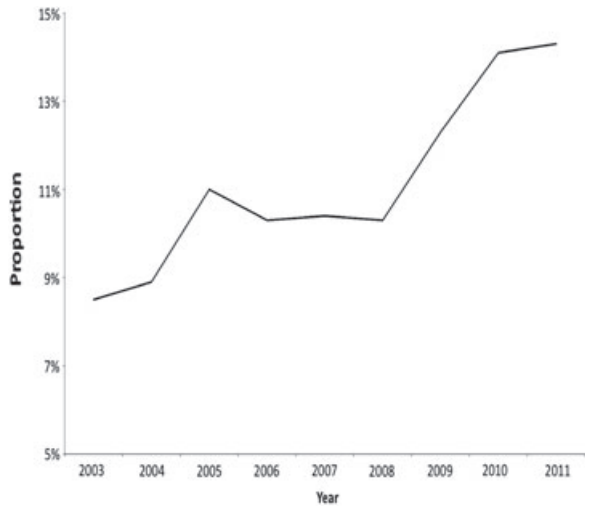

Fig. 1. The proportion of children referred annually out of all children in the cohort (n = 2594).

allergens listed by frequency of positive reactions, and the rate of sensitization listed by groups of allergens. Table 3 shows the most common sources of exposure.

Nickel was by far the most common allergen. Of the 2587 children tested with nickel, 9.7% were sensitized, and the associated relevance was 69.0%. The next most common sensitizers from the European baseline series were cobalt chloride (4.4%), PPD (3.5%), and fragrance mix I (2.5%). This pattern appeared from the age of 5 years. As patients sensitized to caine mix or benzocaine may show cross-reactivity to PPD, we also examined concomitant reactions to PPD and caine mix; 3.7% of the 434 children tested with both PPD and caine mix reacted to both substances. Among the 2079 children tested with both PPD and benzocaine, 0.6% reacted to both substances. Table 4 shows the most common allergens in the different age groups. Of all pf the children who were sensitized, 40.1% were sensitized to more than one allergen.

The frequency of irritant reactions increased with age; however, the proportions of irritant reactions in the four age groups did not differ significantly. In the youngest age group, of 1–4-year-old children, five irritant reactions were observed in 3 children. These were to cobalt chloride, lanolin (wool alcohols), paraben mix, benzocaine, and mercapto mix, and none were observed in children aged < 4 years. Cobalt chloride was the most frequent irritant, and caused 38.8% of all irritant reactions.

Among the adolescents aged 13–17 years, 3.8% had a positive reaction that was also considered to be work-related. The dermatitis was located on the hands in 81.3% of the cases. The most frequent allergens causing work-related allergy were metals, adhesive chemicals, and PPD.

Discussion

In our retrospective analysis of the results of all patch tests performed on children and adolescents aged 1–17 years in Denmark during 2003–2011, we found a sensitization rate of 25.1% and an associated relevance of 66.4%, which is in agreement with international data. Metals, fragrances and hair dye were the most common sensitizers (Table 2). The frequency of patch testing and the number of both positive and relevant reactions increased with age. However, we found no significant differences with regard to sensitization rates between age groups. This may indicate differences in the threshold for patch testing children, depending on the child's age, and it could also indicate that too few children in the youngest age groups are patch tested.

Almost 45% of the patch tested children had atopic dermatitis. A probable explanation for this high proportion is that many children with treatment-refractory atopic eczema are patch tested to investigate for external aggravating factors such as contact allergy, including contact allergy to medications.

Nickel is by far the most common allergen in Europe, among both children and adults (14). Accordingly, nickel was the most common allergen in all age groups in our

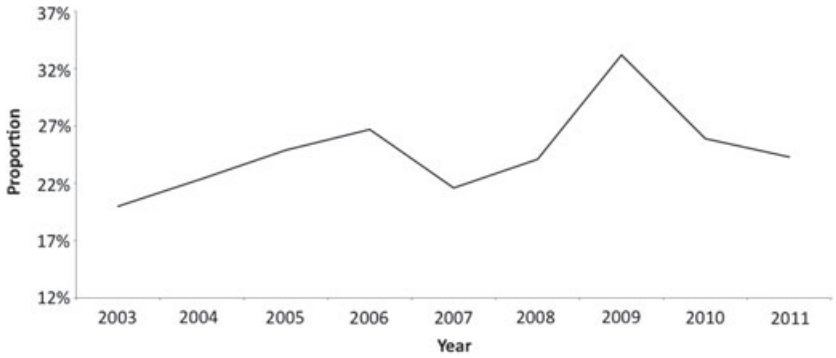

Fig. 2. Sensitization rates during the study period, that is, the proportion of children with at least one positive patch test reaction out of the children patch tested in the specific year.

Table 1. Patch test reactions by age group and sex

	Number referred			Positive reactions				Relevance[a]				Irritant reactions[b]			
Age (years)	Total	Female (%)	Male (%)	Total (%)	Female (%)	Male (%)	*p*-value	Total (%)	Female (%)	Male (%)	*p*-value	Total (%)	Female (%)	Male (%)	*p*-value
1–4	76	31 (40.8)	45 (59.2)	19 (25.0)	9 (29.0)	10 (22.2)	0.5	11 (57.9)	5 (55.6)	6 (60.0)	0.85	3 (3.9)	–	3 (6.7)	0.14
5–8	227	131 (57.7)	96 (42.3)	55 (24.2)	33 (25.2)	22 (22.9)	0.69	37 (67.3)	23 (69.7)	14 (63.6)	0.64	5 (2.2)	5 (3.8)	–	0.05
9–12	579	371 (64.1)	208 (35.9)	152 (26.3)	100 (27.0)	52 (25.0)	0.61	101 (66.4)	68 (68.0))	33 (63.5)	0.57	22 (3.8)	16 (4.3)	6 (2.9)	0.39
13–17	1712	1177 (68.8)	535 (31.3)	425 (24.8)	314 (26.7)	111 (20.7)	< 0.05	283 (66.6)	219 (69.7)	64 (57.7)	< 0.05	75 (4.4)	60 (5.1)	15 (2.8)	< 0.05
Total	2594	1710 (65.9)	884 (34.1)	651 (25.1)	456 (26.7)	195 (22.1)	< 0.05	432 (66.4)	315 (69.1)	117 (60.0)	< 0.05	105 (4.0)	81 (4.7)	24 (2.7)	< 0.05
F-test: equality of age groups:				$p = 0.90$	$p = 0.97$	$p = 0.76$		$p = 0.89$	$p = 0.90$	$p = 0.97$		$p = 0.46$	$p = 0.45$	$p = 0.32$	

[a] Relevance: number of relevant reactions/number of positive reactions.
[b] Irritant reactions: children with at least one irritant patch test reaction out of all children in the specific age group.

study, and the frequency of allergic contact dermatitis caused by nickel increased with age. We found relevant reactions to nickel even in small children aged 1–4 years, and no irritant reactions to nickel sulfate were observed in this age group.

Patch test reactivity to cobalt is often associated with sensitization to nickel (14), as was also shown in our study; 58.8% (n = 67) were co-sensitized with nickel.

Fragrance contact allergy is increasingly common among children, and even small children are exposed (15, 16). It is caused mainly by exposure to cosmetic products, but exposures to household and industrial products may contribute (17). In our study, 2594 children were tested with one or all of the four fragrance markers: fragrance mix I, fragrance mix II, hydroxyisohexyl 3-cyclohexene carboxaldehyde, and *Myroxylon pereirae*. Of these children, 4.7% were sensitized to at least one of the markers. The likelihood of having a positive patch test reaction to one of the fragrant markers did not differ significantly between sexes. This is in contrast to previous studies on adults, which found a significant preponderance of women with contact allergy to fragrance (18, 19). This discrepancy could possibly be explained by the pattern of exposure to fragrance, which is likely to increase with age, especially for women. In order to identify sources of fragrance exposure, we plan to investigate the exposure pattern among Danish children further.

PPD is known as a strong sensitizer (20). Testing with the standard 1% concentration may cause severe allergic reactions, and it has been argued that the patch test concentration should be lowered (21, 22). Furthermore, several authors have stressed the risk of active sensitization from patch testing with PPD (22–24). In our study, 3.5% of the children who were patch tested with PPD had a positive reaction, the youngest being 4 years old. This pattern of sensitization in children is probably attributable to new trends involving products containing PPD, especially temporary black henna tattoos and the use of hair dye at a young age (23, 25), although patch test reactivity may also occur as a result of cross-sensitization with other allergens (20, 23, 26). Unfortunately, we have limited information on what exposures caused the sensitization in our cohort. Patients sensitized to caine mix or benzocaine may show cross-reactivity to PPD. We did not observe enough cross-reactions to explain the high number of positive reactions to PPD. In a similar adult population, Thyssen et al. (27) found sensitization rates of 2.2% among women and 1.7% among men. In contrast to this, we did not find any sex difference with regard to PPD allergy in any age group. Most cases of contact allergy to PPD are caused by contact with hair dyes in either consumer or hairdresser products (14), so it seems likely that a sex difference in exposure to PPD develops with age.

Girls were, overall, significantly more likely to have a positive patch test reaction. This sex difference was mainly driven by nickel. Among girls, nickel accounted for 29.6% of all positive patch test reactions. This figure was 13.5% for boys, and the sex difference in terms of nickel sensitization was significant. Sex differences with regard to sensitization rates reflect the pattern of exposure, and the difference in nickel sensitization could be explained by the fact that girls are more likely to have their ears pierced and wear jewellery at an earlier age (28). It has also previously been suggested that hormonal factors play a role (14, 15, 29, 30).

The rates of sensitization to rubber chemicals and topical steroids were significantly higher among boys. Again, this probably indicates sex differences in exposure patterns. It seems probable that boys, as a result of leisure activities and hobbies, are more exposed to rubber. The sex difference in sensitization to topical steroids calls for further elucidation. It may reflect the group of children with atopic dermatitis, and we plan to investigate this in future work.

Table 2. Allergens listed by frequency of positive reactions

Allergen	Sensitization rate, % ($n_{positive}/n_{tested}$)	Relevance, % ($n_{relevant}/n_{positive}$)	Sensitization rate		*p*-value
			Girls, % ($n_{positive}/n_{tested}$)	Boys, % ($n_{positive}/n_{tested}$)	
Nickel sulfate	9.7 (252/2587)	69.0 (174/252)	12.4 (211/1706)	4.7 (41/881)	< 0.05
Black rubber mix[a]	5.5 (26/472)	30.8 (8/26)	3.9 (11/284)	8.0 (15/188)	0.06
Cobalt chloride	4.4 (114/2593)	39.5 (45/114)	5.3 (91/1709)	2.6 (23/884)	< 0.05
Caine mix[a]	3.8 (19/504)	15.8 (3/19)	2.9 (9/311)	5.2 (10/193)	0.19
p-Phenylenediamine	3.5 (88/2513)	85.2 (75/88)	3.4 (56/1669)	3.8 (32/844)	0.57
Fragrance mix I	2.5 (64/2592)	59.4 (38/64)	2.6 (44/1710)	2.3 (20/882)	0.64
Colophonium	2.4 (62/2593)	61.3 (38/62)	2.4 (41/1709)	2.4 (21/884)	0.97
Fragrance mix II	2.4 (43/1823)	74.4 (32/43)	2.4 (29/1187)	2.2 (14/636)	0.75
Potassium dichromate	1.3 (34/2592)	26.5 (9/34)	1.6 (27/1708)	0.8 (7/899)	0.09
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	1.1 (27/2429)	59.3 (16/27)	1.5 (24/1609)	0.4 (3/820)	< 0.05
Myroxylon pereirae	1.0 (27/2591)	48.1 (13/27)	1.1 (19/1708)	0.9 (8/883)	0.62
Mercaptobenzothiazole	1.0 (27/2591)	81.5 (22/27)	0.8 (14/1708)	1.5 (13/883)	0.12
Lanolin alcohol	1.0 (26/2592)	38.5 (10/26)	1.1 (18/1709)	0.9 (8/883)	0.72
Euxyl™ K 400[a]	1.0 (3/302)	100.0 (3/3)	1.5 (3/202)	0 (0/104)	0.22
Mercapto mix	0.9 (23/2593)	82.6 (19/23)	0.8 (13/1710)	1.1 (10/883)	0.34
MCI/MI	0.8 (21/2593)	42.9 (9/21)	0.8 (14/1709)	0.8 (7/884)	0.94
Thiuram mix	0.8 (21/2594)	52.4 (11/21)	0.6 (11/1710)	1.1 (10/884)	0.19
Sesquiterpene lactone mix	0.8 (20/2542)	65.0 (13/20)	0.6 (10/1678)	1.2 (10/864)	0.13
Formaldehyde	0.7 (18/2593)	50.0 (9/18)	0.7 (12/1710)	0.7 (6/883)	0.95
Benzocaine	0.6 (13/2083)	46.2 (6/13)	0.6 (9/1394)	0.6 (4/691)	0.86
p-tert-Butyl formaldehyde resin	0.6 (16/2590)	43.8 (7/16)	0.4 (7/1707)	1.0 (9/883)	0.06
Budesonide	0.6 (12/1980)	50.0 (6/12)	0.2 (3/1277)	1.3 (9/703)	< 0.05
Carba mix[a]	0.6 (3/507)	33.3 (1/3)	0.6 (2/313)	0.5 (1/194)	0.86
Methyldibromo glutaronitrile	0.6 (14/2451)	35.7 (5/14)	0.7 (12/1605)	0.2 (2/846)	0.11
Paraben mix	0.5 (13/2593)	61.5 (8/13)	0.3 (5/1709)	0.9 (8/899)	< 0.05
Neomycin sulfate	0.5 (12/2592)	16.7 (2/12)	0.4 (7/1705)	0.6 (5/882)	0.58
N-Isopropyl-*N*-phenyl-*p*-phenylenediamine	0.3 (7/2131)	57.1 (4/7)	0.3 (4/1430)	0.4 (3/701)	0.57
Epoxy resin	0.3 (8/2523)	38.0 (3/8)	0.2 (3/1678)	0.6 (5/845)	0.08
Imidazolidinyl urea	0.3 (6/2092)	33.3 (2/6)	0.2 (3/1356)	0.4 (3/750)	0.45
Diazolidinyl urea	0.3 (6/2093)	50.0 (3/6)	0.3 (4/1357)	0.3 (2/736)	0.93
2-Bromo-2-nitropropane-2,3-diol	0.2 (3/1475)	66.7 (2/3)	0.2 (2/952)	1.9 (1/523)	0.94
Quaternium-15	0.2 (4/2593)	50.0 (2/4)	0.2 (4/1709)	0 (0/899)	0.15
Tixocortol 21-pivalate	0.1 (3/2009)	66.7 (2/3)	< 0.1 (1/1300)	0.3 (2/709)	0.26
Primin	0.1 (3/2506)	66.7 (2/3)	< 0.1 (1/1649)	0.2 (2/857)	0.32
Clioquinol	0.1 (2/2133)	50.0 (1/2)	< 0.1 (2/1464)	0 (0/712)	0.32
Quinoline mix[a]	0 (0/459)	–	0 (0/282)	0 (0/187)	–
Groups of allergens					
Metals[b]	12.2 (316/2593)	59.8 (189/316)	15.0 (256/1709)	6.8 (60/884)	< 0.05
Fragrances[c]	4.7 (123/2594)	58.5 (72/123)	5.1 (87/1710)	4.1 (36/884)	0.25
Hair dyes[d]	3.5 (88/2513)	85.2 (75/88)	3.4 (56/1669)	3.8 (32/844)	0.57
Adhesive chemicals[e]	3.2 (84/2593)	56.0 (47/84)	3.0 (51/1709)	3.7 (33/884)	0.31
Rubber chemicals[f]	3.0 (79/2594)	58.2 (46/79)	2.3 (39/1710)	4.5 (40/884)	< 0.05
Preservatives[g]	2.9 (75/2594)	46.7 (35/75)	2.7 (47/1710)	3.2 (28/884)	0.55
Topical drugs[h]	1.8 (46/2592)	26.1 (12/46)	1.6 (27/1709)	2.2 (19/883)	0.3
Plants[i]	0.9 (23/2544)	65.2 (15/23)	0.7 (11/1679)	1.4 (12/865)	0.06
Topical steroids[j]	0.7 (14/2011)	50.0 (7/14)	0.3 (4/1301)	1.4 (10/710)	< 0.05

MCI/MI, methylchloroisothiazolinine/methylisothiazolinone.

Euxyl™ K 400: commerical preservative contatining methyldibromo glutaronitrile and phenoxyethanol.

[a] From TRUE test™.

[b] Nickel sulfate, cobalt chloride, and potassium dichromate.

[c] Fragrance mix I, fragrance mix II, *Myroxylon pereirae*, and hydroxyisohexyl 3-cyclohexene carboxaldehyde.

[d] *p*-Phenylenediamine.

[e] Colophonium, *p*-tert-butyl formaldehyd resin, epoxy resin.

[f] Black rubber mix/*N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine, mercaptobenzothiazole, mercapto mix, thiuram mix, and carba mix.

[g] Euxyl™ K 400, MCI/MI, formaldehyde, methyldibromo glutaronitrile, paraben mix, diazolidinyl urea, imidazolidinyl urea, and quaternium-15,2-bromo-2-nitropropane-1,3-diol.

[h] Caine mix/benzocaine, neomycin sulfate, clioquinol, and quinoline mix.

[i] Sesquiterpene lactone mix and primin.

[j] Budesonide and tixocortol pivalate.

Table 3. Most common source of exposure

Allergen group	Source of exposure
Metals	Jewellery, metal buckles, shoes
Fragrances	Deodorant, shampoo, liquid soap
p-Phenylenediamine	Hair dye, henna tattoo, eyebrow dye
Adhesive chemicals	Plasters, medications, cosmetics
Rubber chemicals	Shoes, gloves
Preservatives	Cleansing wipes, cosmetics
Topical drugs	Medications, not specified
Plants	Plants, not specified
Topical steroids	Medications, not specified

It has previously been suggested that children tend to show non-specific irritant reactions, and therefore have a higher rate of false-positive reactions (31). Some authors have highlighted the difficulties in distinguishing an irritant skin reaction from a positive response (32, 33). In our study, we endeavoured to ensure correct interpretation of the patch test reaction by following the International Contact Dermatitis Research Group guidelines. Almost one-third (28.6%) of the children were, in addition to the first patch test reading, evaluated on D7. We did not observe irritant reactions in children aged < 4 years. Our results are in accordance with those of Belloni Fortina et al. (34), who evaluated patch test reactions in 321 children aged < 3 years, and found 'very few irritant reactions'. One possible limitation of our study is the fact that only 8 children were aged < 1 year. It could be argued that this sample is too small to draw any real conclusions on rates of sensitization or irritant reactions that are representative of this age group.

The recommendations for patch testing children have been controversial, and several authors have suggested that children should be tested with lower concentrations of allergens (4, 35, 36). The high rate of negative patch tests and the low number of irritant reactions in our study indicate that even young children tolerate the same test concentrations as adults.

This was a nationwide study and, to our knowledge, it is the largest study of its kind. Although one should exercise some caution when interpreting the results for the young children in our dataset, because of small sample sizes, our study provides valuable information. The data used in this study were retrieved from 12 different dermatology clinics throughout Denmark. All clinics used standardized preparations of allergens and followed the International Contact Dermatitis Research Group guidelines with regard to application and interpretation of patch test reactions. However, some degree of inconsistency is inevitable, given the large number of clinics reporting to the database. In one area, the patch test methodology differed; two-thirds of patch test reactions were evaluated on D3–D4 only, which implies a risk of missing late reactions (37). Another limitation is the fact that not all children were patch tested with the same allergens, which, to some extent, hinders the drawing of strong conclusions.

Conclusion

This is the first study on the prevalence of allergic contact dermatitis in Danish children referred for patch testing since 1982, and to our knowledge it is the largest study of its kind. Among the 2594 children referred for patch testing during 2003–2011, the sensitization rate was 25.1% and the prevalence of allergic contact dermatitis was 16.7%. The likelihood of having at least one positive patch test reaction and allergic contact dermatitis was associated with being female.

Allergic contact dermatitis in children is a significant clinical problem. Contact allergy should always be considered when children with recalcitrant eczema or a history of specific exposure are encountered, and patch testing is important. On the basis of our data, we recommend using the European baseline series supplemented with allergens according to the child's history and with the same allergen concentrations as used in adults. To avoid missing late reactions, we recommend that patch test readings be carried out D3/D4 and D5–D7.

The number of children referred for patch testing increased steadily throughout the study period, but the rates of sensitization or allergic contact dermatitis did not change significantly. A future retrospective study could

Table 4. Most frequent allergens from the European baseline series (%)

All children	1–4 years old	5–8 years old	9–12 years old	13–17 years old
Nickel sulfate (9.7)	Nickel sulfate (14.5)	Nickel sulfate (8.5)	Nickel sulfate (8.3)	Nickel sulfate (10.2)
Cobalt chloride (4.4)	Sesquiterpene lactone mix (4.5)	Cobalt chloride (3.5)	Cobalt chloride (6.2)	Cobalt chloride (4.0)
PPD (3.5)	MCI/MI (4.0)	PPD (3.4)	PPD (4.5)	PPD (3.2)
Fragrance mix I (2.5)	Potassium dichromate (2.6)	Sesquiterpene lactone mix (2.7)	Fragrance mix I (3.6)	Fragrance mix II (3.0)
Colophonium (2.4)	Cobalt chloride (2.6)	Fragrance mix I (2.2)	Colophonium (3.1)	Colophonium (2.3)

MCI/MI, methylchloroisothazolinone/methylisothiazolnine; PPD, *p*-phenylenediamine.

provide us with additional knowledge on the time trends of allergic contact dermatitis in Danish children.

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References

1 Beattie P E, Lewis-Jones M S. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006: **155**: 145–151.
2 Lewis-Jones M S, Finlay A Y. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995: **132**: 942–949.
3 Clayton T H, Wilkinson S M, Rawcliffe C, Pollock B, Clark S M. Allergic contact dermatitis in children: should pattern of dermatitis determine referral? A retrospective study of 500 children tested between 1995 and 2004 in one UK centre. *Br J Dermatol* 2006: **154**: 114–117.
4 Marcussen P V. Primary irritant patch-test reactions in children. *Arch Dermatol* 1963: **87**: 378–382.
5 Veien N K, Hattel T, Justesen O, Norholm A. Contact dermatitis in children. *Contact Dermatitis* 1982: **8**: 373–375.
6 Weston W L, Weston J A. Allergic contact dermatitis in children. *Am J Dis Child* 1984: **138**: 932–936.
7 Militello G, Jacob S E, Crawford G H. Allergic contact dermatitis in children. *Curr Opin Pediatr* 2006: **18**: 385–390.
8 Simonsen A B, Deleuran M, Johansen J D, Sommerlund M. Contact allergy and allergic contact dermatitis in children – a review of current data. *Contact Dermatitis* 2011: **65**: 254–265.
9 Hogeling M, Pratt M. Allergic contact dermatitis in children: the Ottawa hospital patch-testing clinic experience, 1996 to 2006. *Dermatitis* 2008: **19**: 86–89.
10 Thyssen J P, Johansen J D, Linneberg A, Menné T. The epidemiology of hand eczema in the general population – prevalence and main findings. *Contact Dermatitis* 2010: **62**: 75–87.
11 Bonitsis N G, Tatsioni A, Bassioukas K, Ioannidis J P. Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis. *Contact Dermatitis* 2011: **64**: 245–257.
12 Hanifin J M, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980: **92**: 44–47.
13 Menné T, Johansen J D, Sommerlund M, Veien N K. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis* 2011: **65**: 3–12.
14 Johansen J D, Frosch P J, Lepoittevin J-P (Eds). *Contact Dermatitis*, 5th edition: Berlin, Heidelberg, Springer-Verlag, 2011.
15 Johnke H, Norberg L A, Vach W, Bindslev-Jensen C, Host A, Andersen K E. Reactivity to patch tests with nickel sulfate and fragrance mix in infants. *Contact Dermatitis* 2004: **51**: 141–147.
16 Jacob S E, Castanedo-Tardan M P. Alternatives for fragrance-allergic children. *Pediatr Ann* 2008: **37**: 102–103.
17 Rastogi S C, Heydorn S, Johansen J D, Basketter D A. Fragrance chemicals in domestic and occupational products. *Contact Dermatitis* 2001: **45**: 221–225.
18 Heisterberg M V, Andersen K E, Avnstorp C et al. Fragrance mix II in the baseline series contributes significantly to detection of fragrance allergy. *Contact Dermatitis* 2010: **63**: 270–276.
19 Thyssen J P, Carlsen B C, Menné T, Johansen J D. Trends of contact allergy to fragrance mix I and Myroxylon pereirae among Danish eczema patients tested between 1985 and 2007. *Contact Dermatitis* 2008: **59**: 238–244.
20 Deleo V A. p-Phenylenediamine. *Dermatitis* 2006: **17**: 53–55.
21 Ho S G, White I R, Rycroft R J, McFadden J P. A new approach to patch testing patients with para-phenylenediamine allergy secondary to temporary black henna tattoos. *Contact Dermatitis* 2004: **51**: 213–214.
22 Becker D, Mahler V, Szliska C et al. The concentration of para-phenylenediamine (PPD) for routine patch testing in a standard series needs to be redefined. *Contact Dermatitis* 2005: **53**: 186–187.
23 Schnuch A, Lessmann H, Frosch P J, Uter W. para-Phenylenediamine: the profile of an important allergen. Results of the IVDK. *Br J Dermatol* 2008: **159**: 379–386.
24 Devos S A, Van Der Valk P G. The risk of active sensitization to PPD. *Contact Dermatitis* 2001: **44**: 273–275.
25 Spornraft-Ragaller P, Schnuch A, Uter W. Extreme patch test reactivity to p-phenylenediamine but not to other allergens in children. *Contact Dermatitis* 2011: **65**: 220–226.
26 Malvestio A, Bovenzi M, Hoteit M et al. p-Phenylenediamine sensitization and occupation. *Contact Dermatitis* 2011: **64**: 37–42.
27 Thyssen J P, Carlsen B C, Søsted H, Menné T, Johansen J D. Frequency of p-phenylenediamine sensitization among Danish eczema patients tested between 1985 and 2007. *Contact Dermatitis* 2008: **59**: 184–185.
28 Czarnobilska E, Obtulowicz K, Dyga W, Wsolek-Wnek K, Spiewak R. Contact hypersensitivity and allergic contact dermatitis among school children and teenagers with eczema. *Contact Dermatitis* 2009: **60**: 264–269.
29 Veien N K, Hattel T, Justesen O, Norholm A. Why do young girls become nickel sensitive? *Contact Dermatitis* 1986: **15**: 306–307.
30 Gonçalo S, Gonçalo M, Azenha A et al. Allergic contact dermatitis in children. A multicenter study of the Portuguese Contact Dermatitis Group (GPEDC). *Contact Dermatitis* 1992: **26**: 112–115.
31 Pevny I, Brennenstuhl M, Razinskas G. Patch testing in children. (I) Collective test results; skin testability in children. *Contact Dermatitis* 1984: **11**: 201–206.
32 Bruckner A L, Weston W L, Morelli J G. Does sensitization to contact allergens begin in infancy? *Pediatrics* 2000: **105**: e3.
33 Matiz C, Russell K, Jacob S E. The importance of checking for delayed reactions in pediatric patch testing. *Pediatr Dermatol* 2011: **28**: 12–14.

34 Belloni Fortina A, Romano I, Peserico A, Eichenfield L F. Contact sensitization in very young children. *J Am Acad Dermatol* 2011: **65**: 772–779.
35 Roul S, Ducombs G, Taieb A. Usefulness of the European standard series for patch testing in children. A 3-year single-centre study of 337 patients. *Contact Dermatitis* 1999: **40**: 232–235.
36 Jacob S E, Steele T, Brod B, Crawford G H. Dispelling the myths behind pediatric patch testing – experience from our tertiary care patch testing centers. *Pediatr Dermatol* 2008: **25**: 296–300.
37 Torp Madsen J, Andersen K E. Outcome of a second patch test reading of TRUE Tests(R) on D6/7. *Contact Dermatitis* 2013: **68**: 94–97.

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CLINICAL REPORT

Course of Skin Symptoms and Quality of Life in Children Referred for Patch Testing – A Long-term Follow-up Study

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Children are patch-tested in the same manner as adults, but little has been done to establish whether positive or negative findings influence the course of skin symptoms. To uncover the course of skin symptoms and the impact of persistent eczema on life quality in paediatric patients referred for patch testing, a retrospective questionnaire was sent to children and adolescents referred for patch testing during a 9-year period. Persistent eczema at follow-up was strongly associated to atopic dermatitis, but was not explained by gender, age, contact allergy or time span from patch testing to follow-up. Among patients without atopic dermatitis, 23.5% reported to suffer from chronic eczema. Persistent eczema increased the risk of severe impairment of life quality. Our findings indicate a significant risk of childhood eczema becoming chronic and affecting life quality considerably. Patch testing did not affect the course of eczema, highlighting the difficulties of avoidance behaviour. ***Key words: patch testing; children; adolescents; allergic contact dermatitis; contact allergy; atopic dermatitis.***

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Allergic contact dermatitis (CD) is a common dermatological disorder and often results in ongoing disease and disability (1, 2). Even young children may become sensitised and suffer from allergic CD (3). Early identification and subsequent avoidance of the contact allergen by the patient should reduce the duration and disability of the disease and its progression. However, studies on the outcome of patch testing in children with suspected allergic CD are limited (4) and little has been done to establish whether positive or negative findings influence the course of skin symptoms (5).

It is well known that many skin diseases have a significant impact on quality of life (QoL) (6). This has been demonstrated in children with atopic dermatitis (7) as well as in adult patients with allergic CD (1), but little attention has been paid to children and adolescents suffering from the latter.

The aim of this study was to uncover the course of skin symptoms in paediatric patients referred for patch testing, and to evaluate the impact of skin symptoms on QoL.

METHODS

Patient selection

From 1 January 2003 to 31 December 2011 a total of 2,594 patients aged 1–17 years were patch-tested in 12 dermatological clinics throughout Denmark (The Danish Group for Contact Dermatitis), which is estimated to cover about 1/5 of patients patch-tested in Denmark. All patients either suffered from recalcitrant eczema or had a suspected diagnosis of allergic CD. Characteristics according to the MOAHLFA index (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis) were registered by the dermatologist prior to patch testing. The diagnosis of atopic dermatitis was established according to the Hanifin and Rajka criteria (8).

Patch testing

The children were tested with either the European Baseline Series (allergens retrieved from either Chemotechnique Diagnostics, Malmö, Sweden, or from Almirall Hermal, Reinbek, Germany) or with TRUE test (SmartPractice Denmark, Hilleroed, Denmark) supplemented with the allergens from the European Baseline Series that are not included in the TRUE test. Patch tests were removed on day 2. Readings were performed according to The International Contact Dermatitis Research Group Guideline on minimum day 2 or day 4, and often also day 2 and day 7. Reactions designated either "1+", "2+", or "3+" were regarded as positive.

Follow-up

Of the 2,594 patients in the database, 2,591 were registered in the Danish Civil Registration System, and 2,567 had a valid address in Denmark. Since 307 did not wish to be contacted for research purposes, the questionnaire-based follow-up was conducted on the remaining 2,260 patients in the spring of 2013.

Questionnaire

The questionnaire designed for this follow-up study aimed to describe the skin status of the cohort and to uncover persisting skin symptoms. Since some of the patients were younger children, we made it optional for them to either answer the questionnaire themselves or with help from their parents. To investigate how well the outcome of the patch test was remembered by the patients and/or their parents, they were asked if they had contact allergy to metals, fragrances, preservatives, plants or rubber. To study the current skin status of the patients, they were asked "how often do you/your child have eczema?" with the response options "never",

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"all the time/every day", "every week", "1–3 times every month", "4–6 times every year", and "1–3 times every year". To investigate the QoL of those with persisting skin symptoms, the Children's Dermatology Life Quality Index (CLDQI) questionnaire (9) was used for patients aged 16 or younger. For patients aged 17 and above, the Dermatology Life Quality Index (DLQI) (10) questionnaire was used. The CDLQI and DLQI each consists of 10 questions that focus on the effects of skin disease on activities of daily life during the preceding week. Since this was a follow-up study, the temporal parameter was expanded to the preceding year.

Definitions

To classify the severity of skin symptoms at follow-up and identify the patients that were severely affected, we defined the variables "persistent eczema" as eczema all the time/every day or at least once every week, "frequent eczema" as eczema 1–3 times each month, and "rarely eczema" as episodes of eczema less than 6 times each year.

The CDLQI/DLQI is calculated by summing the score for each question, which results in a maximum score of 30 and a minimum score of 0. The scoring and interpretation was done according to the authors' instructions (9, 11). "Severely affected life quality" was defined as a CDLQI score ≥ 13 or DLQI score ≥ 11 ("very large" or "extremely large" effect on patient's life).

Statistics

Characteristics of participants were compared using the χ_2 test. A binary logistic regression analysis was performed with "persistent eczema" as the dependent variable, and atopic dermatitis, contact allergy, gender, age at patch testing (1–5 years, 6–12 years, and 13–17 years) and follow-up time (2–4 years, 5–7 years, 8–10 years) as independent, explanatory variables. Since atopic dermatitis was a major confounder, the logistic regression model was repeated, including only the patients without atopic dermatitis. The χ_2-test was used to compare groups and assess explanatory parameters of "severely affected life quality". All results were expressed as odds ratios with 95% confidence intervals and employing a 5% significance level.

The data analysis was done using statistical software (Statistical Product and Service Solution package for Windows, Release 19, SPSS® Inc., Chicago, IL, USA).

RESULTS

In total, 1,039 questionnaires were returned after one reminder, giving a response rate of 46%. The demographic characteristics of the cohort and differences between the responders and non-responders are summarised in Table I. Respondents were more likely to be female, younger than 20 years at follow-up, patch-tested less than 5 years ago, and having a diagnosis of atopic dermatitis at the time of patch testing.

The respondents were 3–17 years (mean 12.8 years) at the time of patch testing. Time to follow-up was between 2 and 10 years (mean 5.2 years), and the current age of the respondents was 4–28 years (mean 17.7 years). More than two thirds of the respondents were girls (68.1% vs. 32.9%), 48.6% ($n=505$) had a diagnosis of atopic dermatitis (AD) when patch-tested, and 25% ($n=260$) had at least one positive patch test reaction. Among respondents, there were no sex difference in the likelihood of having at least one positive patch test reaction, and the share that suffered from AD was the same in the 2 groups.

Table I. *Demographic characteristics of responders versus non-responders*

	All patients 2,260 (100) *n* (%)	Responders 1,039 (46) *n* (%)	Non-responders 1,221 (54) *n* (%)	OR (95% CI)
Age, years				
<10	124 (5.5)	84 (8.1)	40 (3.3)	2.60 (1.77–3.82)***
11–15	394 (17.4)	205 (19.7)	189 (15.5)	1.34 (1.08–1.67)**
16–20	990 (43.8)	479 (46.1)	511 (41.9)	1.19 (1.01–1.40)*
>21	752 (33.3)	271 (26.1)	481 (39.4)	0.54 (0.45–0.65)*
Gender				
Male	776 (34.3)	331 (31.9)	445 (36.4)	0.82 (0.68–0.97)*
Female	1,484 (65.7)	708 (68.1)	776 (63.6)	
Atopic dermatitis				
Yes	1,011 (44.7)	505 (48.6)	506 (41.4)	1.34 (1.13–1.58)**
No	1,249 (55.3)	534 (51.4)	715 (58.6)	
Contact allergy				
Yes	556 (25.0)	260 (25.0)	306 (25.1)	1.00 (0.83–1.21)
No	1,694 (75.0)	779 (75.0)	915 (74.9)	
Follow-up, years				
2–4	937 (41.5)	493 (47.4)	444 (36.4)	1.58 (1.34–1.87)***
5–7	691 (30.6)	302 (29.1)	389 (31.9)	0.88 (0.73–1.05)
8–10	632 (28.0)	244 (23.5)	388 (31.8)	0.66 (0.55–0.80)***

*$p<0.05$, **$p<0.005$, ***$p<0.001$.
Odds ratio (OR) found by χ_2 testing across subgroups.
CI: confidence interval.

Skin symptoms at follow-up

Of all respondents, 90.8% ($n=943$) answered the question regarding their current skin status. In this group, 51.5% ($n=486$) had a diagnosis of AD and 80.3% ($n=757$) reported that they still suffer from eczema at least once every year. Persistent eczema at follow-up was reported by 31.1% ($n=293$) and was not surprisingly associated with having AD at the time of patch testing (OR 2.10, CI 1.59–2.78, $p<0.01$), but not with having contact allergy (OR 0.91, CI 0.66–1.25, $p=0.55$) or having 2 or more allergies (OR 0.65, CI 0.40–1.04, $p=0.07$). No difference between genders or across age groups was observed, and the risk of having persistent eczema at follow-up was the same regardless of the time from patch testing to follow-up (Table II). The same applied when the analyses were stratified by AD (Table SI[1]). Among respondents without AD, 70.4% ($n=342$) reported to suffer from eczema at least once every year and 23.5% ($n=114$) suffered from persistent eczema.

Metals, fragrance and rubber chemicals were the most frequent sensitisers, but no specific group of allergens was associated with having continuous eczema at follow-up.

Of the 260 patients who were sensitized to at least one allergen, 66.5% ($n=173$) answered the question regar-

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1911

Table II. *Logistic regression analysis with the outcome "persistent eczema" and different explanatory variables*

Explanatory variables	Persistent eczema[a] % (n/n_{total})	Crude OR[b] (95% CI)	Adjusted OR[b] (95% CI)
Gender			
Male	30.9 (94/304)	1 (ref)	1 (ref)
Female	31.1 (199/639)	1.01 (0.75–1.33)	1.01 (0.74–1.36)
Age, years			
<10	34.6 (27/78)	1 (ref)	1 (ref)
11–15	27.6 (51/185)	0.72 (0.41–1.27)	0.86 (0.48–1.53)
16–20	31.5 (138/438)	0.87 (0.52–1.44)	1.02 (0.60–1.72)
>21	31.8 (77/242)	0.88 (0.51–1.51)	1.22 (0.64–2.32)
Atopic dermatitis			
No	23.5 (114/486)	1 (ref)	1 (ref)
Yes	39.2 (179/457)	2.10 (1.59–2.78)	2.05 (1.54–2.72)*
Contact allergy[c]			
No	31.6 (220/696)	1 (ref)	1 (ref)
Yes	29.6 (73/247)	0.91 (0.66–1.25)	0.98 (0.71–1.35)
Follow-up, years			
2–4	33.8 (152/450)	1 (ref)	1 (ref)
5–7	28.2 (78/277)	0.77 (0.55–1.07)	0.74 (0.52–1.06)
8–10	29.2 (63/216)	0.81 (0.57–1.15)	0.72 (0.45–1.13)

*$p<0.05$.
[a]$n=293$. [b]Adjusted for all explanatory variables. [c]Positive patch test reaction to at least one allergen.
OR: odds ratio; CI: confidence interval.

ding the outcome of the patch test and 55.5% ($n=96$) of these were able to correctly identify the group of allergens to which the specific allergen belonged. The ability to correctly recall the allergen group decreased with time. There was no association between having persistent eczema at follow-up and being unable to identify the correct group of allergens (OR 0.91, CI 0.46–1.81, $p=0.79$).

Life quality

Among those who suffered from eczema at least once a year, 76.1% ($n=576$) answered the CDLQI or DLQI depending on age. The mean CDLQI score was 6.38 (range 0–23) vs. mean DLQI score of 6.81 (range 0–29). The CDLQI/DLQI score was correlated to the severity of the eczema and patients with AD were more affected than patients without this diagnosis in both groups (Fig. S1[1]).

Persistent eczema was a strong and significant risk factor for having severely impaired life quality in both patients ≤16 years and in patients ≥17 years. However, the majority of patients had CDLQI/DLQI scores corresponding to a small or moderate impact on life quality.

In the group of respondents ≤16 years, young children were more likely to have severely affected life quality at follow-up (Table III). This was associated to AD whereas no gender difference was observed. The association to AD did not reach statistical significance at a 5% level, which is likely due to small sample sizes. Because of the strong link between having AD and persistent eczema at follow-up, analyses were stratified by AD. Persistent eczema was still the strongest predictor of severely affected life quality. The pattern was similar in patients ≥17 years. In this age group, the role of AD was less pronounced. As in the youngest age group, the risk of having severely affected life quality increased with the severity of eczema, and this pattern persisted when stratified by AD. There was no age difference within this group but we did observe a significant gender difference, with the life quality of females being more affected than that of males (Table IV).

Table III. *Predictors of having severely affected life quality. Patients ≤16 years*

	All patients		Without atopic dermatitis	
Explanatory variables	CDLQI severely affected ($n=124$) % (n/n_{total})	Crude OR[a] (95% CI)	CDLQI severely affected ($n=54$) % (n/n_{total})	Crude OR[a] (95% CI)
Gender				
Male	15.8 (9/57)	1 (ref)	12.0 (3/25)	1 (ref)
Female	16.4 (11/67)	1.05 (0.40–2.74)	6.9 (2/29)	0.54 (0.08–3.55)
Age, years				
≤10	24.4 (12/49)	1 (ref)	12.5 (2/16)	1 (ref)
11–16	10.76 (8/75)	0.37 (0.14–0.98)*	7.9 (3/38)	0.6 (0.09–3.99)
Atopic dermatitis				
No	9.3 (5/54)	1 (ref)		
Yes	21.4 (15/70)	2.67 (0.91–7.90)**		
Contact allergy[b]				
No	16.0 (15/94)	1 (ref)	9.8 (4/41)	1 (ref)
Yes	16.7 (5/30)	1.05 (0.35–3.19)	7.7 (1/13)	0.77 (0.08–7.58)
Persistent eczema				
No	7.1 (6/84)	1 (ref)	4.8 (2/42)	1 (ref)
Yes	35.0 (14/40)	7.00 (2.44–20.09)*	25.0 (3/12)	6.67 (0.97–45.92)*

[a]Odds ratios (OR) calculated by χ^2 testing across subgroups.
[b]At least one positive patch test reaction.
*$p<0.05$, **$p=0.07$.

DISCUSSION

To our knowledge, this is the first long-term follow-up study exploring the course of skin symptoms in children referred for patch testing.

A significant share of the respondents still suffered from flare-ups of eczema at follow-up and many suffered from persistent eczema. AD was the single most important risk factor for having persistent eczema at follow-up, but even among the children and adolescents without diagnosed AD the share of patients who suffered from persistent eczema was substantial. At baseline, all patients were suspected of having allergic CD either as a complicating factor or as the main cause of disease. However, a positive patch test result was not found to affect the prognosis of eczema. There are several possible explanations for this. First of all, the accuracy of patch testing is multifactorial and depends on the competence of the tester (12). A satisfactory result requires careful consideration of exposures and selection of appropriate allergens for the patch testing. Further, the benefits of patch testing

Table IV. *Predictors of having severely affected life quality. Patients ≥ 17 years*

	All patients		Without atopic dermatitis	
Explanatory variables	DLQI severely affected ($n=452$) % (n/n_{total})	Crude OR[a] (95% CI)	DLQI severely affected ($n=198$) % (n/n_{total})	Crude OR[a] (95% CI)
Gender				
Male	9.5 (11/116)	1 (ref)	6.0 (3/50)	1 (ref)
Female	25.3 (85/336)	3.23 (1.66–6.31)**	22.3 (33/148)	4.50 (1.32–15.38)*
Age, years				
17–21	21.9 (69/315)	1 (ref)	19.1 (26/136)	1 (ref)
≥22	19.7 (27/137)	0.88 (0.53–1.44)	16.1 (10/62)	0.81 (0.36–1.81)
Atopic dermatitis				
No	18.2 (36/198)	1 (ref)		
Yes	23.6 (60/254)	1.39 (0.88–2.21)		
Contact allergy[b]				
No	21.3 (72/338)	1 (ref)	18.4 (4/41)	1 (ref)
Yes	21.1 (24/114)	0.99 (0.59–1.66)	17.7 (11/62)	0.96 (0.44–2.10)
Persistent eczema				
No	11.8 (32/271)	1 (ref)	7.2 (9/125)	1 (ref)
Yes	35.4 (64/181)	4.09 (2.53–6.59)**	37.0 (27/73)	7.57 (3.31–17.32)**

[a]Odds ratios (OR) calculated by χ^2 testing across subgroups.
[b]At least one positive patch test reaction.
*$p<0.05$, **$p<0.001$.

depends on the information given regarding avoidance of allergens (13, 14), and most importantly the patient's ability to recall the results of the patch testing (12) and subsequently avoid the contact allergen.

Avoidance of allergens can be a major challenge, as demonstrated by Lewis et al. (15). Among 43 patients with allergic CD, only half were able to avoid the allergens concerned. Accordingly, our results suggest that the patients who were diagnosed with allergic CD may have had difficulties in adopting suitable avoidance behaviour.

Another aspect of avoidance behaviour is the patient's ability to recall the results of the patch test. Jamil et al. (12) showed that patients' ability to recall the diagnosed allergen decreased over time and at 10-year follow-up only 17% percent were able to recall the correct allergen. In our study only 55.5% were able to correctly identify the group of allergens. We hypothesised that being unable to remember the outcome of the patch test was correlated to having persistent skin symptoms at follow-up. However, we were not able to show that this was the case. It could be argued that our question regarding the outcome of the patch test was too vague, i.e. asking the respondents to name the allergen to which they had a positive reaction would have been more accurate. It is also possible that the challenge of avoidance behaviour biased the result, i.e. those who correctly recalled the outcome, were unable to avoid the specific allergen. In any event, our results indicate that there is a need of reminding patients of any positive results, and this is likely to be even more pronounced if the patch testing is carried out at an early age, where information is primarily given to the parents.

We cannot reject the possibility that AD in some cases were misclassified, which would help explain the large share with persistent skin symptoms. However, it is well known that CD often results in ongoing disease (2), and it could also be that a share of the children and adolescents with skin symptoms not explained by AD or contact allergy, represent a group suffering from irritant CD, indicating that this is a significant problem among children. Other differential diagnoses are nummular eczema, seborroheic dermatitis, and solar dermatitis.

Finally, it is possible that some of the patients developed new contact allergies in the time from primary patch testing to follow up. Mortz et al. (16) recently showed that the incidence rate of contact allergy increased from adolescence to adulthood.

As expected, life quality and disease severity were correlated. Life quality was severely affected in a significant share of patients with persistent eczema. However, in an even larger proportion of patients, persistent eczema only had a small to moderate effect on life quality. This finding may help to explain why so many suffered from persistent eczema, i.e. the impact on life quality is not perceived as significant enough to offset the efforts of implementing avoidance strategies in daily life.

Children aged 3–10 years were more likely to have severely affected life quality than children aged 11–16, which was explained by the interaction effect of AD and persistent eczema. Because of the small size of the subgroups among respondents of the CDLQI, we were unable to make strong conclusions for children ≤16. Statistical analyses with adjustment for gender, age, AD, and any interaction effects between explanatory variables would have been ideal. Unfortunately our sample size did not allow this.

Several studies have explored the impact of different skin disorders on life quality in children and adolescents and most concern AD. Like Gånemo et al. (17) we were unable to show any gender difference in children ≤16 year. We demonstrated a convincing gender difference in our population of patients ≥17 years with ongoing eczema regardless of the natural history. Similar to our results, Ballardini et al. (18) found pre-adolescent girls with mild eczema to have greater impairment of self-perceived health compared to boys. Our finding may well reflect that adolescent girls and young women are more concerned about appearance than males of the same age.

Despite the relatively low response rate of 46%, we did achieve a large sample size of 1039 subjects. The low response rate may to some extent be explained by the large span in follow-up time, i.e. patients may be less likely to respond to questionnaires regarding events that happened several years ago.

There was an overrepresentation of female respondents. The unequal gender distribution was, however, to some degree expected, as two thirds of the patients in our original data set was female and accordingly, several studies have shown that there is a female predominance among patients referred for patch testing (12). In addition, it has previously been demonstrated that young men are more likely to be non-responders than responders (19), and that women are more likely to return a mailed questionnaire (1). Stratified data analyses should eliminate any confounding. Another possible limitation is the fact that patients who suffer from eczema may be more likely to participate in questionnaire surveys concerning skin disease and further, retrospective questionnaire studies imply the inevitable limitation of recall bias. As regards to the assessment of continuous eczema, this was based on the patient's information, and one could argue that a clinical assessment would have been more accurate.

Our findings indicate a significant risk of childhood eczema becoming chronic and affecting life quality considerably. As expected persistent eczema was strongly associated to AD, but was not explained by gender, age, contact allergy or time span from patch testing to follow-up. Persistent eczema at follow-up increased the risk of severe impairment of life quality and this was especially pronounced in females ≥ 17 years. Patch testing did not affect the course of eczema, indicating that it can be extremely difficult to avoid the responsible allergens and further, patients may forget the patch test outcome. Children with skin symptoms should be carefully treated and guided, in order to minimise the disease burden and avoid chronicity and future socioeconomic consequences. We recommend providing each patient with a personal allergy information card.

The subject of this study is largely unexplored and there is a need of further elucidation of the area. Future studies should include clinical follow-up. It would also be of interest to repeat the patch test in order to determine if any new allergies have evolved.

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REFERENCES

1. Kadyk DL, McCarter K, Achen F, Belsito DV. Quality of life in patients with allergic contact dermatitis. J Am Acad Dermatol 2003; 49: 1037–1048.
2. Holness DL. Results of a quality of life questionnaire in a patch test clinic population. Contact Dermatitis 2001; 44: 80–84.
3. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multicentre study. Contact Dermatitis 2014; 70: 104–111.
4. Shah M, Lewis FM, Gawkrodger DJ. Patch testing in children and adolescents: five years' experience and follow-up. J Am Acad Dermatol 1997; 37: 964–968.
5. Trevisan G, Kokelj F. Allergic contact dermatitis due to shoes in children: a 5-year follow-up. Contact Dermatitis 1992; 26: 45.
6. Ryan TJ. Disability in dermatology. Br J Hosp Med 1991; 46: 33–36.
7. Manzoni AP, Pereira RL, Townsend RZ, Weber MB, Nagatomi AR, Cestari TF. Assessment of the quality of life of pediatric patients with the major chronic childhood skin diseases. An Bras Dermatol 2012; 87: 361–368.
8. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; Suppl 92: 44–47.
9. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol 1995; 132: 942–949.
10. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210–216.
11. Finlay AY. Quality of life measurement in dermatology: a practical guide. Br J Dermatol 1997; 136: 305–314.
12. Jamil WN, Erikssohn I, Lindberg M. How well is the outcome of patch testing remembered by the patients? A 10-year follow-up of testing with the Swedish baseline series at the Department of Dermatology in Orebro, Sweden. Contact Dermatitis 2012; 66: 215–220.
13. Woo PN, Hay IC, Ormerod AD. An audit of the value of patch testing and its effect on quality of life. Contact Dermatitis 2003; 48: 244–247.
14. Thomson KF, Wilkinson SM, Sommer S, Pollock B. Eczema: quality of life by body site and the effect of patch testing. Br J Dermatol 2002; 146: 627–630.
15. Lewis FM, Cork MJ, McDonagh AJ, Gawkrodger DJ. An audit of the value of patch testing: the patient's perspective. Contact Dermatitis 1994; 30: 214–216.
16. Mortz CG, Bindslev-Jensen C, Andersen KE. Prevalence, incidence rates and persistence of contact allergy and allergic contact dermatitis in The Odense Adolescence Cohort Study: a 15-year follow-up. Br J Dermatol 2013; 168: 318–325.
17. Gånemo A, Svensson A, Lindberg M, Wahlgren CF. Quality of life in Swedish children with eczema. Acta Derm Venereol 2007; 87: 345–349.
18. Ballardini N, Ostblom E, Wahlgren CF, Kull I. Mild eczema affects self-perceived health among pre-adolescent girls. Acta Derm Venereol 2014; 94: 312–316.
19. Kotaniemi JT, Hassi J, Kataja M, Jonsson E, Laitinen LA, Sovijarvi AR, et al. Does non-responder bias have a significant effect on the results in a postal questionnaire study? Eur J Epidemiol 2001; 17: 809–817.

Manuscript III:

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Children with atopic dermatitis may have unacknowledged contact allergies contributing to their skin symptoms.

Running head: Contact allergy in children with atopic dermatitis.

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Abstract

Background: Whether children with atopic dermatitis have an altered risk of contact allergy than children without atopic dermatitis is frequently debated and studies have been conflicting. Theoretically, the impaired skin barrier in AD facilitates the penetration of potential allergens and several authors have highlighted the risk of underestimating and overlooking contact allergy in children with atopic dermatitis.

Objective: To determine the prevalence of contact allergy in Danish children with atopic dermatitis and explore the problem of unacknowledged allergies maintaining or aggravating the skin symptoms.

Methods: In a cross sectional study, 100 children and adolescents aged 5-17 years with a diagnosis of atopic dermatitis were patch tested with a pediatric series of 31 allergens.

Results: Thirty percent of the children had at least one positive patch test reaction and 17% had at least one contact allergy that was relevant to the current skin symptoms. The risk of contact allergy was significantly correlated to the severity of atopic dermatitis. Metals and components of topical skin care products were the most frequent sensitizers.

Conclusion: Patch testing is relevant as a screening tool in the management of children with atopic dermatitis as they may have unacknowledged contact allergies contributing to or maintaining their skin symptoms. Children with atopic dermatitis seem to be at greater risk of sensitization to certain allergens including metals and components of skin care products.

Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease of childhood. It has a common phenotypic expression, characterized by dry and itchy skin with chronic or recurrent episodes of dermatitis at typical anatomical sites (1). The prevalence of AD has dramatically increased over the last three decades and now affects between 15-30% of children in Western countries (2, 3).

Allergic contact dermatitis (ACD) is the skin manifestation of a delayed-type hypersensitivity reaction that typically develops after prolonged or repeated skin exposure to chemical allergens (4). Although previously considered rare, it is now recognized as a common skin disease in children (5, 6). Clinically, AD and allergic contact dermatitis may be difficult to distinguish as they both present as dermatitis and may co-exist (7). Whether children with AD have an altered risk of contact allergy as compared to children without AD is frequently discussed and past findings have been conflicting. Authors of early experimental studies found reduced sensitization among patients with AD as compared to controls (8-10), but recent research suggests that contact allergy and allergic contact dermatitis may be a significant problem in AD patients (11, 12). The impaired skin barrier in AD facilitates the penetration of potential

allergens (13) and as children with AD are exposed to emollients and topical agents from an early age and for prolonged periods of time (14) this could theoretically increase the risk of contact sensitization to both ingredients and vehicles (4). Although several authors have emphasized the possibility of unacknowledged contact allergies maintaining or worsening the skin symptoms (7, 15-17), children with AD are not routinely patch tested (17). The existing knowledge on contact allergy in children with atopic dermatitis is primarily based on retrospective analyses of children with and without atopic dermatitis that have been referred for patch testing because of suspected allergic contact dermatitis. Since 1977 only 7 studies have been published in which authors have patch tested children with atopic dermatitis without suspecting allergic contact dermatitis and only two address the possible relationship between disease severity and risk of contact sensitization. The weighted average prevalence of contact allergy in the existing studies is 26.2% (18).

With this study, we aimed to determine the prevalence of contact allergy in Danish children with AD, to explore the problem of hidden allergies maintaining or aggravating the skin symptoms, and finally to assess the relationship between severity of atopic dermatitis and risk of contact allergy.

Methods

Patients

This was a prospective study performed on children without a clinical suspicion of allergic contact dermatitis, and thus the patch testing was performed as a screening. During 1 January 2014 – 31 March 2017, 100 children and adolescents aged 5-17 years with a diagnosis of AD were invited to participate. The diagnosis of AD was made by a dermatologist according to the Hanifin & Rajka Criteria (19). All children and adolescents visited one of three dermatology departments in Denmark (Department of Dermatology and Venereology, Aarhus University

Hospital, , and Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen) as part of their regular follow-up. Parents or holders of custody gave written informed consent for participation. Twenty-nine patients were included from the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, 28 from the Department of Dermatology and Allergy Centre, Odense University Hospital, and 43 from the Department of Dermatology and Venereology, Aarhus University Hospital).

At the time of inclusion, the patient's exposure history was noted in order to ensure a targeted patch test, and the severity of AD was assessed according to the SCORAD index (20). SCORAD is a clinical tool used to assess the extent and severity of atopic dermatitis. It is made up of three items. The first item is "Area" i.e. the extent of the dermatitis. This is measured using the rule of 9 to calculate the affected area as a percentage of the whole body. The second item is "Intensity": A representative area of eczema is selected and the intensity of 6 different symptoms (redness, swelling, oozing/crusting, scratch marks, skin thickening, and dryness of the skin without inflammation) is assessed as none (0), mild (1), moderate (2), or severe (3). The third item is the patient's subjective symptoms in terms of sleep loss and itch. This is scored by the patient using a visual analogue scale with 0 being "no itch" (or "no sleep loss") and 10 being "worst imaginable itch" (or "worst imaginable sleep loss").

Patients receiving systemic immunosuppressive treatment were excluded from the study as were patients with severe generalized dermatitis, including dermatitis on the back, in which cases we were unable to apply the patch test.

The study was approved by the National Committee on Health Research Ethics (1-10-72-267-13) and the Danish Data Protection Agency (1-16-02-396-13).

Patch testing

All patients were patch tested with a pediatric series of 31 allergens (supplementary table 1) supplemented by additional allergens as indicated by the child's history as well as the child's own emollients, skin care products, and prescribed topical treatment. At the Department of Dermatology and Venereology, Aarhus University Hospital patients were patch tested with allergens retrieved from AllergEAZE/SmartPractice Denmark (Hilleroed, Denmark). At the Department of Dermatology and Allergy Centre, Odense University Hospital patients were patch tested with allergens retrieved from Chemotechnique Diagnostics (Malmö, Sweden), Almirall Hermal GmbH (Reinbek, Germany), and allergens from TRUE test® retrieved from SmartPractice Denmark (Hilleroed, Denmark). Patch tests were applied in Finn Chambers on Scanpor tape (Norgesplaster®, Vennesla, Norway). At the Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen patients were patch tested with allergens retrieved from Chemotechnique Diagnostics (Malmö, Sweden), and AllergEAZE/SmartPractice Denmark (Hilleroed, Denmark).

After patch test application at day 0 (D0) and allergen exposure for 2 days, readings were performed D3-4 and D7. In one department patch tests were also evaluated on the day of removal (D2). Patch test reactions were classified as "+1", "+2", "+3", "+?", "IR", or "negative" according to the International Contact Dermatitis Research Group criteria (21, 22). For a patch test reaction to be considered positive, homogeneous infiltration and erythema of the entire test area was required for a weak positive reaction (+ 1), with additional vesicles defining a strong positive (+2) and coalescing vesicles an extreme positive (+3) reaction. An irritant reaction, doubtful reaction or negative reading was interpreted as a negative (non-allergic) response.

Relevance of the positive reactions was evaluated according to national guidelines (23) based on patient history, product labels, spot tests or product analyses.

Statistics

A SCORAD <25 was designated as "mild AD" (grade 1), ≥25-50 as "moderate AD" (grade 2), and ≥50 as "severe AD" (grade 3) (24). Crude odds ratios were calculated using Fisher's exact test. To adjust for possible confounding factors, a binary logistic regression analysis was performed with "at least one positive patch test" as the dependent variable, and gender, age group (5-10 years, 11-17 years), and SCORAD severity (grade 1-3) as independent, explanatory variables. To evaluate the risk of contact allergy by localization of eczema another binary logistic regression analysis was performed with "at least one positive patch test" as the dependent variable and localization (face and neck, hands, arms, trunk, thighs, lower legs and knees, feet) as independent, explanatory variables.

Results were expressed as odds ratios (OR) with 95% confidence intervals (CI) and employing a 5% significance level. Statistical significance was predefined as a p-value of <0.05.

The data analysis was done using statistical software (STATA statistical software, College Station, TX: StataCorp LP. Release 12).

Results

Sixty-one girls and 39 boys aged 5-17 years (mean age 9.8 years) were included in the study. The severity of AD as assessed by the SCORAD index ranged from 0-64.3 (mean SCORAD 29.6). According to the SCORAD index, 44% of the patients had mild AD (SCORAD <25), 45% had moderate AD (SCORAD ≤25-50), and 11% suffered from severe AD (SCORAD ≥50).

Thirty percent (n=30) of the children had at least one positive patch test reaction (table 1). Eleven children were sensitized to more than one allergen and 17 children had at least one positive patch test reaction that was relevant to the current skin symptoms. The number of irritant reactions was 15 and 140 reactions were designated as doubtful. The rate of doubtful reactions was the same in children with mild, moderate, or severe AD. No irritant reactions were observed among children with severe disease and the rate of irritant reactions did not differ between children with mild or moderate AD.

Positive patch test reactions

Table 2 shows the allergens listed by frequency of positive reactions. Fifty percent (n=24) of the positive reactions were to metals (nickel sulphate, cobalt chloride, and/or potassium dichromate) with cobalt chloride being the allergen that most often gave a positive reaction as well as the highest number of doubtful and irritant reactions. Co-sensitization to more than one metal allergen was seen in three children and one third of the positive reactions were considered relevant to the current skin symptoms.

Allergens found in skin care products (formaldehyde, fragrance mix I, diazolidinyl urea, imidazolidinyl urea, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), methylisothiazolinone (MI), and Quaternium 15) constituted 22.9% (n=11) of the positive reactions and 54.5% (n=6) of these reactions were considered relevant to the current dermatitis. Formaldehyde was the allergen that most often gave relevant reactions (75%). Three children had relevant reactions to Sesquiterpene Lactone Mix and all had widespread dermatitis including facial dermatitis. One child reacted to one of the corticosteroid markers (hydrocortisone 17 butyrate). This reaction was of current relevance and was only positive on day 7.

Table 3 shows the results of the statistical analysis. The risk of having contact allergy was significantly higher among girls but was not associated to age.

Severity of atopic dermatitis and risk of contact allergy

Having at least one contact allergy was significantly correlated to the severity of AD. Among children with severe AD, 54.5% had at least one positive patch test reaction as compared to 35.6% and 18.2% among children with moderate and mild AD, respectively. We further found a significant association between having hand eczema and contact allergy (table 4).

Discussion

Our findings confirm that contact allergy is a significant problem in children with AD. In the present study, 30% had one or more unacknowledged contact allergies and in 17% of the children, the allergy was considered relevant to the current skin symptoms, which corresponds well to the latest research (17, 18, 25, 26).

As in other similar material on children with AD, metals were the most common allergens. Previous studies have reported the same pattern of sensitization in adult patients (27-29) and an increased risk of metal contact allergy in patients with AD has been suggested (30, 31). In a recent study by Malajian and Belsito (31) positive patch test reactions to nickel sulphate, cobalt chloride, and potassium dichromate were significantly more frequent among patients with AD as compared to controls. The association between AD and filaggrin is well established (32). Based on a recent study on nickel, which was shown to bind strongly to filaggrin (33), it has been hypothesized that filaggrin deficiency might facilitate percutaneous penetration of metal allergens (13).

Worldwide, nickel is the most common allergen in children as well as in adults (34, 35). However, in the present study cobalt chloride gave the highest rate of positive patch test reactions. This was somewhat surprising but very interesting, since cobalt was named allergen of the year in 2016, the reason being that new information regarding potential sources of exposure to cobalt has come into light (36). Historically, cobalt allergy was

linked to concomitant exposure to nickel. However, it is increasingly recognized as an independent sensitizer (37). Eight out of the 11 positive reactions to cobalt were solitary and similar high rates of isolated positive reactions to cobalt have been reported by others (37-39). In a previous Danish study, the prevalence of isolated reactions to cobalt chloride was associated to AD (40).

In this study, the relevance was assessed by reviewing the child's current and past history of exposure. Although many occupational exposures to cobalt are well known (41), the knowledge regarding causative consumer exposures to cobalt have been limited (37) and this is likely even more pronounced with regards to children. Although recent reports have called attention to new cobalt exposure sources among adult patients such as furniture (42), laptop computers (43), and cosmetics (44), sources of exposure are often difficult to identify, making the clinical relevance of a positive patch test reaction to cobalt chloride difficult to determine (40). Thus, it is possible that the rate of relevant reactions to cobalt chloride in the present study could be underestimated. Potential recognized sources of cobalt exposure in children include jewelry, buttons, zippers, snaps, leather shoes, and laptop computers,

Cobalt chloride is a strong sensitizer and is considered a difficult substance to use for testing, as it may result in irritant or doubtful reactions (41, 45), which was also the case in our study. Furthermore, Rystedt (45) have highlighted the difficulties of reproducing weak (+1) patch test reactions to cobalt chloride, and thus it could be argued that the high number of positive reactions does not necessarily reflect true cobalt allergy.

Contact allergy to components in skin care products was found in 8% of the children, supporting the hypothesis that prolonged use of skin care products increases the risk of contact sensitization to both ingredients and vehicles. Our finding is in accordance with the results of a recent Dutch study (46), in which the authors found that children with AD were significantly more likely to have contact allergy to components of skin care products as compared to children without AD. In another frequently cited study of 641 children with AD, emollients and antiseptics were the most frequent sensitizers (47). Similarly, a general population study found that AD patients had a higher prevalence of contact allergy to ingredients in topical products than those without AD (48).

Fragrance is a common sensitizer in children (49). Further, the authors of a large study from the European Surveillance System on Contact Allergies (5), found that the prevalence of contact allergy to fragrance mix is increasing in children. Patients with AD may be at greater risk of fragrance allergy. In several studies, authors have found a significantly higher prevalence of fragrance allergy in AD patients compared to patients without AD (11, 16, 27, 50, 51). We found a low frequency of contact allergy to fragrance, which is in accordance with similar studies in which children with AD were patch tested (17, 25, 26, 52-55). This could reflect that children with AD, implying sensitive skin since early childhood, to a large extend are treated with fragrance free emollients and skin care products carefully selected by the caregiver. Other allergenic ingredients in skin care products may not be as transparent and recognizable to the consumer. In a recent report, Hamann et al. (56) found that 89% of 187 different skin care products marketed as pediatric and labeled as "hypoallergenic", "dermatologist recommended/tested", fragrance free", or "paraben free" contained at least one contact allergen.

Although corticosteroids are not potent sensitizers (57), contact allergy and allergic contact dermatitis from topical corticosteroids is not infrequent (58). Children with AD are likely exposed to topical corticosteroids since early childhood. The combination of a dysfunctional

skin barrier and the prolonged exposure to topical product should in theory increase the risk of sensitization and an association between AD and contact allergy to corticosteroids has been suggested (57, 59). However, the authors of previous studies on children with AD have found low frequencies of positive patch test reactions to corticosteroid markers (25, 47, 54, 55) as was the case in our study. Thus, contact allergy to corticosteroids does not seem to constitute a significant problem in children with AD. The possibility of a complicating contact allergy to topical steroids should nonetheless never be ignored in the evaluation of a child with recalcitrant AD.

Compositae contact allergy caused widespread dermatitis in three children. Compositae allergy was previously considered uncommon in children (5, 60), but it has been suggested that this impression is due to an inadequate screen (61, 62). We used Sesquiterpene Lactone Mix as a screen for compositae allergy. However, it could be argued that adding compositae-mix would have provided a more thorough screen. Patients with AD appear to be in greater risk of sensitization to compositae (63). In previous studies on patch test reactions in children, contact allergy to sesquiterpene lactone mix was significantly associated to AD (18). The causality of this relationship is unclear. As compositae contact allergy may mimic AD (64, 65) it is an important allergy to consider, especially in cases with dermatitis located to hands or face, widespread dermatitis, or aggravation of skin symptoms during spring or summer (60, 63). Furthermore, children with AD should be warned against topical use of cosmetics and herbal remedies containing compositae extracts (66).

Girls were significantly more likely to have contact allergy as compared to boys. This gender difference has been demonstrated in several studies in children (39, 67-70) as well as in adults (71, 72). The gender difference observed in similar material is often driven by nickel, and this was also the case in our study (shown in table 1).

We found a strong and significant correlation between the severity of AD and the risk of contact allergy. In contrast to this, Forsbeck et al. (8) and Uehara et al. (73) in early experimental studies, found that patients with severe AD were more difficult to sensitize to dinitrochlorobenzene as compared to patients with mild AD. However, recent clinical studies of patients with AD have demonstrated an association between disease severity and risk of contact allergy (16, 25, 28, 47) in line with the present study. This could reflect that children with severe AD are more exposed to various emollients and topical treatments as compared to children with limited skin involvement. In a Swedish study, children with moderate to severe AD used moisturizers and topical corticosteroids more frequently than children with mild AD (74). It has also been suggested that the disturbed skin barrier and inherent immune alterations in AD promotes the development of contact sensitization (75) and this may be more pronounced in patients with severe skin symptoms.

Another important consideration in this aspect is, that contact allergy to certain allergens may mimic widespread AD (64, 65, 76). It has even been suggested that contact sensitization could result in AD (11, 77). Thus, patients with widespread AD are likely to have unacknowledged contact allergies maintaining the skin symptoms and the possibility of a contact allergy even causing apparent AD should never be rejected.

The risk of contact allergy was significantly increased in children with hand dermatitis. This is in accordance with a recent study by Isaksson et al. (17) who patch tested 82 children with AD and found a significantly higher frequency of contact allergy in children with hand and/or foot dermatitis. AD is a strong predisposing factor for hand eczema at any age (70, 78, 79) and the association between hand eczema and contact allergy is well known (79, 80). In agreement with a recent report by Heede et al. (78), our findings indicate that children with AD and hand eczema stand out and seem to be at greater risk of contact sensitization.

A limitation of this study is the relatively small sample size, which may weaken the statistical calculations to some extend. The children were tested for the purpose of this study i.e. they were screened for any unknown contact allergy. However, although all consecutive patients eligible for the study were invited to participate, we cannot reject the possibility that children and parents who suspected ACD were more likely to accept to participate in the study. This would bias our results and cause an overestimation of the frequency of contact allergy.

We patch tested the children with a selected series of allergens and it could be argued that this selection was too limited, thus implying a risk of missing important contact allergies that would have been detected with a broader series of allergens.

Finally, it is well known that patch testing patients with atopic dermatitis implies a risk of false positive reactions due to hyper-reactive skin (81). However, we found a relatively low number of positive reactions as compared to other studies of its kind and we do not believe that false positive reactions constituted a major source of bias.

Conclusion

Children with AD may have unacknowledged contact allergies contributing to or maintaining their skin symptoms and should be patch tested to exclude any underlying allergy, especially if they have severe AD or hand eczema. Special attention should be paid to metals and ingredients in skin care products, whereas allergy to topical steroids does not seem to constitute a significant problem. Caregivers should be advised to use non-scented products with as few components as possible.

1. Friedmann PS, Holden C.A. Rook's Textbook of Dermatology. In: Burns T BS, Cox N, Griffiths C, editor. 1. 7 ed: Blackwell Publishing Company; 2004.

2. Sabin BR, Peters N, Peters AT. Chapter 20: Atopic dermatitis. Allergy Asthma Proc. 2012;33 Suppl 1:S67-9.

3. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483-94. doi: 10.056/NEJMra074081.

4. Thyssen JP, McFadden JP, Kimber I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. Allergy. 2014;69(1):28-36. doi: 10.1111/all.12358. Epub 2013 Dec 26.

5. Belloni Fortina A, Cooper SM, Spiewak R, Fontana E, Schnuch A, Uter W. Patch test results in children and adolescents across Europe Analysis of the ESSCA Network feminine 2002-2010. Pediatr Allergy Immunol. 2015:12397.

6. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Acta Derm Venereol. 2002;82(5):352-8.

7. Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R. A half of schoolchildren with 'ISAAC eczema' are ill with allergic contact dermatitis. J Eur Acad Dermatol Venereol. 2011;25(9):1104-7. doi: 10.11/j.468-3083.2010.03885.x. Epub 2010 Nov 4.

8. Forsbeck M, Hovmark A, Skog E. Patch testing, tuberculin testing and sensitization with dinitrochlorobenzene and nitrosodimethylanilini of patients with atopic dermatitis. Acta Derm Venereol. 1976;56(2):135-8.

9. Jones HE, Lewis CW, McMarlin SL. Allergic contact sensitivity in atopic dermatitis. Arch Dermatol. 1973;107(2):217-22.

10. Rees J, Friedmann PS, Matthews JN. Contact sensitivity to dinitrochlorobenzene is impaired in atopic subjects. Controversy revisited. Arch Dermatol. 1990;126(9):1173-5.

11. Thyssen JP, Linneberg A, Engkilde K, Menne T, Johansen JD. Contact sensitization to common haptens is associated with atopic dermatitis: new insight. Br J Dermatol. 2012;166(6):1255-61.

12. Hamann CR, Hamann D, Egeberg A, Johansen JD, Silverberg J, Thyssen JP. Association between atopic dermatitis and contact sensitization: A systematic review and meta-analysis. J Am Acad Dermatol. 2017:001.

13. Engebretsen KA, Thyssen JP. Skin Barrier Function and Allergens. Curr Probl Dermatol. 2016;49:90-102.(doi):10.1159/000441548. Epub 2016 Feb 4.

14. Fontana E, Belloni Fortina A. Allergic contact dermatitis in children. G Ital Dermatol Venereol. 2014;149(6):693-701. Epub 2014 Oct 15.

15. Schena D, Papagrigoraki A, Tessari G, Peroni A, Sabbadini C, Girolomoni G. Allergic contact dermatitis in children with and without atopic dermatitis. Dermatitis. 2012;23(6):275-80.

16. Herro EM, Matiz C, Sullivan K, Hamann C, Jacob SE. Frequency of contact allergens in pediatric patients with atopic dermatitis. J Clin Aesthet Dermatol. 2011;4(11):39-41.

17. Isaksson M, Olhardt S, Radehed J, Svensson A. Children with Atopic Dermatitis Should Always be Patch-tested if They Have Hand or Foot Dermatitis. Acta Derm Venereol. 2015;95(5):583-6. doi: 10.2340/00015555-1995.

18. Simonsen AB, Johansen JD, Deleuran M, Mortz CG, Sommerlund M. Contact allergy in children with atopic dermatitis: a systematic review. Br J Dermatol. 2017:15628.

19. Hanifin JM RG. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;92:44-7.

20. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23-31.

21. Fregert S. Manual of Contact Dermatitis. Copenhagen: Munksgaard; 1974.

22. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015;73(4):195-221. doi: 10.1111/cod.12432. Epub 2015 Jul 14.

23. Menne T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis. 2011;65(1):3-12.

24. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol. 2007;157(4):645-8. Epub 2007 Aug 21.

25. Akan A, Toyran M, Vezir E, Azkur D, Kaya A, Erkocoglu M, et al. The patterns and clinical relevance of contact allergen sensitization in a pediatric population with atopic dermatitis. Turk J Med Sci. 2015;45(6):1207-13.

26. Silny W, Bartoszak L, Jenerowicz D, Zukiewicz-Sobczak W, Gozdziewska M. Prevalence of contact allergy in children suffering from atopic dermatitis, seborrhoeic dermatitis and in healthy controls. Ann Agric Environ Med. 2013;20(1):55-60.

27. Heine G, Schnuch A, Uter W, Worm M. Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). Allergy. 2006;61(5):611-6.

28. Belhadjali H, Mohamed M, Youssef M, Mandhouj S, Chakroun M, Zili J. Contact sensitization in atopic dermatitis: results of a prospective study of 89 cases in Tunisia. Contact Dermatitis. 2008;58(3):188-9.

29. Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Menne T, Thyssen JP. Chromium allergy and dermatitis: prevalence and main findings. Contact Dermatitis. 2015;73(5):261-80. doi: 10.1111/cod.12436. Epub 2015 Jun 24.

30. Ruff CA, Belsito DV. The impact of various patient factors on contact allergy to nickel, cobalt, and chromate. J Am Acad Dermatol. 2006;55(1):32-9. Epub 2006 May 16.

31. Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. J Am Acad Dermatol. 2013;69(2):232-7. doi: 10.1016/j.jaad.2013.03.012. Epub Apr 11.

32. Thyssen JP, Godoy-Gijon E, Elias PM. Ichthyosis vulgaris: the filaggrin mutation disease. Br J Dermatol. 2013;168(6):1155-66. doi: 10.11/bjd.12219. Epub 2013 May 6.

33. Ross-Hansen K, Ostergaard O, Tanassi JT, Thyssen JP, Johansen JD, Menne T, et al. Filaggrin is a predominant member of the denaturation-resistant nickel-binding proteome of human epidermis. J Invest Dermatol. 2014;134(4):1164-6. doi: 10.038/jid.2013.445. Epub Oct 24.

34. Belloni Fortina A, Fontana E, Peserico A. Contact Sensitization in Children: A Retrospective Study of 2,614 Children from a Single Center. Pediatr Dermatol. 2016;33(4):399-404. doi: 10.1111/pde.12873. Epub 2016 May 31.

35. Thyssen JP, Johansen JD, Carlsen BC, Menne T. Prevalence of nickel and cobalt allergy among female patients with dermatitis before and after Danish government regulation: a 23-year retrospective study. J Am Acad Dermatol. 2009;61(5):799-805.

36. Fowler JF, Jr. Cobalt. Dermatitis. 2016;27(1):3-8. doi: 10.1097/DER.0000000000000154.

37. Liden C, Andersson N, Julander A, Matura M. Cobalt allergy: suitable test concentration, and concomitant reactivity to nickel and chromium. Contact Dermatitis. 2016;74(6):360-7. doi: 10.1111/cod.12568. Epub 2016 Mar 21.

38. Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. Allergy. 2005;60(3):372-8.

39. Lagrelius M, Wahlgren CF, Matura M, Kull I, Liden C. High prevalence of contact allergy in adolescence: results from the population-based BAMSE birth cohort. Contact Dermatitis. 2016;74(1):44-51. doi: 10.1111/cod.12492. Epub 2015 Nov 5.

40. Thyssen JP, Menne T, Liden C, Julander A, Jensen P, Jakobsen SS, et al. Cobalt release from implants and consumer items and characteristics of cobalt sensitized patients with dermatitis. Contact Dermatitis. 2012;66(3):113-22. doi: 10.1111/j.600-0536.2011.02001.x. Epub 2011 Dec 16.

41. Thyssen JP. Cobalt sensitization and dermatitis: considerations for the clinician. Dermatitis. 2012;23(5):203-9.

42. Bregnbak D, Opstrup MS, Jellesen MS, Johansen JD, Thyssen JP. Allergic contact dermatitis caused by cobalt in leather - clinical cases. Contact Dermatitis. 2017;76(6):366-8. doi: 10.1111/cod.12721.

43. Midander K, Hurtig A, Borg Tornberg A, Julander A. Allergy risks with laptop computers - nickel and cobalt release. Contact Dermatitis. 2016;74(6):353-9. doi: 10.1111/cod.12525. Epub 2016 Jan 19.

44. Lee HJ, Byun JY, Choi YW, Choi HY. Two cases of eyelid dermatitis caused by cobalt in colour cosmetics. Contact Dermatitis. 2016;75(6):390-2. doi: 10.1111/cod.12669.

45. Rystedt I. Evaluation and relevance of isolated test reactions to cobalt. Contact Dermatitis. 1979;5(4):233-8.

46. Lubbes S, Rustemeyer T, Sillevis Smitt JH, Schuttelaar ML, Middelkamp-Hup MA. Contact sensitization in Dutch children and adolescents with and without atopic dermatitis - a retrospective analysis. Contact Dermatitis. 2017;76(3):151-9. doi: 10.1111/cod.12711. Epub 2016 Nov 11.

47. Mailhol C, Lauwers-Cances V, Rance F, Paul C, Giordano-Labadie F. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. Allergy. 2009;64(5):801-6.

48. Thyssen JP, Johansen JD, Linneberg A, Menne T, Nielsen NH, Meldgaard M, et al. The association between null mutations in the filaggrin gene and contact sensitization to nickel and other chemicals in the general population. Br J Dermatol. 2010.

49. Bonitsis NG, Tatsioni A, Bassioukas K, Ioannidis JP. Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis. Contact Dermatitis. 2011;64(5):245-57.

50. Lubbes S, Rustemeyer T, Sillevis Smitt JH, Schuttelaar MA, Middelkamp-Hup MA. Contact sensitization in Dutch children and adolescents with and without atopic dermatitis - a retrospective analysis. Contact Dermatitis. 2016:12711.

51. Lammintausta K, Kalimo K, Havu VK. Contact allergy in atopics, who perform wet work in hospital. Derm Beruf Umwelt. 1982;30(6):184-8.

52. Angelini G, Meneghini CL. Contact and bacterial allergy in children with atopic dermatitis. Contact Dermatitis. 1977;3(3):163-7.

53. Oranje AP, Bruynzeel DP, Stenveld HJ, Dieges PH. Immediate- and delayed-type contact hypersensitivity in children older than 5 years with atopic dermatitis: a pilot study comparing different tests. Pediatr Dermatol. 1994;11(3):209-15.

54. Giordano-Labadie F, Rance F, Pellegrin F, Bazex J, Dutau G, Schwarze HP. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. Contact Dermatitis. 1999;40(4):192-5.

55. Foti C, Bonifazi E, Casulli C, Bonamonte D, Conserva A, Angelini G. Contact allergy to topical corticosteroids in children with atopic dermatitis. Contact Dermatitis. 2005;52(3):162-3.

56. Hamann CR, Bernard S, Hamann D, Hansen R, Thyssen JP. Is there a risk using hypoallergenic cosmetic pediatric products in the United States? J Allergy Clin Immunol. 2015;135(4):1070-1. doi: 10.16/j.jaci.2014.07.066. Epub Nov 7.

57. Vind-Kezunovic D, Johansen JD, Carlsen BC. Prevalence of and factors influencing sensitization to corticosteroids in a Danish patch test population. Contact Dermatitis. 2011;64(6):325-9. doi: 10.1111/j.600-0536.2011.01898.x. Epub 2011 Apr 3.

58. Browne F, Wilkinson SM. Effective prescribing in steroid allergy: controversies and cross-reactions. Clin Dermatol. 2011;29(3):287-94. doi: 10.1016/j.clindermatol.2010.11.007.

59. Baeck M, Chemelle JA, Terreux R, Drieghe J, Goossens A. Delayed hypersensitivity to corticosteroids in a series of 315 patients: clinical data and patch test results. Contact Dermatitis. 2009;61(3):163-75. doi: 10.1111/j.600-0536.2009.01602.x.

60. Belloni Fortina A, Romano I, Peserico A. Contact sensitization to Compositae mix in children. J Am Acad Dermatol. 2005;53(5):877-80.

61. Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of Compositae plants. Contact Dermatitis. 1993;29(1):6-10.

62. Orion E, Paulsen E, Andersen KE, Menne T. Comparison of simultaneous patch testing with parthenolide and sesquiterpene lactone mix. Contact Dermatitis. 1998;38(4):207-8.

63. Paulsen E, Otkjaer A, Andersen KE. Sesquiterpene lactone dermatitis in the young: is atopy a risk factor? Contact Dermatitis. 2008;59(1):1-6.

64. Aerts O, Cattaert N, Lambert J, Goossens A. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. Contact Dermatitis. 2013;68(4):250-1.

65. Crounse RG. Plant dermatitis due to the Compositae (Asteraceae) family. J Am Acad Dermatol. 1980;2(5):417-24.

66. Paulsen E, Chistensen LP, Andersen KE. Cosmetics and herbal remedies with Compositae plant extracts - are they tolerated by Compositae-allergic patients? Contact Dermatitis. 2008;58(1):15-23.

67. Clayton TH, Wilkinson SM, Rawcliffe C, Pollock B, Clark SM. Allergic contact dermatitis in children: should pattern of dermatitis determine referral? A retrospective study of 500 children tested between 1995 and 2004 in one U.K. centre. Br J Dermatol. 2006;154(1):114-7.

68. Milingou M, Tagka A, Armenaka M, Kimpouri K, Kouimintzis D, Katsarou A. Patch tests in children: a review of 13 years of experience in comparison with previous data. Pediatr Dermatol. 2010;27(3):255-9.

69. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing - a nationwide multicentre study. Contact Dermatitis. 2014;70(2):104-11.

70. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol. 2001;144(3):523-32.

71. Peiser M, Tralau T, Heidler J, Api AM, Arts JHE, Basketter DA, et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects: Current knowledge assembled at an international workshop at BfR, Germany. Cell Mol Life Sci. 2012;69(5):763-81. Epub 2011 Oct 14 doi:10.1007/s00018-011-0846-8.

72. Thyssen JP, Linneberg A, Menne T, Johansen JD. The epidemiology of contact allergy in the general population--prevalence and main findings. Contact Dermatitis. 2007;57(5):287-99.

73. Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. Arch Dermatol. 1989;125(3):366-8.

74. Ballardini N, Kull I, Soderhall C, Lilja G, Wickman M, Wahlgren CF. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. Br J Dermatol. 2013;168(3):588-94. doi: 10.1111/bjd.12196.

75. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol. 2013;131(2):300-13. doi: 10.1016/j.jaci.2012.06.048. Epub Aug 28.

76. Mohamoud AA, Andersen F. Allergic contact dermatitis caused by textile dyes mimicking atopic dermatitis. Contact Dermatitis. 2017;76(2):119-20. doi: 10.1111/cod.12630.

77. Calnan CD. Nickel dermatitis. Br J Dermatol. 1956;68(7):229-36.

78. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. Br J Dermatol. 2016;175(2):287-95. doi: 10.1111/bjd.14476. Epub 2016 May 24.

79. Toledo F, Garcia-Bravo B, Fernandez-Redondo V, De la Cuadra J, Gimenez-Arnau AM, Borrego L, et al. Patch testing in children with hand eczema. A 5-year multicentre study in Spain. Contact Dermatitis. 2011;65(4):213-9.

80. Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75-87.

81. Memon AA, Friedmann PS. 'Angry back syndrome': a non-reproducible phenomenon. Br J Dermatol. 1996;135(6):924-30.

Table 1. Characteristics of the children with contact allergy.

Patient	**Age**	**Gender**	**Atopic dermatitis Severity[a]**	**Positive patch test**	**Maximum strength**	**Relevance**
1	5	F	Mild	PTBP	+2	Glue
2	5	F	Moderate	Potassium dichromate Black rubber mix Formaldehyde	+1 +1 +2	- - Shoes
3	5	M	Moderate	Potassium dichromate	+1	Leather apparel
4	6	F	Moderate	Fragrance mix I	+1	-
5	6	F	Mild	Potassium dichromate PTPB	+1 +1	- -
6	6	F	Moderate	Carba mix	+1	-
7	6	M	Moderate	Nickel sulphate Cobalt chloride Potassium dichromate Sesquiterpene lactone mix	+1 +1 +1 +2	- - - Plants
8	6	M	Moderate	Cobalt chloride Potassium dichromate	+1 +1	- -
9	7	F	Severe	Cobalt chloride	+1	-
10	8	F	Mild	Nickel sulphate	+1	Necklace
11	8	F	Moderate	Formaldehyde	+1	Emollient
12	9	F	Moderate	Nickel sulphate	+1	-
13	9	F	Moderate	Cobalt chloride	+1	-
14	9	F	Mild	Cobalt chloride	+2	-
15	9	F	Severe	Cobalt chloride	+2	Jewellery
16	10	F	Moderate	Fragrance mix I	+2	Emollient
17	10	F	Mild	Cobalt chloride	+1	Earrings
18	11	F	Moderate	Colophonium	+1	-
19	11	F	Severe	Cobalt chloride	+1	-

				Formaldehyde Sesquiterpene lactone mix	+1 +3	Emollients Plants
20	11	F	Severe	Nickel suphate Colophonium	+1 +1	Hair clip -
21	11	M	Moderate	Potassium Dichromate		-
22	12	F	Severe	Cobalt chloride Potassium dichromate	+1 +1	Leather shoe Leather shoe
23	12	M	Severe	Carba mix	+1	Shin pads
24	13	F	Mild	Nickel sulphate	+1	Relevant, source not given
25	13	F	Moderate	Hydrocortisone-17-butyrate	+1	Topical corticosteroid
26	13	F	Moderate	Cobalt chloride MCI/MI MI	+1 +2 +3	- Liquid soap Shampoo, sunscreen
27	14	F	Moderate	Diazolidinyl urea Imidazolidinyl urea	+1 +1	- -
28	14	M	Moderate	Cobalt chloride Formaldehyde Quaternium 15 Sesquiterpene lactone mix	+1 +1 +1 +2	- - - Plants
29	15	F	Mild	Nickel sulphate	+2	-
30	15	M	Mild	Carba mix Colophonium	+1 +1	- -

[a] Severity of atopic dermatitis according to the SCORAD.

- = unknown or no relevance to current skin symptoms

Table 2. Allergens listed by frequency of positive patch test reactions.

Allergen	**Positive**	**Relevant**	**Doubtful**	**Irritant**
Cobalt chloride	11	3	19	8
Potassium dichromate	7	2	14	4
Nickel sulfate	6	3	18	1
Formaldehyde	4	3	3	0
Carba mix	3	1	9	0
Sesquiterpene lactone mix	3	3	0	0
Colophonium	3	0	2	0
Fragrance mix I	2	1	15	0
P-tert butylphenol formaldehyd resin	2	1	2	0
Black rubber mix	1	0	2	0
Diazolidinyl urea	1	0	3	0
Imidazolidinyl urea	1	0	0	0
Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)	1	1	2	0
Methylisothiazolinone	1	1	2	0
Quaternium 15	1	0	0	0
Hydrocortison 17 butyrat	1	1	1	0
Fragrance mix II	0	0	7	1
Balsam of Peru	0	0	1	0
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	0	0	1	0
Mercaptobenzothiazole	0	0	4	0
Mercapto mix	0	0	1	0
Thiuram mix	0	0	3	0
Paraben mix	0	0	4	1
Lanolin alcohol	0	0	9	0
Tixocortol pivalate	0	0	2	0
Budesonid	0	0	2	0
Ethylene diamine	0	0	4	0
Benzyl alcohol	0	0	0	0
Benzyl benzoate	0	0	3	0
Triethanolamine	0	0	5	0
Phenoxyethanol	0	0	2	0
Total	48	20	140	15

Table 3. The risk of contact allergy as defined by a positive patch test and explanatory variables.

Explanatory variables	**PPT[a] % (n/n_{total})**	**OR[b] with 95% CI[c]**	**p-value**
Gender			
Male	17.9 (7/39)	1 (ref)	
Female	37.7 (23/61)	3.13 (1.14-8.62)	**0.03**
Age			
5-10 years	30.3 (17/56)	1 (ref)	
11-17 years	29.6 (13/44)	0.79 (0.31-2.01)	0.62
SCORAD			
< 25	18.2 (8/44)	1 (ref)	
25-50	35.6 (16/45)	2.79 (1.01-7.66)	**0.05**
≥50[d]	54.5 (6/11)	6.31 (1.42-28.07)	**0.02**

[a] PPT = at least one positive patch test reaction

[b] OR = odds ratio adjusted for gender, age, and severity of atopic dermatitis according to total SCORAD.

[c] CI = confidence interval

[d] No significant difference between children with SCORAD 25-50 and ≥50, respectively (p=0.25).

Table 4. Localization of dermatitis and risk of contact allergy.

Localization of dermatitis	**Number of children**	**Children with PPT[a] n (%)[b]**	**OR[c] (95% CI[d])**	**p-value**
Face and neck	51	19 (37.3)	2.32 (0.87-6.17)	0.09
Hands	46	19 (41.3)	2.83 (1.04-7.66)	**0.04**
Arms	65	21 (32.3)	1.17 (0.04-3.40)	0.78
Trunk	30	10 (33.3)	0.82 (0.27-2.51)	0.73
Thighs	21	9 (42.9)	2.30 (0.70-7.56)	0.18
Knees and lower legs	44	17 (38.6)	1.75 (0.67-4.58)	0.25
Feet	15	7 (46.7)	1.59 (0.42-5.99)	0.44

[a] PPT = at least one positive patch test

[b] Share of children with at least one positive patch test out of all children with dermatitis at the specific localization

[c] OR = odds ratio

[d] CI = confidence interval

5. Comments on methodology

5.1 Study I

One of the major advantages of register studies is the size of the cohorts that can be studied. This provides, per se, more valid statistical estimates and strengthens the conclusions drawn from the statistical calculations. Among the disadvantages of retrospective studies are that the possibilities of data analysis is limited by the information provided in the register. Among biases that may negatively impact the veracity of this type of study are selection bias and misclassification or information bias as a result of the retrospective design, i.e. the information provided in the database relies solely on the information entered, meaning that the conductors of retrospective studies cannot control the clinical assessment but instead need to rely on others for accurate recordkeeping. As the patients were seen in 12 different dermatology clinics, there is a risk of some degree of inter-observer variability, i.e. the interpretation of patch test reaction could vary. However, the personnel who performed the patch test readings were all experienced and conform to the International Contact Dermatitis Group guidelines for patch testing and interpreting results (7).

The children were tested with either the European Baseline Series supplemented with the allergens from the European Baseline Series that are not included in the TRUE test. In Denmark, children are patch tested with the same allergens and allergen concentration as adults. Some authors have questioned whether the allergen series used for adults is also useful for the patch testing of children (15, 146). However, several studies, review articles and meta-analyses have shown that the most common allergens in children and adults are the same (13, 14, 48, 60, 147-149). It has also previously been proposed that the allergen concentration should be lowered in children (16, 150) but the general consensus today is that children tolerate the same patch test concentrations as adults (151-153).

Patch tests were removed on day 2 and readings were performed on day 3 or day 4, and often also day 2 and day 7. It is well known that a late reading at day 7 is optimal in order not to miss late patch test reactions. Thus, late readings could have been missed in some cases as not all children were evaluated on day 7 (6, 154). This is especially important when patch testing with corticosteroids (155, 156). However, it is the general practice to instruct the patients or

parents of patients to call the physician if any reaction in the patch tested area occurs after the final reading and with this, the possibility of missing late reactions should be limited.

5.2 Study II

Follow-up procedures are an important component of all research and can be designed as either face-to-face interviews, clinical examinations, telephone interviews, or questionnaires by e-mail or mail (157). Because of the size and geographical distribution of our cohort, we decided to do the follow-up by questionnaire. Questionnaires are very cost effective when compared to face-to-face interviews (158). This is especially true for studies involving large sample sizes and large geographic areas. Written questionnaires become even more cost effective as the number of research questions increases (159) and they are easy to analyze. Web-based questionnaires are less costly than paper versions, but as studies have found paper-and-pencil questionnaires superior with regards to response rate (160, 161), we decided to send out the questionnaires by mail.

A questionnaire study is based on and may therefore also be biased by the researchers' opinions and suppositions. Thus, the overall questionnaire designed for this study was based on our decisions and assumptions on what was important to ask in order to get the information needed to answer our research question.

The participation rate is generally considered a measure of representativeness. Thus, in order to reduce the risk of selection bias, the participation rate should be as high as possible (162). We may have achieved a higher participation rate by sending out more than one reminder. It could also be argued that we would have benefitted from giving the patients a second option for answering the questionnaire i.e. we could have made it possible to answer a web-based questionnaire in addition to the paper version.

Our results may be biased to some extent, as respondents were more likely to be female, younger than 20 years at follow-up, patch tested less than 5 years ago, and having a diagnosis of atopic dermatitis at the time of patch testing.

The unequal gender distribution was to some degree expected, as two thirds of the patients in the original data set were female. Accordingly, several studies have shown that there is a female predominance among patients referred for patch testing (163). In addition, it has previously been demonstrated that young men are more likely to be non-responders than responders (164), and that women are more likely to return a mailed questionnaire (31).

It is possible that patients, who suffer from eczema, are more likely to participate in questionnaire surveys concerning skin disease, which would result in an overestimation of the share of patients with chronic eczema at follow-up. Furthermore, retrospective questionnaire studies imply the inevitable problem of recall bias. Regarding the assessment of continuous eczema, this was based on the patient's information. A clinical assessment may have been more accurate; however, this would have required a different study design and setup and with the given time frame and resources available for the study, the study population would have been much smaller.

The choice of HRQoL measure is a trade-off between pros and cons of the available instruments. We decided to use the DLQI/CDLQI for the assessment of HRQoL among the patch tested children and adolescents for several reasons. First of all, the DLQI is the most commonly applied instrument used to measure QoL among allergic contact dermatitis patients (115). It is reliable, valid, and easy to use (165). Further, as the participants consisted of both children and adults, we needed an instrument that could be used for both, and the CDLQI is the only dermatology-specific questionnaire that has been validated for the use in children (126). As not all participants suffered from allergic contact dermatitis, it was necessary to use a generic questionnaire that allowed us to compare different skin diseases. It could be argued that using a disease specific instrument would have captured the impact on QoL more accurately. However, it was not applicable for this study, as we did not have an a priori knowledge concerning the skin symptoms i.e. we did not know who suffered from persistent allergic contact dermatitis, contact dermatitis, or atopic dermatitis at the time of follow-up.

5.3 Study III

We wanted to investigate the problem of unacknowledged contact allergy in children and adolescents with atopic dermatitis. To obtain the largest study population possible, we conducted the study in three different hospital departments. The diagnosis of atopic dermatitis was made by the dermatologist at the time of inclusion and based on the Hanifin & Rajka criteria (166). This is a well-known and highly recognized set of diagnostic criteria based on three or more major features plus three or more minor features. Several other diagnostic criteria for atopic dermatitis exist (167). Although the UK Diagnostic criteria (168, 169) are the most extensively validated (167), the Hanifin & Rajka criteria were chosen for

this study because they are specifically intended for use in hospital settings and in clinical trials.

Because the children were seen by different dermatologists there may have been inter-observer variability in the assessment of SCORAD. However, as the dermatologists were all experienced and used to evaluating children with atopic dermatitis, we do not believe the possible inter-observer variability have caused any major bias. There may have been some variation in the individual score, but we believe the assessment of "mild", "moderate", or "severe" atopic dermatitis was straightforward and uniform.

In Denmark, patients with very mild or moderate atopic dermatitis are usually treated and followed by the family doctor or by the local private practicing dermatologist. It could be argued that patients who are followed at the hospital departments are more severely affected and therefore may not be representative of patients with mild or moderate atopic dermatitis. However, the SCORAD of the patients in the study ranged from 0-64.3, 44% of patients had mild atopic dermatitis (SCORAD <25), 45% of patients had moderate atopic dermatitis (SCORAD ≤25-50), and only 11% suffered from severe atopic dermatitis (SCORAD ≥50). Thus, we believe our cohort was representative of children with atopic dermatitis in general.

We used a relatively limited series of allergens and it is possible that we would have detected even more contact allergies if we had included more allergens. An allergen is suggested for inclusion in a baseline series if the sensitization rate to the specific allergen exceeds 0.5-1% in routine patch testing of patients with suspected allergic contact dermatitis. It is generally agreed that around 20-30 allergens is appropriate in a standard series, as this will also allow room for patient-supplied products and additional allergen series (170). We included most of the allergens from the European Baseline Series that gave positive reactions in >0.5% of Danish children referred for patch testing (171) as well as selected allergens from topical skin care products. The children were further patch tested with their own prescribed topical products, skin care products, and supplemental allergen series if indicated by the history. Thus, we find the chosen methodology suitable for the screening that was intended in our study.

The sample size of 100 implies a limitation because it may weaken the statistical calculations to some extent. Although all consecutive patients eligible for the study were invited to participate, we only managed to recruit 100 patients. Patch testing is a time consuming

procedure, and we believe this was the main reason for families to decline. However, a clinical study involving 100 children is not insignificant.

We cannot reject the possibility that patients and parents of patients who suspected allergic contact dermatitis had a greater incentive to participate, which could potentially bias the result. However, it is well known that several other factors such as altruism, trust in their treating physician, and beliefs that they will receive superior treatment, closer monitoring, and better quality care, also have a significant influence on patients' decisions to participate in research (172, 173).

6. Discussion

6.1 Contact allergy in children referred for patch testing

6.1.1 Prevalence

The prevalence of contact allergy in Danish children and adolescents referred for patch testing during 2003-2011 was 25.1%. The associated relevance was 66.4% giving a prevalence of allergic contact dermatitis of 16.7%. Contact allergy in Danish children had not been studied since Veien et al. (42) published their report in 1982. Among 168 children ≤ 14 years who were patch tested during a 5-year period, 46% had at least one positive patch test reaction. This was a single center study and we believe the higher prevalence in this cohort reflects differences in referral threshold rather than a decrease in the prevalence of contact allergy. Our findings were similar to those reported in concurrent studies from other Northern European countries (58, 174-177) whereas studies from countries in other parts of the world have reported higher sensitization rates in children (64, 65, 146, 148, 152, 153, 178-180). A major strength of our study is the size of the study population, which is one of the largest ever described in the research area of contact allergy in children and adolescents, and at the time of publication, it was the largest study of its kind. Since then, only two studies have analyzed equally large data (56, 60). In the largest study so far, the patch test data on 6708 pediatric patients from 11 countries across Europe (the ESSCA network) was analyzed and the overall prevalence of at least one positive patch test reaction was 36.5% (60).
There are several possible explanations for the discrepancy in the reported sensitization rates throughout the world. First of all, the existing studies are difficult to compare as populations differ in size, have different age- and gender distribution, and use different patch test methodologies. Another possible explanation for the different prevalence in Denmark compared to other countries is that patch testing is free and as a consequence it may in some cases be used as a screening tool to exclude the possibility of allergic contact dermatitis rather than to confirm a suspicion. In other countries, with a different health system, the expenses associated with patch testing could be a barrier for referral, so that children are only patch tested if the suspicion of contact allergy is strong. This would result in a higher prevalence of contact allergy in the study population.

It is also possible that the relatively low prevalence of contact allergy reflects an effective legislation with regards to contact allergens. One example of this is the Danish nickel regulation: To reduce nickel contact allergy, the Danish government passed the nickel regulation in 1990. This prohibited certain consumer products intended to come into direct and prolonged contact with the skin, if they released more than 0.5 µg nickel/cm2/week (181, 182). In 1994, The European Union followed and introduced legislation to control nickel content and release from jewellery and other consumer items through the EU Nickel Directive, which came into force in 2001 (183). In other parts of the world there is limited or no legislation. Throughout the world, nickel is the most common allergen of all in children as well as in adults (4) and limiting the exposure to nickel will undoubtedly affect the overall prevalence of contact allergy.

6.1.2 Age

From analyzing data from study I, we found that the frequency of patch testing and the number of both positive and relevant reactions increased with age, but we found no significant differences regarding sensitization rates between age groups. This could illustrate differences in the threshold for patch testing children depending on the child's age, i.e. very young children may only be patch tested when the suspicion of allergic contact dermatitis is strong. Although some authors have reported higher sensitization rates among very young children, as compared to older children and adolescents (152, 153, 184), it is generally agreed that the risk of contact allergy increases with age (4, 10, 48, 185-187). It has been suggested that this could be due to a reduced sensitization potential in very young children (16, 43). Uhr et al. (188) found that preterm infants were less easily sensitized to DNCB as compared to infants born at term and infants aged 2-12 months, and Epstein (189) reported a similar pattern when experimentally sensitizing infants and older children with a purified allergen (pentacedyl catechol) from rhus. In contrast to this, others have demonstrated high frequencies of sensitization to common allergens in infants and young children. Bruckner et al. (24) found that 24.5% of unselected children aged 6 months to 5 years were sensitized to at least one allergen and that half of the sensitized children were younger than 18 months. To limit the number of false positive reactions, the authors only included +2 and +3 reactions. Motolese et al. (190) patch tested 53 children aged three months – two years. Thirty-two of the children were sensitized to at least one allergen and 62.5% of these (n=20) had a contact

allergy that was of current relevance. A similar high prevalence of contact allergy in infants and young children was reported by Belloni Fortina et al. (21). Thus, the general opinion today is that even infants may become sensitized to contact allergens, but the prevalence of contact allergy increases with age because of increased environmental exposure (4).
We found relevant patch test reactions even in small children aged 1-4 years, and we did not observe irritant reactions in this age group. Our results are in accordance with those of Belloni Fortina et al. (21) who evaluated the patch test reactions in 321 children younger than 3 years old and found "very few irritant reactions". In the 2594 patch tested children we found only 160 irritant reactions. The frequency of irritant reactions increased with age but the proportions of irritant reactions in the four age groups did not differ significantly, and our findings confirm that children tolerate the same patch test concentrations as adults.

	Number referred			Positive reactions				Relevance[a]				Irritant reactions[b]			
Age (years)	Total	Female (%)	Male (%)	Total (%)	Female (%)	Male (%)	*p*-value	Total (%)	Female (%)	Male (%)	*p*-value	Total (%)	Female (%)	Male (%)	*p*-value
1–4	76	31 (40.8)	45 (59.2)	19 (25.0)	9 (29.0)	10 (22.2)	0.5	11 (57.9)	5 (55.6)	6 (60.0)	0.85	3 (3.9)	–	3 (6.7)	0.14
5–8	227	131 (57.7)	96 (42.3)	55 (24.2)	33 (25.2)	22 (22.9)	0.69	37 (67.3)	23 (69.7)	14 (63.6)	0.64	5 (2.2)	5 (3.8)	–	0.05
9–12	579	371 (64.1)	208 (35.9)	152 (26.3)	100 (27.0)	52 (25.0)	0.61	101 (66.4)	68 (68.0))	33 (63.5)	0.57	22 (3.8)	16 (4.3)	6 (2.9)	0.39
13–17	1712	1177 (68.8)	535 (31.3)	425 (24.8)	314 (26.7)	111 (20.7)	< 0.05	283 (66.6)	219 (69.7)	64 (57.7)	< 0.05	75 (4.4)	60 (5.1)	15 (2.8)	< 0.05
Total	2594	1710 (65.9)	884 (34.1)	651 (25.1)	456 (26.7)	195 (22.1)	< 0.05	432 (66.4)	315 (69.1)	117 (60.0)	< 0.05	105 (4.0)	81 (4.7)	24 (2.7)	< 0.05
F-test: equality of age groups:				$p = 0.90$	$p = 0.97$	$p = 0.76$		$p = 0.89$	$p = 0.90$	$p = 0.97$		$p = 0.46$	$p = 0.45$	$p = 0.32$	

[a] Relevance: number of relevant reactions/number of positive reactions.
[b] Irritant reactions: children with at least one irritant patch test reaction out of all children in the specific age group.

Table 2. Patch test reactions by age and sex.

6.1.3 Sex

Girls were significantly more likely to have a positive patch test reaction and this sex difference became apparent after the age of 13. Some authors have found a similar prevalence of contact allergy in boys and girls (45, 70, 152, 177, 191), while others, like us, have reported a higher prevalence among girls (174, 180, 184, 192, 193). The effect of sex on the induction and elicitation of allergic contact dermatitis has been discussed for decades (194). In the most recent review article on the subject, the authors found no evidence for any differences in intrinsic, predisposing skin characteristics between males and females, and the prevailing opinion today is that the observed differences are due to different exposure patterns (195). As demonstrated in previous publications (42, 196) the gender difference observed in study I was mainly driven by nickel, which could be explained by the fact that girls are more likely to

have their ears pierced and wear jewelry at an earlier age (197). It has also previously been suggested that hormonal factors play a role (4, 17, 198, 199).

6.1.4 Allergens

The most common allergens in Danish children referred for patch testing were metals, fragrances, black dye, adhesive chemicals and rubber chemicals.

Nickel continues to be the most common allergen in children (60, 147) as well as in adults worldwide (200-202). The prevalence of nickel contact allergy in our cohort was similar to that reported in other material reporting patch test results in children (60). It was the most common allergen in all age groups and the frequency of nickel contact allergy increased with age. In the latest review article, the authors found that the reported prevalence of nickel contact allergy in patch tested children varied from 7.76% to 46.0% (178). Children become sensitized to nickel at an early age (63) and the exposures are numerous. Nickel sensitization may occur from the contact with jewelry, in particular earrings, metal buttons, zippers, hair clips, snaps, safety pins, jeans and belt buckles, coins, metal toys, medallions, magnets, keys, door handles, etc. (203-205). Cell phones, computers, and gaming devices have been reported as new causes of nickel sensitization (206-208).

Fragrance proved to be a common sensitizer in children as also demonstrated by others (147). Even small children are exposed (17, 209) and the prevalence of fragrance contact allergy increases with age (60). The frequency of fragrance allergy did not differ significantly between genders. This is in contrast to previous studies on adults that found a significant preponderance of women with contact allergy to fragrance (210, 211). This discrepancy is likely explained by the pattern of exposure to fragrance, which is likely to increase with age, especially for women.

Para-phenylenediamine (PPD) is a strong sensitizer (212) and accordingly, it was a common allergen among Danish children referred for patch testing. PPD gave a positive patch test reaction in 3.5% (n=88) of the children patch tested with PPD and 85.2% (n=75) of the reactions were considered relevant. The high prevalence of allergic contact dermatitis caused by PPD may be explained by new trends involving products containing PPD, especially temporary black henna tattoos and use of hair dye at a young age (213, 214), although patch test reactivity may also occur as a result of cross-sensitization with other allergens (212, 214, 215). Unfortunately, we have limited information on what exposures caused the sensitization

in our cohort but from our clinical experience, we find that common exposures are temporary black henna tattoos, hair dye, and eyelash- and brow tint.

Contact allergy to adhesive chemicals is a common problem (216) as also demonstrated in study I. Adhesive chemicals (colophonium, p-tert butyl formaldehyd resin, epoxy resin) gave positive patch test reactions in 3.2% (n=84) of the children. Although glues and adhesives are especially prevalent in occupations such as construction, manufacturing, packaging, and beauty salon industries, they are also relevant allergens in the pediatric population as they can be found in widely different consumer products. Cases of allergic contact dermatitis in children caused by adhesive chemicals have been reported from exposure to shoes (217), a temporary tattoo (218), a bra (219), athletic tape (220), a limp prosthesis (221), and orthopedic braces (222).

Three percent (n=79) of the patch tested children were sensitized to at least one rubber chemical (black rubber mix/IPPD, mercaptobenzothiazole, mercapto mix, thiuram mix, carba mix). Rubber chemicals are the main allergens responsible for shoe dermatitis in children (223, 224). Other exposures that have been reported to cause allergic contact dermatitis in children are balloons (225), rubber sponges used to apply cosmetics (226), and items used for sports (227) such as rubber balls (228) or shin guards (229). We found a significantly higher prevalence of contact allergy to rubber chemicals among boys and speculate that this could reflect a difference in the exposure pattern, i.e. boys could be more exposed to rubber from certain leisure activities and sports.

All children	1–4 years old	5–8 years old	9–12 years old	13–17 years old
Nickel sulfate (9.7)	Nickel sulfate (14.5)	Nickel sulfate (8.5)	Nickel sulfate (8.3)	Nickel sulfate (10.2)
Cobalt chloride (4.4)	Sesquiterpene lactone mix (4.5)	Cobalt chloride (3.5)	Cobalt chloride (6.2)	Cobalt chloride (4.0)
PPD (3.5)	MCI/MI (4.0)	PPD (3.4)	PPD (4.5)	PPD (3.2)
Fragrance mix I (2.5)	Potassium dichromate (2.6)	Sesquiterpene lactone mix (2.7)	Fragrance mix I (3.6)	Fragrance mix II (3.0)
Colophonium (2.4)	Cobalt chloride (2.6)	Fragrance mix I (2.2)	Colophonium (3.1)	Colophonium (2.3)

MCI/MI, methylchloroisothazolinone/methylisothiazolnine; PPD, *p*-phenylenediamine.

Table 3. Most frequent allergens from the European Baseline Series in children referred for patch testing.

6.2 Course of skin symptoms in children referred for patch testing

We showed that that there is a substantial risk of childhood eczema becoming chronic, regardless of the nature of the eczema. A significant share of the respondents still suffered from flare-ups of eczema at follow-up 2-10 years later and many suffered from persistent

eczema. Not surprisingly, atopic dermatitis was the single most important risk factor for having persistent eczema at follow-up, but even among the children and adolescents without diagnosed atopic dermatitis, the share of patients who suffered from persistent eczema was substantial. At baseline, all patients were suspected of having allergic contact dermatitis either as a complicating factor or as the main cause of disease. However, a positive patch test result was not found to affect the prognosis of eczema, which was also demonstrated in a similar study on adult patch tested patients (26).

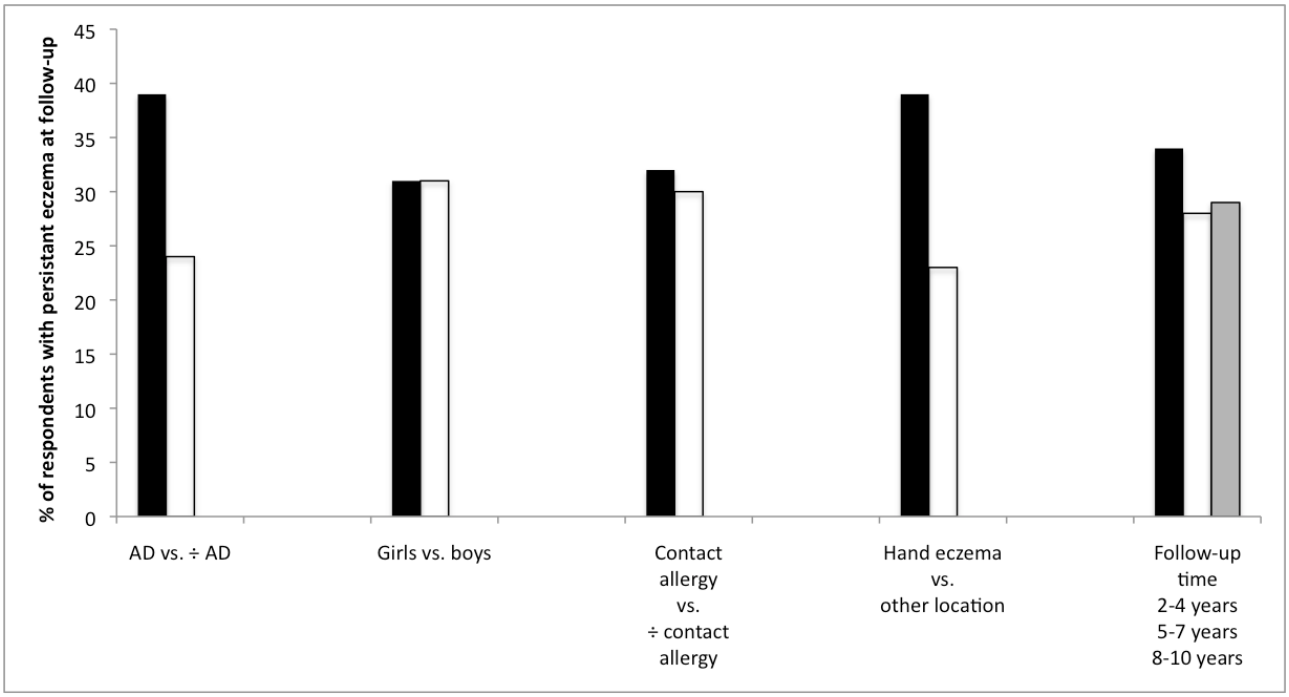

Figure 2. Predictors of having persistent eczema at follow-up.

There are several possible explanations for the large share of patients with ongoing skin symptoms in our study. First of all, the accuracy of patch testing depends on the competence of the tester (163) and requires careful consideration of exposures as well as selection of appropriate allergens for patch testing. We cannot completely reject the possibility that the patch testing in some cases was insufficient, i.e. the causative contact allergy may have been missed. Further, the benefits of patch testing depend on the patient's ability to avoid the allergen. Thus, the information given to the patient regarding the allergen as well as allergen avoidance is crucial (26, 27). The importance of patient education was reflected by the finding of Lewis et al. (30). Two to three months after patch testing, 27.6% of 105 adult patients did not recall receiving information regarding the outcome of the patch test and Woo et al. (26) found that 28% of patients felt that the result of the patch testing was insufficiently explained.

The inadequacy of the patient information will be reflected in the patients' difficulties in avoiding allergens and our results suggest that the patients who were diagnosed with allergic contact dermatitis may have had difficulties in adopting suitable avoidance behaviour. This can be a major challenge, as demonstrated by Clemmensen et al. (29). At two-year follow-up, 31% of 199 patients were still exposed to the causative occupational allergen. In line with this, Lewis et al. (30) found that out of 43 patients, only half were able to avoid the allergens concerned, and Agner et al. (230) found that 77.6% of 49 patients with formaldehyde allergy were still exposed to formaldehyde at follow-up 1-5 years after patch testing.

Another essential factor is the patient's ability to recall the results of the patch testing as well as the information given, in order to subsequently avoid the contact allergen (163) and it is possible that difficulties remembering the causative allergens played a role. In a Swedish study with follow-up one, 5 and 10 years after patch testing, 21% of patients did not even remember that they had a positive patch test reaction. For the patients who did remember, the ability to recall the specific allergen decreased over time and at 10-year follow-up only 17% percent were able to recall the correct allergen (163).

The diagnosis of atopic dermatitis was made by the dermatologist at the time of referral for patch testing. We cannot reject the possibility that atopic dermatitis in some cases were misclassified, which would help explain the large share with persistent skin symptoms. However, it is well known that contact dermatitis often results in chronic disease (28, 231), and it could also be that a share of the children and adolescents with skin symptoms not explained by atopic dermatitis or contact allergy, represent a group suffering from irritant contact dermatitis. Other differential diagnoses are nummular eczema, seborrheic dermatitis, and solar dermatitis.

Finally, it is possible that some of the children in our study developed new contact allergies from the time of primary patch testing to follow up. Mortz et al. (232) recently showed that the incidence rate of contact allergy increased from adolescence to adulthood.

Our results highlight two important issues: 1) There is a need of reminding patients of any positive patch test results, and this could be even more pronounced if the patch testing is carried out in childhood, where information is primarily given to the parents or caretakers. And 2) information and education is crucial in the management of patients with allergic contact dermatitis.

6.3 Quality of life among patients referred for patch testing

Persistent eczema was a strong and significant risk factor for having severely impaired life quality. The CDLQI/DLQI score was correlated to the severity of the eczema and patients with atopic dermatitis were more affected than patients without this diagnosis in both groups. This was somewhat expected as several studies have demonstrated that atopic dermatitis affects life quality significantly (233). In the majority of patients, however, persistent eczema only had a small to moderate effect on life quality. This could help explain why so many suffered from persistent eczema, i.e. if the impact on life quality is not perceived as significant, avoidance strategies in daily life are not implemented.

The life quality of adolescent girls was significantly more affected than that of adolescent boys. This age-dependent gender difference is in line with the findings of Gånemo et al. (234). Heisterberg et al. (106) reported the same pattern in adult patients with fragrance allergy. Thus, female eczema patients seem to be more affected than males, particularly after puberty. This could reflect that adolescent girls and young women are more concerned about appearance than males of the same age.

6.4 Contact allergy in children with atopic dermatitis

Contact allergy in children with atopic dermatitis is currently a “hot topic”. As the prevalent belief has been that these children were less likely to be sensitized, they are not routinely patch tested. The true prevalence of contact allergy and allergic contact dermatitis in children with atopic dermatitis is unknown, as most authors report patch test results from referred populations. The reported prevalence of contact allergy among children with atopic dermatitis referred for patch testing either because of recalcitrant atopic dermatitis or because of suspected allergic contact dermatitis, range from 22.7-88.9% (weighted average 41.7%) (104). In few studies, authors have patch tested unselected children with atopic dermatitis and sensitization rates range from 9.3-45.2% with a weighted average of 26.2%, which corresponds well to our findings. Among 100 children and adolescents with atopic dermatitis, 30% had one or more unacknowledged contact allergies and in 17% of the patients, the allergy was considered relevant to the current skin symptoms. Thus, our study confirms that contact allergy is common in children with atopic dermatitis and patch testing is relevant as a screening tool in the management of these patients.

As in other similar materials on children with atopic dermatitis, metals were the most common allergens. Previous studies have reported the same pattern of sensitization in adult patients (235-237) and an increased risk of metal contact allergy in patients with atopic dermatitis has been suggested (238, 239). Nickel has been shown to strongly bind to filaggrin (240) which has led to the hypothesis that filaggrin deficiency might facilitate percutaneous penetration of metal allergens (241).

Nickel is ubiquitous and continues to be the most common allergen in both children with and without atopic dermatitis (104, 147). However, in our study, cobalt chloride gave more positive reactions than nickel and chromium. This was unexpected but indeed very interesting, since cobalt was named allergen of the year in 2016. During recent years cobalt has received increased attention. Although many occupational exposures are well known (242), the knowledge regarding causative consumer exposures to cobalt have been limited (243). Recent reports have called attention to new cobalt exposure sources such as furniture (244), laptop computers (245), and cosmetics (246). The relevance of the positive reactions to cobalt chloride in our study was relatively low, which may reflect a need of searching for new sources of cobalt exposure. It should, however, be remembered that cobalt chloride is a strong sensitizer and may give irritant or doubtful reactions, as was also the case in our study. It is considered a difficult substance to use for testing (242, 247) and the risk of falsely interpreting reactions that are truly irritant in nature as positive reactions, is well known (248). Furthermore, authors have highlighted the difficulties of reproducing weak (+1) patch test reactions to cobalt chloride (247). Thus, it could be questioned whether the high number of positive reactions reflect true cobalt allergy.

Previous studies have suggested an increased risk of contact allergy to components in skin care products in children with atopic dermatitis (104), supporting the hypothesis that prolonged use of skin care products increases the risk of contact sensitization to both ingredients and vehicles. Our findings support this, as 8% of the children were sensitized to ingredients in skin care products, which is in line with the results of a recent Dutch study, (249) in which the authors found that children with atopic dermatitis were significantly more likely to have contact allergy to components of skin care products as compared to children without atopic dermatitis . In a general population study it was found that atopic dermatitis patients had a higher prevalence of contact allergy to ingredients in topical products than those without atopic dermatitis (250).

In several previous reports, authors have demonstrated a significantly higher prevalence of fragrance allergy in atopic dermatitis patients compared to patients without atopic dermatitis (65, 100, 235, 249, 251). However, we found a low prevalence of contact allergy to fragrance, which is in accordance with similar studies (103, 252-257). This may reflect a higher awareness among caregivers of children with atopic dermatitis, making them select fragrance-free emollients and skin care products.

A frequent concern expressed by caregivers is the possible adverse effects of topical corticosteroids. Since early childhood, children with atopic dermatitis are likely exposed to various topical treatments including topical corticosteroids. Although corticosteroids are not potent sensitizers (258), contact allergy and allergic contact dermatitis from topical corticosteroids is not infrequent (259). The combination of a dysfunctional skin barrier and the prolonged exposure should in theory increase the risk of sensitization to ingredients of the treatment products and in previous studies an association between atopic dermatitis and contact allergy to topical corticosteroids was suggested (258, 260). However, the reported frequencies of positive patch test reactions to corticosteroid markers in children with atopic dermatitis are low (254, 255, 257, 261), as was the case in our study. Diagnosing contact allergy to corticosteroids can be a major challenge and the particular importance of late readings, is well known (155, 156). All children were subjected to readings on day 7, which should limit the risk of missing late reactions. Even though contact allergy to corticosteroids, based on our data, does not seem to constitute a significant problem in children with atopic dermatitis, the possibility of a complicating contact allergy to topical steroids exists and should not be ignored in the evaluation of a child with recalcitrant atopic dermatitis.

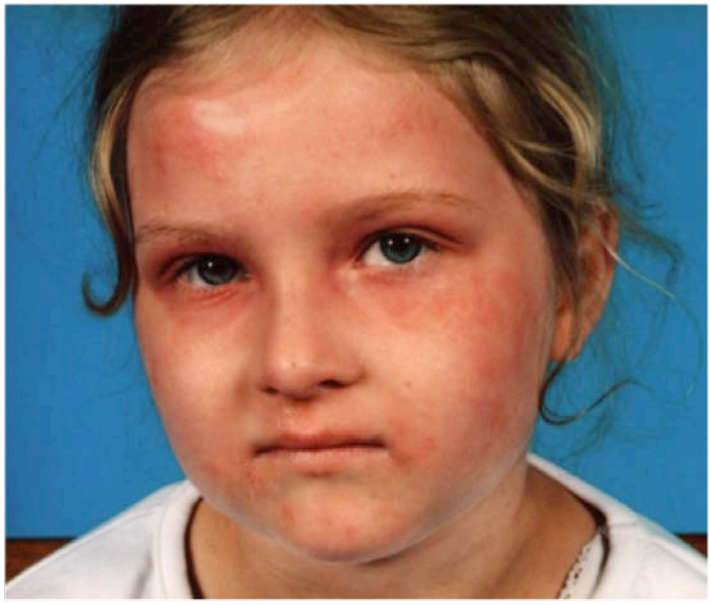

Figure 3. A girl with atopic dermatitis and compositae contact dermatitis.

Compositae contact allergy caused widespread dermatitis in three children. We used Sesquiterpene Lactone-mix (SL-mix) as a screen for compositae allergy. However, authors have previously pointed out that SL-mix is inadequate (262, 263) and it could be argued that adding compositae-mix would have provided a more thorough screen. Compositae allergy was previously considered uncommon in children (60, 264), but it has been suggested that this impression is due to an inadequate screen and that compositae allergy is in fact more common than formerly assumed (265). Patients with atopic dermatitis appear to be in greater risk of sensitization. In previous studies on patch test reactions in children, contact allergy to SL-mix was significantly associated to atopic dermatitis (104). In a study by Belloni Fortina et al. (264) 12 out of 17 children who reacted to compositae mix suffered from atopic dermatitis. Thus, it is reasonable to recommend that children with atopic dermatitis are patch tested with both SL- and compositae mix. Importantly, compositae contact dermatitis may mimic atopic dermatitis (97, 98) and the risk of misdiagnosing a child with atopic dermatitis who in fact suffers from compositae allergy should be kept in mind. Moreover, children, and especially those with atopic dermatitis, should be warned against topical use of cosmetics and herbal remedies containing compositae extracts (266).

6.5 Severity of atopic dermatitis and risk of contact allergy

We found a strong and significant correlation between the severity of atopic dermatitis and the risk of contact allergy. Although patients with severe atopic dermatitis in previous studies proved to be more difficult to sensitize to DNCB as compared to patients with mild atopic dermatitis (86, 90), recent clinical studies have demonstrated an association between atopic dermatitis disease severity and risk of contact allergy (65, 236, 257, 261), in line with our findings. This could reflect that children with severe atopic dermatitis are more exposed to various emollients and topical treatments as compared to children with limited skin involvement. It has also been suggested that the disturbed skin barrier and inherent immune alterations in atopic dermatitis promote the development of contact sensitization (267) and this may be even more pronounced in patients with severe skin symptoms. The fact that children with severe atopic dermatitis were more likely to be sensitized to contact allergens highlights the importance of patch testing children with atopic dermatitis. It is well known that contact allergy to certain allergens may mimic widespread atopic dermatitis (97-99) and it has even been suggested that contact sensitization could result in atopic dermatitis (96, 100). It is possible that the atopic dermatitis was in fact aggravated by the unacknowledged contact allergy, increasing the SCORAD and making the atopic dermatitis more severe.

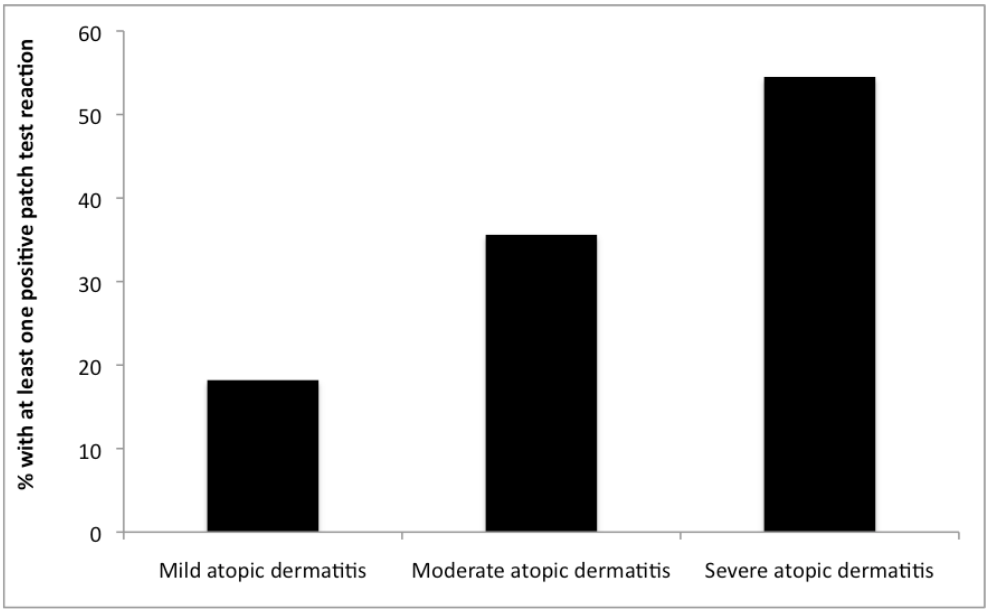

Figure 4. Share of children with mild, moderate and severe atopic dermatitis and at least one positive patch test reaction.

6.6 Localization of eczema and risk of contact allergy in children with atopic dermatitis

The risk of contact allergy was significantly increased in children with hand dermatitis, which is in accordance with a recent study by Isaksson et al. (103). Atopic dermatitis is a strong predisposing factor for hand eczema at any age and this may be even more pronounced in children (268-270). In a study by Mortz et al. (268), 24.5% of unselected children with atopic dermatitis had a history of hand eczema whereas this was only the case in 5.1% of the children without atopic dermatitis. Similarly, Dotterud et al. (71) found that 90% of children with hand eczema had atopic dermatitis. In a recent Danish study, the authors showed that atopic dermatitis increases the risk of early onset hand eczema, especially in atopic dermatitis patients with filaggrin mutations. Among filaggrin mutation carriers with atopic dermatitis, 40% developed hand eczema before the age of 6 years and 60% before the age of 18 (271). The association between hand eczema and contact allergy is well established (270, 272, 273). The hands are more exposed to the surrounding environment than any other body part and thus come into contact with several different allergens. In children, Toledo et al. (270) found that allergic contact dermatitis was the most common cause of hand eczema.

In agreement with a recent report by Heede et al. (269), our findings indicate that children with atopic dermatitis and hand eczema seem to be at greater risk of contact sensitization. As childhood hand eczema is considered the most important factor for the development of hand eczema in adulthood (274), early detection, or even better prevention, is extremely important.

7. Conclusion

In this thesis, we explored contact allergy and allergic contact dermatitis in children on several levels. First of all, we found that contact allergy and allergic contact dermatitis are common diagnoses in children and adolescents. One fourth of children and adolescents referred for patch testing in 12 different dermatology clinics during 2003-2011 had one or more contact allergies and the prevalence of allergic contact dermatitis was 16.7%. We demonstrated that, as in Danish adults, metals are the most common allergens in children, but also fragrances, hair dye, adhesive chemicals, and rubber chemicals are important causative agents. Our findings prove that patch testing is a valuable endeavor in children of all ages. Further, the results of our follow-up study indicated a significant risk of childhood eczema becoming chronic, regardless of the nature of the skin disease. Having persistent eczema was associated to severely affected life quality, emphasizing the importance of implementing preventive measures in order to avoid the development of contact allergy and allergic contact dermatitis. We also demonstrated the need for thorough and possibly repeated information for the children and caretakers, in order to implement sufficient avoidance behavior.
Finally and contrary to what was the prevailing opinion, we showed that children with atopic dermatitis may have unacknowledged contact allergies contributing to or maintaining the skin symptoms. Children with atopic dermatitis seem to be at greater risk of sensitization to certain allergens including metals and components of skin care products, and caregivers should be advised to use non-scented products with as few components as possible.
Based on this thesis we recommend that children with recalcitrant eczema or a history suggestive of allergic contact dermatitis are patch tested. If a relevant contact allergy is found, the child and the caretaker should receive thorough oral and written information of how to avoid the allergen and this information should be repeated regularly.
In children with atopic dermatitis, patch testing proved to be relevant as a screening tool and should always be performed in cases of recalcitrant skin symptoms, widespread dermatitis, hand dermatitis, or if allergic contact dermatitis is suspected from the child's history.

8. Future research

Although contact allergy in children is not a new research area, there are still several unanswered questions. Conducting the research for the present thesis has opened up several doors and brought new research questions into light.

With the National Database of Contact Allergy we have a unique opportunity to continuously monitor contact allergy in children. Repeating study I, i.e. analyzing data on children and adolescents referred for patch testing from 2012 till now will provide us with knowledge on trends in sensitization rates to different allergens and enable us to detect any changes in what allergens are the most common. This can be used in preventive measures.

One limitation of our follow-up study was that the diagnosis of persistent eczema was based on the patients answer to the questionnaire. It would be interesting to make a follow-up study with a clinical examination in order to grade and classify any persistent skin symptoms. In the same cohort, we would like to do a repeated patch testing in order to explore both the reproducibility of previous positive patch tests as well as the emergence of new contact allergies since the time of primary patch testing.

In the same manner, we would like to explore the issue of contact allergy in children with atopic dermatitis further. First of all, it would be valuable to conduct a follow-up study on the children with atopic dermatitis who were patch tested in study III, to determine the effect of allergen avoidance on the skin symptoms. As cobalt chloride, somewhat surprisingly, was the most common allergen in this group, it would be highly interesting to repeat the patch test in order to see if the positive patch test reactions to cobalt chloride could be reproduced, indicating true allergy. If so, more thorough exposure analyses as well as testing products with the cobalt spot test should be performed in order to establish the clinical relevance and throw light on cobalt exposure sources in children.

Our follow-up study indicated a need of thorough and repeated information about the causative allergen and instructions on allergen avoidance and we would like to explore this further. We would like to quantify the problem of remembering the information given concerning the result of patch testing as well as any difficulties in implementing avoidance behavior. A study exploring different information techniques and how to optimize instructions and information given to this patient group would also be highly valuable in the daily practice of the clinician.

English summary

Contact allergy is an acquired immunological response to cutaneous contact with specific allergens. It will manifest in the skin as allergic contact dermatitis. Contact allergy and allergic contact dermatitis was traditionally considered uncommon among children due to the widely held misconceptions that the immune system of children was immature and that children's exposure to contact allergens was limited.

The impaired skin barrier in atopic dermatitis facilitates the penetration of allergens. As children with atopic dermatitis are exposed to emollients and topical agents from an early age and for prolonged periods of time, this could theoretically increase the risk of contact sensitization. Whether hidden contact allergies can play a role in the skin symptoms in patients with atopic eczema and to what extent is unclear.

Early identification of the causative allergen and subsequent allergen avoidance is crucial in order to reduce the duration and durability of the disease and its progression, but how the positive or negative findings influence the course of skin symptoms in children referred for patch testing had never previously been explored.

This thesis consists of three studies: An epidemiological study, a follow-up study, and a clinical study. The overall objectives were 1) to estimate the prevalence of contact allergy in Danish children and adolescents referred for patch testing, 2) to investigate the course of skin symptoms and effect of contact allergy and allergic contact dermatitis on the children's quality of life, and 3) to assess the problem of contact allergy in children with atopic dermatitis.

Based on the results of the three studies we found that allergic contact dermatitis is a common diagnosis among Danish children and adolescents with eczema. The results of our follow-up study indicated that there is a significant risk of childhood eczema becoming chronic, regardless of the nature of the eczema, and that having persistent eczema is a strong and significant risk factor for having severely impaired life quality.

Finally, we showed that children with atopic dermatitis have unacknowledged contact allergies that may contribute to or maintain the skin symptoms. The risk of contact allergy was significantly correlated to the severity of atopic dermatitis. In children with atopic dermatitis, metals and components of topical skin care products were the most frequent sensitizers.

Dansk resumé

Kontaktallergi er et erhvervet immunologisk respons på hudkontakt med specifikke allergener. Det viser sig i huden som allergisk kontakteksem. Kontaktallergi og allergisk kontakteksem blev tidligere betragtet som sjældent blandt børn, fordi man opfattede barnets immunsystem som umodent, og fordi man mente at børns udsættelse for potentielle allergener var begrænset.

Den nedsatte hudbarriere hos børn med atopisk dermatitis faciliterer hudpenetrationen af allergener. Børn med atopisk dermatitis smøres, ofte fra den tidlige barnealder og i længere perioder, med fugtighedscremer og receptpligtige topikale behandlingsmidler, hvilket teoretisk set vil øge risikoen for kontaktallergi over for indholdsstofferne. Hvorvidt skjulte kontaktallergier spiller en rolle for hudsymptomerne hos patienter med atopisk dermatitis og i hvilken grad, er uafklaret.

Tidlig identificering og efterfølgende undgåelse af de allergifremkaldende stoffer, er afgørende for prognosen af allergisk kontakteksem. Forløbet af hudsymptomerne hos børn som er udredt for kontaktallergi med lappetest, er aldrig tidligere undersøgt.

Denne afhandling består af tre studier: En epidemiologisk undersøgelse, en follow-up undersøgelse og et klinisk studie.

De overordnede mål var 1) at estimere forekomsten af kontaktallergi hos danske børn og unge henvist til lappetest, 2) at undersøge forløbet af hudsymptomerne hos den samme gruppe børn og unge, samt vurdere hvorledes livskvaliteten påvirkes af kontaktallergi og allergisk kontakteksem og 3) at undersøge forekomsten af kontaktallergi og allergisk kontakteksem hos børn med atopisk dermatitis.

Baseret på resultaterne fra de tre undersøgelser fandt vi, at allergisk kontakteksem er en hyppig diagnose blandt danske børn og unge med eksem. Resultaterne af vores follow-up undersøgelse viste, at der er en betydelig risiko for, at eksemsygdom i barndommen bliver kronisk, uanset hvilken type eksem der er tale om, og at vedvarende eksem er en stærk og betydelig risikofaktor for nedsat livskvalitet.

Endelig viste vi, at børn med atopisk dermatitis meget vel kan have uerkendt kontaktallergi, der kan bidrage til eller forværre hudsymptomerne. Risikoen for kontaktallergi var signifikant korreleret med sværhedsgraden af atopisk dermatitis. Hos børn med atopisk dermatitis var metaller og indholdsstoffer i fugtighedscremer og hudplejeprodukter de hyppigste allergener.

References

1. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9(3):165-9.
2. Koppes SA, Engebretsen KA, Agner T, Angelova-Fischer I, Berents T, Brandner J, et al. Current knowledge on biomarkers for contact sensitization and allergic contact dermatitis. Contact Dermatitis. 2017;77(1):1-16. doi: 0.1111/cod.12789. Epub 2017 May 12.
3. Vocanson M, Hennino A, Rozieres A, Poyet G, Nicolas JF. Effector and regulatory mechanisms in allergic contact dermatitis. Allergy. 2009;64(12):1699-714. doi: 10.111/j.398-9995.2009.02082.x. Epub 2009 Oct 12.
4. Johansen JD, Frosch, P.J., Lepoittevin, J-P., editor. Contact Dermatitis 5ed. Berlin Heidelberg: Springer Verlag; 2011.
5. Textbook of Contact Dermatitis. 3rd ed. Rycroft RJG MT, Frosch PJ, Lepoittevin, J-P, editor. Berlin, Heidelberg, New York: Springer-Verlag; 2001.
6. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015;73(4):195-221. doi: 10.1111/cod.12432. Epub 2015 Jul 14.
7. Fregert S. Manual of Contact Dermatitis. Copenhagen: Munksgaard; 1974.
8. Lachapelle JM. Evolution of patch testing. Dermatitis. 2009;20(6):316-21.
9. Fisher AA. Contact Dermatitis. 3rd ed. Philadelphia: Lea & Febiger; 1986.
10. Weston WL, Weston JA. Allergic contact dermatitis in children. Am J Dis Child. 1984;138(10):932-6.
11. Rademaker M, Forsyth A. Contact dermatitis in children. Contact Dermatitis. 1989;20(2):104-7.
12. Beattie PE, Green C, Lowe G, Lewis-Jones MS. Which children should we patch test? Clin Exp Dermatol. 2007;32(1):6-11.
13. de Waard-van der Spek FB, Oranje AP. Patch tests in children with suspected allergic contact dermatitis: a prospective study and review of the literature. Dermatology. 2009;218(2):119-25.
14. de Waard-van der Spek FB, Darsow U, Mortz CG, Orton D, Worm M, Muraro A, et al. EAACI position paper for practical patch testing in allergic contact dermatitis in children. Pediatr Allergy Immunol. 2015;26(7):598-606. doi: 10.1111/pai.12463.
15. Jacob SE, Steele T, Brod B, Crawford GH. Dispelling the myths behind pediatric patch testing-experience from our tertiary care patch testing centers. Pediatr Dermatol. 2008;25(3):296-300.
16. Marcussen PV. Primary irritant patch-test reactions in children. Arch Dermatol. 1963;87:378-82.
17. Johnke H, Norberg LA, Vach W, Bindslev-Jensen C, Host A, Andersen KE. Reactivity to patch tests with nickel sulfate and fragrance mix in infants. Contact Dermatitis. 2004;51(3):141-7.
18. Mortz CG, Kjaer HF, Eller E, Osterballe M, Norberg LA, Host A, et al. Positive nickel patch tests in infants are of low clinical relevance and rarely reproducible. Pediatr Allergy Immunol. 2013;24(1):84-7.
19. Fisher AA. Allergic contact dermatitis in early infancy. Cutis. 1994;54(5):300-2.
20. Epstein E. Contact dermatitis in children. Pediatr Clin North Am. 1971;18(3):839-52.

21. Belloni Fortina A, Romano I, Peserico A, Eichenfield LF. Contact sensitization in very young children. J Am Acad Dermatol. 2011;65(4):772-9.
22. Jacob SE, Herro EM. Patch testing in young children should not be overlooked. Dermatitis. 2013;24(5):258-9.
23. Jacob SE, Burk CJ, Connelly EA. Patch testing: another steroid-sparing agent to consider in children. Pediatr Dermatol. 2008;25(1):81-7.
24. Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? Pediatrics. 2000;105(1):e3.
25. Rajagopalan R, Anderson R. Impact of patch testing on dermatology-specific quality of life in patients with allergic contact dermatitis. Am J Contact Dermat. 1997;8(4):215-21.
26. Woo PN, Hay IC, Ormerod AD. An audit of the value of patch testing and its effect on quality of life. Contact Dermatitis. 2003;48(5):244-7.
27. Thomson KF, Wilkinson SM, Sommer S, Pollock B. Eczema: quality of life by body site and the effect of patch testing. Br J Dermatol. 2002;146(4):627-30.
28. Holness DL. Results of a quality of life questionnaire in a patch test clinic population. Contact Dermatitis. 2001;44(2):80-4.
29. Clemmensen KK, Caroe TK, Thomsen SF, Ebbehoj NE, Agner T. Two-year follow-up survey of patients with allergic contact dermatitis from an occupational cohort: is the prognosis dependent on the omnipresence of the allergen? Br J Dermatol. 2014;170(5):1100-5. doi: 10.11/bjd.12795.
30. Lewis FM, Cork MJ, McDonagh AJ, Gawkrodger DJ. An audit of the value of patch testing: the patient's perspective. Contact Dermatitis. 1994;30(4):214-6.
31. Kadyk DL, McCarter K, Achen F, Belsito DV. Quality of life in patients with allergic contact dermatitis. J Am Acad Dermatol. 2003;49(6):1037-48.
32. Ramirez F, Chren MM, Botto N. A review of the impact of patch testing on quality of life in allergic contact dermatitis. J Am Acad Dermatol. 2017;76(5):1000-4. doi: 10.16/j.jaad.2016.12.011.
33. Coca AF. Studies in specific hypersensitiveness: VII. The age incidence of serumdisease and of dermatitis venenata as compared with that of the natural allergies. . J Immunol. 1922;7:193-9.
34. Spain WC. Studies in specific hypersensitiveness: VI. Dermatitis venenata. J Immunol. 1922;7:179-91.
35. Straus HW. Artificial sensitization of infants to poison ivy. The Journal of Allergy. 1931;2(3):7.
36. Kierland RR, McCleary JF. Contact dermatitis. Pediatr Clin North Am. 1956:649-64.
37. Marcussen PV. Specificity of epicutaneous tests in children. Preliminary report. Acta Derm Venereol. 1963;43:219-25.
38. Fregert S, Moller H. Contact allergy to balsam of Peru in children. Br J Dermatol. 1963;75:218-20.
39. Fontana VJ. Allergic dermatitis in children. J Med Soc N J. 1973;70(11):819-25.
40. Huntley CC. Atopic dermatitis and contact dermatitis in children. Am Fam Physician. 1977;16(2):111-8.
41. Levy A, Hanau D, Foussereau J. Contact dermatitis in children. Contact Dermatitis. 1980;6(4):260-2.

42. Veien NK, Hattel T, Justesen O, Norholm A. Contact dermatitis in children. Contact Dermatitis. 1982;8(6):373-5.
43. Pevny I, Brennenstuhl M, Razinskas G. Patch testing in children. (I) Collective test results; skin testability in children. Contact Dermatitis. 1984;11(4):201-6.
44. Pevny I, Brennenstuhl M, Razinskas G. Patch testing in children (II). Results and case reports. Contact Dermatitis. 1984;11(5):302-10.
45. Weston WL, Weston JA, Kinoshita J, Kloepfer S, Carreon L, Toth S, et al. Prevalence of positive epicutaneous tests among infants, children, and adolescents. Pediatrics. 1986;78(6):1070-4.
46. Romaguera C, Alomar A, Camarasa JM, Garcia Bravo B, Garcia Perez A, Grimalt F, et al. Contact dermatitis in children. Contact Dermatitis. 1985;12(5):283-4.
47. Mortz CG, Andersen KE. Allergic contact dermatitis in children and adolescents. Contact Dermatitis. 1999;41(3):121-30.
48. Simonsen AB, Deleuran M, Johansen JD, Sommerlund M. Contact allergy and allergic contact dermatitis in children - a review of current data. Contact Dermatitis. 2011;65(5):254-65.
49. Lembo S, Lembo C, Patruno C, Cuomo P, Ayala F, Balato N, et al. Contact sensitization of children referred to the Dermatology Department of the University Federico II of Naples, Italy: a two-decade years history. G Ital Dermatol Venereol. 2017:05466-9.
50. Ortiz Salvador JM, Esteve Martinez A, Subiabre Ferrer D, Victoria Martinez AM, de la Cuadra Oyanguren J, Zaragoza Ninet V. Pediatric Allergic Contact Dermatitis: Clinical and Epidemiological Study in a Tertiary Hospital. Actas Dermosifiliogr. 2017:018.
51. Ascha M, Irfan M, Bena J, Taylor JS, Sood A. Pediatric patch testing: A 10-year retrospective study. Ann Allergy Asthma Immunol. 2016;117(6):661-7. doi: 10.1016/j.anai.2016.09.445.
52. Lubbes S, Rustemeyer T, Sillevis Smitt JH, Schuttelaar ML, Middelkamp-Hup MA. Contact sensitization in Dutch children and adolescents with and without atopic dermatitis - a retrospective analysis. Contact Dermatitis. 2017;76(3):151-9. doi: 10.1111/cod.12711. Epub 2016 Nov 11.
53. Meena S, Garg T, Chander R. Patch Testing in Children and Adolescents With Suspected Allergic Contact Dermatitis. Skinmed. 2016;14(4):253-8. eCollection 2016.
54. Goldenberg A, Mousdicas N, Silverberg N, Powell D, Pelletier JL, Silverberg JI, et al. Pediatric Contact Dermatitis Registry Inaugural Case Data. Dermatitis. 2016;27(5):293-302. doi: 10.1097/DER.0000000000000214.
55. Mortazavi H, Ehsani A, Sajjadi SS, Aghazadeh N, Arian E. Patch testing in Iranian children with allergic contact dermatitis. BMC Dermatol. 2016;16(1):10. doi: .1186/s12895-016-0047-0.
56. Belloni Fortina A, Fontana E, Peserico A. Contact Sensitization in Children: A Retrospective Study of 2,614 Children from a Single Center. Pediatr Dermatol. 2016;33(4):399-404. doi: 10.1111/pde.12873. Epub 2016 May 31.
57. Rodrigues DF, Goulart EM. Patch test results in children and adolescents. Study from the Santa Casa de Belo Horizonte Dermatology Clinic, Brazil, from 2003 to 2010. An Bras Dermatol. 2015;90(5):671-83. doi: 10.1590/abd806-4841.20153902.
58. Smith VM, Clark SM, Wilkinson M. Allergic contact dermatitis in children: trends in allergens, 10 years on. A retrospective study of 500 children tested between 2005 and 2014 in one UK centre. Contact Dermatitis. 2016;74(1):37-43. doi: 10.1111/cod.12489. Epub 2015 Nov 13.

59. Bhat YJ, Hassan I, Akhter S, Rasool F, Mubashir S. Patch testing in children: An experience from Kashmir. Indian J Dermatol Venereol Leprol. 2016;82(2):186-8. doi: 10.4103/0378-6323.168938.
60. Belloni Fortina A, Cooper SM, Spiewak R, Fontana E, Schnuch A, Uter W. Patch test results in children and adolescents across Europe Analysis of the ESSCA Network feminine 2002-2010. Pediatr Allergy Immunol. 2015:12397.
61. Zug KA, Pham AK, Belsito DV, DeKoven JG, DeLeo VA, Fowler JF, Jr., et al. Patch testing in children from 2005 to 2012: results from the North American contact dermatitis group. Dermatitis. 2014;25(6):345-55. doi: 10.1097/DER.0000000000000083.
62. Vongyer GA, Green C. Allergic contact dermatitis in children; has there been a change in allergens? Clin Exp Dermatol. 2015;40(1):31-4. doi: 10.1111/ced.12460. Epub 2014 Sep 23.
63. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing - a nationwide multicentre study. Contact Dermatitis. 2014;70(2):104-11.
64. Schena D, Papagrigoraki A, Tessari G, Peroni A, Sabbadini C, Girolomoni G. Allergic contact dermatitis in children with and without atopic dermatitis. Dermatitis. 2012;23(6):275-80.
65. Herro EM, Matiz C, Sullivan K, Hamann C, Jacob SE. Frequency of contact allergens in pediatric patients with atopic dermatitis. J Clin Aesthet Dermatol. 2011;4(11):39-41.
66. Kuljanac I, Knezevic E, Cvitanovic H. Epicutaneous patch test results in children and adults with allergic contact dermatitis in Karlovac county: a retrospective survey. Acta Dermatovenerol Croat. 2011;19(2):91-7.
67. Moustafa M, Holden CR, Athavale P, Cork MJ, Messenger AG, Gawkrodger DJ. Patch testing is a useful investigation in children with eczema. Contact Dermatitis. 2011;65(4):208-12.
68. Jacob SE, Herro EM, Sullivan K, Matiz C, Eichenfield L, Hamann C. Safety and efficacy evaluation of TRUE TEST panels 1.1, 2.1, and 3.1 in children and adolescents. Dermatitis. 2011;22(4):204-10.
69. Röckl H, Müller, E., Hiltermann, W. Zum Aussagewert positiver Epicutantests bei Säuglingen und Kindern. Archv für klinische und experimentelle Dermatologie. 1966;226:407-19.
70. Barros MA, Baptista A, Correia TM, Azevedo F. Patch testing in children: a study of 562 schoolchildren. Contact Dermatitis. 1991;25(3):156-9.
71. Dotterud LK, Falk ES. Contact allergy in relation to hand eczema and atopic diseases in north Norwegian schoolchildren. Acta Paediatr. 1995;84(4):402-6.
72. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Acta Derm Venereol. 2002;82(5):352-8.
73. Machovcova A. The frequency of contact allergy in children and adolescents in the Czech Republic. Acta Dermatovenerol Croat. 2012;20(2):75-9.
74. Friedmann PS, Holden C.A. Rook's Textbook of Dermatology. In: Burns T BS, Cox N, Griffiths C, editor. 1. 7 ed: Blackwell Publishing Company; 2004.
75. Sabin BR, Peters N, Peters AT. Chapter 20: Atopic dermatitis. Allergy Asthma Proc. 2012;33 Suppl 1:S67-9.

76. Williams HC. Epidemiology of atopic dermatitis. Clin Exp Dermatol. 2000;25(7):522-9.
77. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483-94. doi: 10.056/NEJMra074081.
78. Eyerich K, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. Allergy. 2013;68(8):974-82. doi: 10.1111/all.12184. Epub 2013 Jul 29.
79. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. Allergol Int. 2013;62(2):151-61. doi: 10.2332/allergolint.13-RAI-0564.
80. Halling-Overgaard AS, Kezic S, Jakasa I, Engebretsen KA, Maibach H, Thyssen JP. Skin absorption through atopic dermatitis skin: a systematic review. Br J Dermatol. 2016:15065.
81. Cabanillas B, Novak N. Atopic dermatitis and filaggrin. Curr Opin Immunol. 2016;42:1-8.(doi):10.1016/j.coi.2016.05.002. Epub May 17.
82. Harding CR, Aho S, Bosko CA. Filaggrin - revisited. Int J Cosmet Sci. 2013;35(5):412-23. doi: 10.1111/ics.12049. Epub 2013 Apr 18.
83. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 2014;134(4):792-9. doi: 10.1016/j.jaci.2014.06.014. Epub Jul 25.
84. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38(4):441-6.
85. Epstein S, Mohajerin AH. Incidence of Contact Sensitivity in Atopic Dermatitis. Arch Dermatol. 1964;90:284-7.
86. Forsbeck M, Hovmark A, Skog E. Patch testing, tuberculin testing and sensitization with dinitrochlorobenzene and nitrosodimethylanilini of patients with atopic dermatitis. Acta Derm Venereol. 1976;56(2):135-8.
87. Palacios J, Fuller EW, Blaylock WK. Immunological capabilities of patients with atopic dermatitis. J Invest Dermatol. 1966;47(5):484-90.
88. Jones HE, Lewis CW, McMarlin SL. Allergic contact sensitivity in atopic dermatitis. Arch Dermatol. 1973;107(2):217-22.
89. Rees J, Friedmann PS, Matthews JN. Contact sensitivity to dinitrochlorobenzene is impaired in atopic subjects. Controversy revisited. Arch Dermatol. 1990;126(9):1173-5.
90. Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. Arch Dermatol. 1989;125(3):366-8.
91. Rystedt I. Contact sensitivity in adults with atopic dermatitis in childhood. Contact Dermatitis. 1985;13(1):1-8.
92. Thyssen JP, Johansen JD, Linneberg A, Menne T, Engkilde K. The association between contact sensitization and atopic disease by linkage of a clinical database and a nationwide patient registry. Allergy. 2012;67(9):1157-64.
93. Martin SF. Immunological mechanisms in allergic contact dermatitis. Curr Opin Allergy Clin Immunol. 2015;15(2):124-30. doi: 10.1097/ACI.0000000000000142.
94. Thyssen JP, McFadden JP, Kimber I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. Allergy. 2014;69(1):28-36. doi: 10.1111/all.12358. Epub 2013 Dec 26.
95. McFadden JP, Dearman RJ, White JM, Basketter DA, Kimber I. The Hapten-Atopy hypothesis II: the 'cutaneous hapten paradox'. Clin Exp Allergy. 2011;41(3):327-37. doi: 10.1111/j.365-2222.010.03684.x. Epub 2011 Jan 24.

96. Calnan CD. Nickel dermatitis. Br J Dermatol. 1956;68(7):229-36.
97. Crounse RG. Plant dermatitis due to the Compositae (Asteraceae) family. J Am Acad Dermatol. 1980;2(5):417-24.
98. Aerts O, Cattaert N, Lambert J, Goossens A. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. Contact Dermatitis. 2013;68(4):250-1.
99. Mohamoud AA, Andersen F. Allergic contact dermatitis caused by textile dyes mimicking atopic dermatitis. Contact Dermatitis. 2017;76(2):119-20. doi: 10.1111/cod.12630.
100. Thyssen JP, Linneberg A, Engkilde K, Menne T, Johansen JD. Contact sensitization to common haptens is associated with atopic dermatitis: new insight. Br J Dermatol. 2012;166(6):1255-61.
101. Fontana E, Belloni Fortina A. Allergic contact dermatitis in children. G Ital Dermatol Venereol. 2014;149(6):693-701. Epub 2014 Oct 15.
102. Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R. A half of schoolchildren with 'ISAAC eczema' are ill with allergic contact dermatitis. J Eur Acad Dermatol Venereol. 2011;25(9):1104-7. doi: 10.11/j.468-3083.2010.03885.x. Epub 2010 Nov 4.
103. Isaksson M, Olhardt S, Radehed J, Svensson A. Children with Atopic Dermatitis Should Always be Patch-tested if They Have Hand or Foot Dermatitis. Acta Derm Venereol. 2015;95(5):583-6. doi: 10.2340/00015555-1995.
104. Simonsen AB, Johansen JD, Deleuran M, Mortz CG, Sommerlund M. Contact allergy in children with atopic dermatitis: a systematic review. Br J Dermatol. 2017:15628.
105. Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomas-Aragones L, et al. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. Br J Dermatol. 2017;176(5):1170-8. doi: 10.11/bjd.15280. Epub 2017 Apr 10.
106. Heisterberg MV, Menne T, Johansen JD. Fragrance allergy and quality of life - a case-control study. Contact Dermatitis. 2014;70(2):81-9. doi: 10.1111/cod.12128.
107. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006;155(1):145-51.
108. Amaral CS, March Mde F, Sant'Anna CC. Quality of life in children and teenagers with atopic dermatitis. An Bras Dermatol. 2012;87(5):717-23.
109. Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. Br J Dermatol. 2004;150(2):284-90.
110. Randa H, Todberg T, Skov L, Larsen LS, Zachariae R. Health-related Quality of Life in Children and Adolescents with Psoriasis: A Systematic Review and Meta-analysis. Acta Derm Venereol. 2017;97(5):555-63. doi: 10.2340/00015555-2600.
111. Dertlioglu SB, Cicek D, Balci DD, Halisdemir N. Dermatology life quality index scores in children with vitiligo: comparison with atopic dermatitis and healthy control subjects. Int J Dermatol. 2013;52(1):96-101.
112. [Available from: https://www.collinsdictionary.com.
113. Wells GA, Russell AS, Haraoui B, Bissonnette R, Ware CF. Validity of quality of life measurement tools--from generic to disease-specific. J Rheumatol Suppl. 2011;88:2-6.(doi):10.3899/jrheum.110906.
114. Halioua B, Beumont MG, Lunel F. Quality of life in dermatology. Int J Dermatol. 2000;39(11):801-6.

115. Skoet R, Zachariae R, Agner T. Contact dermatitis and quality of life: a structured review of the literature. Br J Dermatol. 2003;149(3):452-6.
116. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outcomes. 2006;4:35.
117. Chamlin SL, Chren, M-M. Quality-of-life outcomes and measurement in childhood atopic dermatitis. Immunol Allergy Clin North Am. 2010;30(3):281-8.
118. Martin AR, Lookingbill DP, Botek A, Light J, Thiboutot D, Girman CJ. Health-related quality of life among patients with facial acne -- assessment of a new acne-specific questionnaire. Clin Exp Dermatol. 2001;26(5):380-5.
119. Lilly E, Lu PD, Borovicka JH, Victorson D, Kwasny MJ, West DP, et al. Development and validation of a vitiligo-specific quality-of-life instrument (VitiQoL). J Am Acad Dermatol. 2013;69(1):e11-8. doi: 0.1016/j.jaad.2012.01.038. Epub Feb 25.
120. Vinding GR, Christensen KB, Esmann S, Olesen AB, Jemec GB. Quality of life in non-melanoma skin cancer--the skin cancer quality of life (SCQoL) questionnaire. Dermatol Surg. 2013;39(12):1784-93. doi: 10.111/dsu.12353. Epub 2013 Nov 14.
121. Ofenloch RF, Weisshaar E, Dumke AK, Molin S, Diepgen TL, Apfelbacher C. The Quality of Life in Hand Eczema Questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. Br J Dermatol. 2014;171(2):304-12. doi: 10.1111/bjd.12819. Epub 2014 Jun 18.
122. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726-39. Epub 007 Nov 8.
123. Heisterberg MV, Menne T, Johansen JD. Fragrance allergy and quality of life - development and validation of a disease-specific quality of life instrument. Contact Dermatitis. 2013:12153.
124. Ayala F, Nino M, Fabbrocini G, Panariello L, Balato N, Foti C, et al. Quality of life and contact dermatitis: a disease-specific questionnaire. Dermatitis. 2010;21(2):84-90.
125. Menne T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis. 2011;65(1):3-12.
126. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132(6):942-9.
127. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
128. Finlay AY. Quality of life measurement in dermatology: a practical guide. Br J Dermatol. 1997;136(3):305-14.
129. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23-31.
130. Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996-2009. Br J Dermatol. 2011;164(6):1316-25. doi: 10.111/j.65-2133.011.10253.x. Epub 2011 May 11.
131. Zirwas MJ, Stechschulte SA. Moisturizer allergy: diagnosis and management. J Clin Aesthet Dermatol. 2008;1(4):38-44.
132. Curry EJ, Warshaw EM. Benzyl alcohol allergy: importance of patch testing with personal products. Dermatitis. 2005;16(4):203-8.
133. Jacob SE, Barron GS. Benzyl alcohol: a covert fragrance. Dermatitis. 2007;18(4):232-3.

134. White MI. Contact dermatitis from ethylenediamine. Contact Dermatitis. 1978;4(5):291-3.
135. Goossens A, Baret I, Swevers A. Allergic contact dermatitis caused by tetrahydroxypropyl ethylenediamine in cosmetic products. Contact Dermatitis. 2011;64(3):161-4. doi: 10.1111/j.600-0536.2010.01823.x.
136. Pruitt C, Warshaw EM. Allergic contact dermatitis from ethylenediaminetetraacetic Acid. Dermatitis. 2010;21(2):121-2.
137. Hogan DJ. Allergic contact dermatitis to ethylenediamine. A continuing problem. Dermatol Clin. 1990;8(1):133-6.
138. Chow ET, Avolio AM, Lee A, Nixon R. Frequency of positive patch test reactions to preservatives: The Australian experience. Australas J Dermatol. 2013;54(1):31-5. doi: 10.1111/j.440-0960.2012.00958.x. Epub 2012 Oct 22.
139. Travassos AR, Claes L, Boey L, Drieghe J, Goossens A. Non-fragrance allergens in specific cosmetic products. Contact Dermatitis. 2011;65(5):276-85. doi: 10.1111/j.600-0536.2011.01968.x. Epub 2011 Sep 21.
140. Schnuch A, Mildau G, Kratz EM, Uter W. Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. Contact Dermatitis. 2011;65(3):167-74. doi: 10.1111/j.600-0536.2011.01939.x. Epub 2011 Jun 21.
141. Rastogi SC, Johansen JD, Menne T, Frosch P, Bruze M, Andersen KE, et al. Contents of fragrance allergens in children's cosmetics and cosmetic-toys. Contact Dermatitis. 1999;41(2):84-8.
142. Schnuch A, Uter W, Geier J, Lessmann H, Frosch PJ. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis. 2007;57(1):1-10.
143. Schmutz JL, Barbaud A, Trechot P. [Contact allergy to triethanolamine in ear drops and shampoo]. Ann Dermatol Venereol. 2007;134(1):105.
144. Chu CY, Sun CC. Allergic contact dermatitis from triethanolamine in a sunscreen. Contact Dermatitis. 2001;44(1):41-2.
145. Silva EA, Bosco MR, Mozer E. Study of the frequency of allergens in cosmetics components in patients with suspected allergic contact dermatitis. An Bras Dermatol. 2012;87(2):263-8.
146. Manzini BM, Ferdani G, Simonetti V, Donini M, Seidenari S. Contact sensitization in children. Pediatr Dermatol. 1998;15(1):12-7.
147. Bonitsis NG, Tatsioni A, Bassioukas K, Ioannidis JP. Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis. Contact Dermatitis. 2011;64(5):245-57.
148. Admani S, Jacob SE. Allergic contact dermatitis in children: review of the past decade. Curr Allergy Asthma Rep. 2014;14(4):421.
149. Jacob SE, Yang A, Herro E, Zhang C. Contact allergens in a pediatric population: association with atopic dermatitis and comparison with other north american referral centers. J Clin Aesthet Dermatol. 2010;3(10):29-35.
150. Hjorth N. Contact dermatitis in children. Acta Derm Venereol Suppl (Stockh). 1981;95:36-9.
151. Zug KA, McGinley-Smith D, Warshaw EM, Taylor JS, Rietschel RL, Maibach HI, et al. Contact allergy in children referred for patch testing: North American Contact Dermatitis Group data, 2001-2004. Arch Dermatol. 2008;144(10):1329-36.

152. Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. Pediatr Dermatol. 2005;22(1):1-5.
153. Roul S, Ducombs G, Taieb A. Usefulness of the European standard series for patch testing in children. A 3-year single-centre study of 337 patients. Contact Dermatitis. 1999;40(5):232-5.
154. Torp Madsen J, Andersen KE. Outcome of a second patch test reading of TRUE Tests(R) on D6/7. Contact Dermatitis. 2013;68(2):94-7.
155. Isaksson M. Corticosteroid contact allergy--the importance of late readings and testing with corticosteroids used by the patients. Contact Dermatitis. 2007;56(1):56-7.
156. Dooms-Goossens A, Degreef H. Clinical aspects of contact allergy to corticosteroids. Dermatology. 1994;189(Suppl 2):54-5.
157. Encyclopedia of Research Design Salkind NJ, editor. California, United States of America: SAGE Publications, Inc.; 2010.
158. Jones S, Murphy F, Edwards M, James J. Doing things differently: advantages and disadvantages of Web questionnaires. Nurse Res. 2008;15(4):15-26.
159. Cartwright A. Interviews or postal questionnaires? Comparisons of data about women's experiences with maternity services. Milbank Q. 1988;66(1):172-89.
160. Kongsved SM, Basnov M, Holm-Christensen K, Hjollund NH. Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions. J Med Internet Res. 2007;9(3):e25.
161. Zuidgeest M, Hendriks M, Koopman L, Spreeuwenberg P, Rademakers J. A comparison of a postal survey and mixed-mode survey using a questionnaire on patients' experiences with breast care. J Med Internet Res. 2011;13(3):e68. doi: 10.2196/jmir.1241.
162. Mindell J, Aresu M, Becares L, Tolonen H. Representativeness of participants in a cross-sectional health survey by time of day and day of week of data collection. Eur J Public Health. 2012;22(3):364-9. doi: 10.1093/eurpub/ckr093. Epub 2011 Sep 29.
163. Jamil WN, Erikssohn I, Lindberg M. How well is the outcome of patch testing remembered by the patients? A 10-year follow-up of testing with the Swedish baseline series at the Department of Dermatology in Orebro, Sweden. Contact Dermatitis. 2012;66(4):215-20.
164. Kotaniemi JT, Hassi J, Kataja M, Jonsson E, Laitinen LA, Sovijarvi AR, et al. Does non-responder bias have a significant effect on the results in a postal questionnaire study? Eur J Epidemiol. 2001;17(9):809-17.
165. Nijsten T. Dermatology life quality index: time to move forward. J Invest Dermatol. 2012;132(1):11-3. doi: 0.1038/jid.2011.354.
166. Hanifin JM RG. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;92:44-7.
167. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol. 2008;158(4):754-65. doi: 10.1111/j.365-2133.007.08412.x. Epub 2008 Jan 30.
168. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131(3):383-96.
169. Williams HC, Burney PG, Strachan D, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. Br J Dermatol. 1994;131(3):397-405.

170. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White IR. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. Contact Dermatitis. 1999;41(5):241-50.
171. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing - a nationwide multicentre study. Contact Dermatitis. 2013.
172. Moorcraft SY, Marriott C, Peckitt C, Cunningham D, Chau I, Starling N, et al. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. Trials. 2016;17:17.(doi):10.1186/s13063-015-1105-3.
173. Godskesen T, Hansson MG, Nygren P, Nordin K, Kihlbom U. Hope for a cure and altruism are the main motives behind participation in phase 3 clinical cancer trials. Eur J Cancer Care (Engl). 2015;24(1):133-41. doi: 10.1111/ecc.12184. Epub 2014 Jan 28.
174. Clayton TH, Wilkinson SM, Rawcliffe C, Pollock B, Clark SM. Allergic contact dermatitis in children: should pattern of dermatitis determine referral? A retrospective study of 500 children tested between 1995 and 2004 in one U.K. centre. Br J Dermatol. 2006;154(1):114-7.
175. Kuiters GR, Smitt JH, Cohen EB, Bos JD. Allergic contact dermatitis in children and young adults. Arch Dermatol. 1989;125(11):1531-3.
176. Pambor M, Kruger G, Winkler S. Results of patch testing in children. Contact Dermatitis. 1992;27(5):326-8.
177. Stables GI, Forsyth A, Lever RS. Patch testing in children. Contact Dermatitis. 1996;34(5):341-4.
178. Rodrigues DF, Goulart EM. Patch-test results in children and adolescents: systematic review of a 15-year period. An Bras Dermatol. 2016;91(1):64-72. doi: 10.1590/abd806-4841.20163927.
179. Hogeling M, Pratt M. Allergic contact dermatitis in children: the Ottawa hospital patch-testing clinic experience, 1996 to 2006. Dermatitis. 2008;19(2):86-9.
180. Fernandez Vozmediano JM, Armario Hita JC. Allergic contact dermatitis in children. J Eur Acad Dermatol Venereol. 2005;19(1):42-6.
181. Thyssen JP. Nickel and cobalt allergy before and after nickel regulation--evaluation of a public health intervention. Contact Dermatitis. 2011;65(Suppl 1):1-68. doi: 10.1111/j.600-0536.2011.01957.x.
182. Menne T, Rasmussen K. Regulation of nickel exposure in Denmark. Contact Dermatitis. 1990;23(1):57-8.
183. Garg S, Thyssen JP, Uter W, Schnuch A, Johansen JD, Menne T, et al. Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. Br J Dermatol. 2013;169(4):854-8. doi: 10.1111/bjd.12556.
184. Wohrl S, Hemmer W, Focke M, Gotz M, Jarisch R. Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. Pediatr Dermatol. 2003;20(2):119-23.
185. Balato N, Lembo G, Patruno C, Ayala F. Patch testing in children. Contact Dermatitis. 1989;20(4):305-7.
186. Sevila A, Romaguera C, Vilaplana J, Botella R. Contact dermatitis in children. Contact Dermatitis. 1994;30(5):292-4.
187. Wilkowska A, Grubska-Suchanek E, Karwacka I, Szarmach H. Contact allergy in children. Cutis. 1996;58(2):176-80.

188. Uhr JW, Dancis J, Neumann CG. Delayed-type hypersensitivity in premature neonatal humans. Nature. 1960;187:1130-1.
189. Epstein WL. Contact-type delayed hypersensitivity in infants and children: Induction of rhus sensitivity. Pediatrics. 1961(27):51-3.
190. Motolese A MB, Donini M. . Patch testing in infants. Am J Contact Dermat. 1995;6:153-6.
191. Milingou M, Tagka A, Armenaka M, Kimpouri K, Kouimintzis D, Katsarou A. Patch tests in children: a review of 13 years of experience in comparison with previous data. Pediatr Dermatol. 2010;27(3):255-9.
192. Onder M, Adisen E. Patch test results in a Turkish paediatric population. Contact Dermatitis. 2008;58(1):63-5.
193. Duarte I, Lazzarini R, Kobata CM. Contact dermatitis in adolescents. Am J Contact Dermat. 2003;14(4):200-2.
194. Kwangsukstith C, Maibach HI. Effect of age and sex on the induction and elicitation of allergic contact dermatitis. Contact Dermatitis. 1995;33(5):289-98.
195. Modjtahedi BS, Modjtahedi SP, Maibach HI. The sex of the individual as a factor in allergic contact dermatitis. Contact Dermatitis. 2004;50(2):53-9.
196. Walton S, Nayagam AT, Keczkes K. Age and sex incidence of allergic contact dermatitis. Contact Dermatitis. 1986;15(3):136-9.
197. Czarnobilska E, Obtulowicz K, Dyga W, Wsolek-Wnek K, Spiewak R. Contact hypersensitivity and allergic contact dermatitis among school children and teenagers with eczema. Contact Dermatitis. 2009;60(5):264-9.
198. Veien NK, Hattel T, Justesen O, Norholm A. Why do young girls become nickel sensitive? Contact Dermatitis. 1986;15(5):306-7.
199. Goncalo S, Goncalo M, Azenha A, Barros MA, Bastos AS, Brandao FM, et al. Allergic contact dermatitis in children. A multicenter study of the Portuguese Contact Dermatitis Group (GPEDC). Contact Dermatitis. 1992;26(2):112-5.
200. Diepgen TL, Ofenloch RF, Bruze M, Bertuccio P, Cazzaniga S, Coenraads PJ, et al. Prevalence of contact allergy in the general population in different European regions. Br J Dermatol. 2016;174(2):319-29. doi: 10.1111/bjd.14167. Epub 2015 Dec 26.
201. Uter W, Gefeller O, Gimenez-Arnau A, Frosch P, Duus Johansen J, Schuttelaar ML, et al. Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009-2012. Contact Dermatitis. 2015;73(2):82-90. doi: 10.1111/cod.12409. Epub 2015 May 13.
202. Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: results from two cross-sectional studies. Contact Dermatitis. 2009;61(6):342-8. doi: 10.1111/j.600-0536.2009.01625.x. Epub 2009 Oct 6.
203. Tuchman M, Silverberg JI, Jacob SE, Silverberg N. Nickel contact dermatitis in children. Clin Dermatol. 2015;33(3):320-6. doi: 10.1016/j.clindermatol.2014.12.008. Epub Dec 8.
204. Jacob SE, Goldenberg A, Pelletier JL, Fonacier LS, Usatine R, Silverberg N. Nickel Allergy and Our Children's Health: A Review of Indexed Cases and a View of Future Prevention. Pediatr Dermatol. 2015;32(6):779-85. doi: 10.1111/pde.12639. Epub 2015 Jul 27.
205. Silverberg NB, Licht J, Friedler S, Sethi S, Laude TA. Nickel contact hypersensitivity in children. Pediatr Dermatol. 2002;19(2):110-3.

206. Thyssen JP, Johansen JD, Zachariae C, Menne T. The outcome of dimethylglyoxime testing in a sample of cell phones in Denmark. Contact Dermatitis. 2008;59(1):38-42.
207. Jacob SE. Xbox--a source of nickel exposure in children. Pediatr Dermatol. 2014;31(1):115-6.
208. Jensen P, Jellesen MS, Moller P, Frankild S, Johansen JD, Menne T, et al. Nickel allergy and dermatitis following use of a laptop computer. J Am Acad Dermatol. 2012;67(4):e170-1. doi: 10.1016/j.jaad.2012.01.033.
209. Jacob SE, Castanedo-Tardan MP. Alternatives for fragrance-allergic children. Pediatr Ann. 2008;37(2):102-3.
210. Heisterberg MV, Andersen KE, Avnstorp C, Kristensen B, Kristensen O, Kaaber K, et al. Fragrance mix II in the baseline series contributes significantly to detection of fragrance allergy. Contact Dermatitis. 2010;63(5):270-6.
211. Thyssen JP, Carlsen BC, Menne T, Johansen JD. Trends of contact allergy to fragrance mix I and Myroxylon pereirae among Danish eczema patients tested between 1985 and 2007. Contact Dermatitis. 2008;59(4):238-44.
212. DeLeo VA. p-Phenylenediamine. Dermatitis. 2006;17(2):53-5.
213. Spornraft-Ragaller P, Schnuch A, Uter W. Extreme patch test reactivity to p-phenylenediamine but not to other allergens in children. Contact Dermatitis. 2011;65(4):220-6.
214. Schnuch A, Lessmann H, Frosch PJ, Uter W. para-Phenylenediamine: the profile of an important allergen. Results of the IVDK. Br J Dermatol. 2008;159(2):379-86.
215. Malvestio A, Bovenzi M, Hoteit M, Belloni Fortina A, Peserico A, Corradin MT, et al. p-Phenylenediamine sensitization and occupation. Contact Dermatitis. 2011;64(1):37-42.
216. Herro E, Jacob SE. p-tert-Butylphenol formaldehyde resin and its impact on children. Dermatitis. 2012;23(2):86-8.
217. Warshaw EM, Schram SE, Belsito DV, DeLeo VA, Fowler JF, Jr., Maibach HI, et al. Shoe allergens: retrospective analysis of cross-sectional data from the north american contact dermatitis group, 2001-2004. Dermatitis. 2007;18(4):191-202.
218. Rodrigo-Nicolas B, de la Cuadra J, Sierra C, Miquel J. Contact dermatitis from a temporary tattoo in a boy with contact allergy to p-tert butyl phenol formaldehyde resin. Dermatitis. 2014;25(1):37-8.
219. Herro EM, Friedlander SF, Jacob SE. Bra-associated allergic contact dermatitis: p-tert-butylphenol formaldehyde resin as the culprit. Pediatr Dermatol. 2012;29(4):540-1.
220. Shono M, Ezoe K, Kaniwa MA, Ikarashi Y, Kojima S, Nakamura A. Allergic contact dermatitis from para-tertiary-butylphenol-formaldehyde resin (PTBP-FR) in athletic tape and leather adhesive. Contact Dermatitis. 1991;24(4):281-8.
221. Sood A, Taylor JS, Billock JN. Contact dermatitis to a limb prosthesis. Am J Contact Dermat. 2003;14(3):169-71.
222. Simonsen AB, Deleuran M, Sommerlund M. Allergic Contact Dermatitis Caused by P-Tert-Butylphenol-Formaldehyde Resin in Orthopedic Braces. Pediatr Dermatol. 2016;33(3):e204-e5. doi: 10.1111/pde.12836. Epub 2016 Apr 13.
223. Roul S, Ducombs G, Leaute-Labreze C, Labbe L, Taieb A. Footwear contact dermatitis in children. Contact Dermatitis. 1996;35(6):334-6.
224. Cockayne SE, Shah M, Messenger AG, Gawkrodger DJ. Foot dermatitis in children: causative allergens and follow-up. Contact Dermatitis. 1998;38(4):203-6.
225. Rudzki E, Rebandel P. 2 cases of dermatitis from rare sources of sensitization to frequent contactants. Contact Dermatitis. 1995;32(6):361.

226. Fisher AA. Contact allergy in children. Part I: Rubber allergy. Cutis. 1994;54(3):138-40.
227. Ventura MT, Dagnello M, Matino MG, Di Corato R, Giuliano G, Tursi A. Contact dermatitis in students practicing sports: incidence of rubber sensitisation. Br J Sports Med. 2001;35(2):100-2.
228. Rodriguez-Serna M, Molinero J, Febrer I, Aliaga A. Persistent hand eczema in a child. Am J Contact Dermat. 2002;13(1):35-6.
229. Marzario B, Burrows D, Skotnicki S. Contact Dermatitis to Personal Sporting Equipment in Youth. J Cutan Med Surg. 2016;20(4):323-6. doi: 10.1177/1203475415611377. Epub 2015 Oct 15.
230. Agner T, Flyvholm MA, Menne T. Formaldehyde allergy: A follow-up study. Am J Contact Dermat. 1999;10(1):12-7.
231. Wall LM, Gebauer KA. A follow-up study of occupational skin disease in Western Australia. Contact Dermatitis. 1991;24(4):241-3.
232. Mortz CG, Bindslev-Jensen C, Andersen KE. Prevalence, incidence rates and persistence of contact allergy and allergic contact dermatitis in The Odense Adolescence Cohort Study: a 15-year follow-up. Br J Dermatol. 2013;168(2):318-25.
233. Chernyshov PV, Tomas-Aragones L, Manolache L, Marron SE, Salek MS, Poot F, et al. Quality of life measurement in atopic dermatitis. Position paper of the European Academy of Dermatology and Venereology (EADV) Task Force on quality of life. J Eur Acad Dermatol Venereol. 2017;31(4):576-93. doi: 10.1111/jdv.14058. Epub 2017 Jan 17.
234. Ganemo A, Svensson A, Lindberg M, Wahlgren CF. Quality of life in Swedish children with eczema. Acta Derm Venereol. 2007;87(4):345-9.
235. Heine G, Schnuch A, Uter W, Worm M. Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). Allergy. 2006;61(5):611-6.
236. Belhadjali H, Mohamed M, Youssef M, Mandhouj S, Chakroun M, Zili J. Contact sensitization in atopic dermatitis: results of a prospective study of 89 cases in Tunisia. Contact Dermatitis. 2008;58(3):188-9.
237. Bregnbak D, Johansen JD, Jellesen MS, Zachariae C, Menne T, Thyssen JP. Chromium allergy and dermatitis: prevalence and main findings. Contact Dermatitis. 2015;73(5):261-80. doi: 10.1111/cod.12436. Epub 2015 Jun 24.
238. Ruff CA, Belsito DV. The impact of various patient factors on contact allergy to nickel, cobalt, and chromate. J Am Acad Dermatol. 2006;55(1):32-9. Epub 2006 May 16.
239. Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. J Am Acad Dermatol. 2013;69(2):232-7. doi: 10.1016/j.jaad.2013.03.012. Epub Apr 11.
240. Ross-Hansen K, Ostergaard O, Tanassi JT, Thyssen JP, Johansen JD, Menne T, et al. Filaggrin is a predominant member of the denaturation-resistant nickel-binding proteome of human epidermis. J Invest Dermatol. 2014;134(4):1164-6. doi: 10.038/jid.2013.445. Epub Oct 24.
241. Engebretsen KA, Thyssen JP. Skin Barrier Function and Allergens. Curr Probl Dermatol. 2016;49:90-102.(doi):10.1159/000441548. Epub 2016 Feb 4.
242. Thyssen JP. Cobalt sensitization and dermatitis: considerations for the clinician. Dermatitis. 2012;23(5):203-9.

243. Liden C, Andersson N, Julander A, Matura M. Cobalt allergy: suitable test concentration, and concomitant reactivity to nickel and chromium. Contact Dermatitis. 2016;74(6):360-7. doi: 10.1111/cod.12568. Epub 2016 Mar 21.
244. Bregnbak D, Opstrup MS, Jellesen MS, Johansen JD, Thyssen JP. Allergic contact dermatitis caused by cobalt in leather - clinical cases. Contact Dermatitis. 2017;76(6):366-8. doi: 10.1111/cod.12721.
245. Midander K, Hurtig A, Borg Tornberg A, Julander A. Allergy risks with laptop computers - nickel and cobalt release. Contact Dermatitis. 2016;74(6):353-9. doi: 10.1111/cod.12525. Epub 2016 Jan 19.
246. Lee HJ, Byun JY, Choi YW, Choi HY. Two cases of eyelid dermatitis caused by cobalt in colour cosmetics. Contact Dermatitis. 2016;75(6):390-2. doi: 10.1111/cod.12669.
247. Rystedt I. Evaluation and relevance of isolated test reactions to cobalt. Contact Dermatitis. 1979;5(4):233-8.
248. Jensen P, Hamann D, Hamann CR, Jellesen MS, Jacob SE, Thyssen JP. Nickel and cobalt release from children's toys purchased in Denmark and the United States. Dermatitis. 2014;25(6):356-65. doi: 10.1097/DER.0000000000000084.
249. Lubbes S, Rustemeyer T, Sillevis Smitt JH, Schuttelaar MA, Middelkamp-Hup MA. Contact sensitization in Dutch children and adolescents with and without atopic dermatitis - a retrospective analysis. Contact Dermatitis. 2016:12711.
250. Thyssen JP, Johansen JD, Linneberg A, Menne T, Nielsen NH, Meldgaard M, et al. The association between null mutations in the filaggrin gene and contact sensitization to nickel and other chemicals in the general population. Br J Dermatol. 2010.
251. Lammintausta K, Kalimo K, Havu VK. Contact allergy in atopics, who perform wet work in hospital. Derm Beruf Umwelt. 1982;30(6):184-8.
252. Angelini G, Meneghini CL. Contact and bacterial allergy in children with atopic dermatitis. Contact Dermatitis. 1977;3(3):163-7.
253. Oranje AP, Bruynzeel DP, Stenveld HJ, Dieges PH. Immediate- and delayed-type contact hypersensitivity in children older than 5 years with atopic dermatitis: a pilot study comparing different tests. Pediatr Dermatol. 1994;11(3):209-15.
254. Giordano-Labadie F, Rance F, Pellegrin F, Bazex J, Dutau G, Schwarze HP. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. Contact Dermatitis. 1999;40(4):192-5.
255. Foti C, Bonifazi E, Casulli C, Bonamonte D, Conserva A, Angelini G. Contact allergy to topical corticosteroids in children with atopic dermatitis. Contact Dermatitis. 2005;52(3):162-3.
256. Silny W, Bartoszak L, Jenerowicz D, Zukiewicz-Sobczak W, Gozdziewska M. Prevalence of contact allergy in children suffering from atopic dermatitis, seborrhoeic dermatitis and in healthy controls. Ann Agric Environ Med. 2013;20(1):55-60.
257. Akan A, Toyran M, Vezir E, Azkur D, Kaya A, Erkocoglu M, et al. The patterns and clinical relevance of contact allergen sensitization in a pediatric population with atopic dermatitis. Turk J Med Sci. 2015;45(6):1207-13.
258. Vind-Kezunovic D, Johansen JD, Carlsen BC. Prevalence of and factors influencing sensitization to corticosteroids in a Danish patch test population. Contact Dermatitis. 2011;64(6):325-9. doi: 10.1111/j.600-0536.2011.01898.x. Epub 2011 Apr 3.
259. Browne F, Wilkinson SM. Effective prescribing in steroid allergy: controversies and cross-reactions. Clin Dermatol. 2011;29(3):287-94. doi: 10.1016/j.clindermatol.2010.11.007.

260. Baeck M, Chemelle JA, Terreux R, Drieghe J, Goossens A. Delayed hypersensitivity to corticosteroids in a series of 315 patients: clinical data and patch test results. Contact Dermatitis. 2009;61(3):163-75. doi: 10.1111/j.600-0536.2009.01602.x.
261. Mailhol C, Lauwers-Cances V, Rance F, Paul C, Giordano-Labadie F. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. Allergy. 2009;64(5):801-6.
262. Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of Compositae plants. Contact Dermatitis. 1993;29(1):6-10.
263. Orion E, Paulsen E, Andersen KE, Menne T. Comparison of simultaneous patch testing with parthenolide and sesquiterpene lactone mix. Contact Dermatitis. 1998;38(4):207-8.
264. Belloni Fortina A, Romano I, Peserico A. Contact sensitization to Compositae mix in children. J Am Acad Dermatol. 2005;53(5):877-80.
265. Rasmussen A, Jacob SE. Dandelion: An Important Allergen in Atopic Children. Dermatitis. 2017;28(2):166. doi: 10.1097/DER.0000000000000262.
266. Paulsen E, Chistensen LP, Andersen KE. Cosmetics and herbal remedies with Compositae plant extracts - are they tolerated by Compositae-allergic patients? Contact Dermatitis. 2008;58(1):15-23.
267. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol. 2013;131(2):300-13. doi: 10.1016/j.jaci.2012.06.048. Epub Aug 28.
268. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol. 2001;144(3):523-32.
269. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. Br J Dermatol. 2016;175(2):287-95. doi: 10.1111/bjd.14476. Epub 2016 May 24.
270. Toledo F, Garcia-Bravo B, Fernandez-Redondo V, De la Cuadra J, Gimenez-Arnau AM, Borrego L, et al. Patch testing in children with hand eczema. A 5-year multicentre study in Spain. Contact Dermatitis. 2011;65(4):213-9.
271. Heede NG, Thuesen BH, Thyssen JP, Linneberg A, Szecsi PB, Stender S, et al. Hand eczema, atopic dermatitis and filaggrin mutations in adult Danes: a registry-based study assessing risk of disability pension. Contact Dermatitis. 2017;77(2):95-105. doi: 10.1111/cod.12786. Epub 2017 Apr 20.
272. Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75-87.
273. Nielsen NH, Linneberg A, Menne T, Madsen F, Frolund L, Dirksen A, et al. The association between contact allergy and hand eczema in 2 cross-sectional surveys 8 years apart. Contact Dermatitis. 2002;47(2):71-7.
274. Rystedt I. Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. Contact Dermatitis. 1985;12(4):185-91.

Appendices

Appendix 1

Questionnaire (English translation)

QUESTIONNAIRE

Name _____

CPR number _____

Addresse _____

_____

_____

Phone number _____

E-mail _____

The questionnaire is filled out by:

☐ The patient's

☐ The patient's mom/dad/guardian

☐ The patient with help from a parent

1. ECZEMA

Your child was seen by a dermatologist and patch tested during 2003-2011 because of eczema.

1.1. Where was the eczema located?
Please tick one or more of the following options.

1. Face
   - 1☐ Around the eyes
   - 2☐ Around the mouth
   - 3☐ Cheeks
   - 4☐ Neck
   - 5☐ Ears
   - 6☐ Scalp

2. Hands
   - 1☐ Palms
   - 2☐ Back of hands
   - 3☐ Fingers

3. Legs
   - 1☐ Feet
   - 2☐ Ancles
   - 3☐ Lower legs
   - 4☐ Back of the knee joint
   - 5☐ Thighs
   - 6 ☐ Groin

4. Arms
   - 1☐ Wrists
   - 2☐ Forearm
   - 3☐ The anterior depression at the elbow
   - 4☐ Upper arm
   - 5☐ Armpit

5. Body
   - 1☐ Abdomen/chest
   - 2☐ Back

1.2. Did the patch test reveal that you/ your child had any contact allergy?

1☐ No. If no, go to question 2.1.

2☐ Yes

1.3. What are you/ what is your child allergic to? (the result of the patch test)

1☐ Fragrance

2☐ Metals

3☐ Rubber

4☐ Leather

5☐ Plants

6☐ Preservatives

7☐ Other? Please specify: _____

1.4. Did you /did your child suffer from eczema after you found out what caused the eczema?

1☐ No

2☐ Yes, but the eczema has improved

3☐ Yes, and the eczema is the same

4☐ Yes, and the eczema is worse

2.Products

2.1. What products do you/ your child use on a regular basis? Regular is more than once every week. Please tick one or more options.

1. Cleaning products/soap

1☐ Wet wipes
2☐ Facial wash
3☐ Cleanser for removing make-up
4☐ Eye make-up remover
5☐ Body wash/shower gel

2. Skin care:

1☐ Lotion/emollient cream/moisturizer with fragrance
2☐ Lotion/emollient cream/moisturizer with out fragrance
3☐ Facial cream/facial moisturizer

4☐ Sunscreen

3. Makeup:

1☐ Mascara

2☐ Eyeliner

3☐ Eye shadow

4☐ Foundation

5☐ Powder
6☐ Lipstick
7☐ Lip gloss

8☐ Lip balm

4. Other

2.2. Did you/your child ever develop a rash from using any of the following products?

1. Cleaning products/soap

1☐ Wet wipes
2☐ Facial wash
3☐ Cleanser for removing make-up
4☐ Eye make-up remover
5☐ Body wash/shower gel with fragrance
6☐ Body wash/shower gel with out fragrance

2. Skin care:

1☐ Lotion/emollient cream/moisturizer with fragrance
2☐ Lotion/emollient cream/moisturizer with out fragrance
3☐ Facial cream/facial moisturizer

4☐ Sunscreen

3. Makeup:

1☐ Mascara

2☐ Eyeliner

3☐ Eye shadow

4☐ Foundation

5☐ Powder
6☐ Lipstick
7☐ Lip gloss

8☐ Lip balm

4. Other

1☐ Perfume

2☐ Essential oils

3☐ Herbal remedies

3.PIERCINGER & METAL PRODUCTS

3.1. Do you / does your child have body piercings?

1☐ No – if no, please go to question 3.4.
2☐ Yes

3.2. Where do you/ your child have an ear piercing?
1☐ Ears
2☐ Nose
3☐ Belly button
4☐ Eyebrow
5☐ Other

3.3. How old were you/was your child when the first piercing was made? _____

3.4. Did you/your child ever develop a rash (eczema) after skin contact with metal? (metal buttons, hair clips, jewelry, etc.)

1☐ No
2☐ Yes

3.5. Did you /your child ever wear dental braces?

1☐ No
2☐ Yes
If yes, at what age? _____

4. HAIR

4.1. Did you/your child ever use permanent hair dye? Permanent dye is dye that cannot be washed out.

1☐ No – if no, please go to question 4.7.
2☐ Yes

4.2. If yes, how many times did you/your child use hair dye?
1☐ Once
2☐ Less than 5 times
3☐ Less than 10 times
4☐ More than 10 times

4.3. What colour did you/your child use?
1☐ Dark colours
2☐ Light colours
3☐ Bleaching
4☐ It varies
5☐ I don't know

4.4. How old were you/your child when you /your child died the hair for the first time?
_____

4.5. Did you/your child ever develop a rash (eczema) from using hair dye?

1☐ No
2☐ Yes

4.6. Did you/your child ever experience skin swelling from dying the hair?

1☐ No
2☐ Yes

4.7. What hair products are used regularly?

1☐ Hair wax
2☐ Mousse
3☐ Hair spray
4☐ Shampoo
5☐ Conditioner
6☐ Hair treatment

4.8. Did you/your child ever develop a rash (eczema) from using one of the following products?

1☐ Hair wax
2☐ Mousse
3☐ Hair spray
4☐ Shampoo
5☐ Conditioner
6☐ Hair treatment

5. TATTOOS

5.1. Did you/ your child ever have a black henna tattoo? This is also called a temporary tattoo. It lasts about 3 weeks.

1☐ No – if no, please go to question 5.4.
2☐ Yes

5.2. How old were you / your child?_____

5.3. Did you/your child develop a rash in the tattoo?
1☐ No
2☐ Yes

5.4. Do you/ does your child have a real permanent tattoo?

1☐ No - If no, please go to question 6.1.
2☐ Yes

5.5. How old were you/ your child when this was made?
_____

5.6. Did you /your child develop a rash in the tattoo?

1☐ No
2☐ Yes

6. SHOES

6.1. Did you /your child ever have a rash (eczema) on the feet?

1☐ No - If no, please go to question 7.1.
2☐ Yes

6.2. If the answer is yes: Did the eczema on the feet become worse because you /your child used certain shoes?

1☐ No - If no, please go to question 7.1.
2☐ Yes

6.3. Was it leather shoes /leather sandals?

1☐ No
2☐ Yes

6.4. Was it rubber shoes / shoes with a rubber sole?

1☐ No
2☐ Yes

6.5. Was it shoes made of leather *and* rubber?

1☐ No
2☐ Yes

7. LEISURE ACTIVITIES

7.1. What leisure activities do you/ does your child participate in?
I.E. Sport and hobbies:
1☐ Ball games
2☐ Water sports
3☐ Gymnastics/dance
4☐ Cycling
5☐ Horse riding
6☐ Flower arranging/gardening
7☐ Computer games
8☐ Pets
9☐ Music
10 ☐Other? Please specify:
_____

7.2. Do you/your child use any specific equipment for this?

1☐ Wet suit
2☐ Shin guards
3☐ Gloves
4☐ Resin
5☐ None of the above

7.3. Do you/your child have a spare time job/temping job/permanent job or are you/your child an apprentice?

1☐ No - If no, please go to question 7.11.
2☐ Yes

7.4. What kind of job?

1☐ Sparetime job Specify:_____

2☐ Temping job Specify:_____

3☐ Permanent job Specify:_____

4☐ Apprentice Specify:_____

7.5. How many hours a week?

1☐ less than 6 hours
2☐ 6-12 hours
3☐ 12-20 hours
4☐ 20-40 hours
5☐ more than 40 hours

7.6. Do you/does your child do ”wet work” – i.e. work where the hands are wet or exposed to water, for instance dish washing, cleaning, handling of foods, frequent hand washing?

1☐ No - If no, please go to question 7.8.
2☐ Yes

7.7. How many hours per day do you/does your child have wet work?

1☐ less than ½ time
2☐ ½ - 1 hour
3☐ 1-4 hours
4☐ more than 4 hours

7.8. Do you/does your child wear gloves at work?

1☐ No - If no, please go to question 7.11.
2☐ Yes

7.9. How many hours per working day do you/does your child wear gloves?

1☐ less than ½ hour

2☐ ½ - 1 hour
3☐ 1-4 hours
4☐ more than 4 hours

7.10. What gloves do you/?

1☐ Synthetic rubber (for instance nitrile, neoprene)
2☐ Natural rubber/latex

3☐ Plastic (f.eks. vinyle, PVC, polyethylene)
4☐ Leather

5☐ Cotton gloves under plastic- or rubber gloves
6☐ Fabric gloves

7☐ Other

8☐ I don't know

7.11. Did your /your child's rash (eczema) affect any decisions regarding future occupation or education?

1☐ No
2☐ Yes, because of contact allergy from rubber
3☐ Yes, because of contact allergy from fragrance
4☐ Yes, because I/he/she must avoid wet work
5☐ Yes, Yes, because I/he/she must avoid certain substances that I/he/she am/is allergic to.
Please specify:_____

7.12. Did you/your child have pets growing up (dog, cat, rabbit, guinea pig, hamster, birds)?

1☐ No
2☐ Yes

7.13. Did you/your child grow up on a farm with animals (cows, pigs, sheep, etc.)

1☐ No
2☐ Yes

8. CURRENT ECZEMA

8.1. On a scale of 0-10, how bad was your/your child's eczema when it was the worst?
0 = No eczema
10 = Very severe eczema

0	1	2	3	4	5	6	7	8	9	10
No eczema										Very severe eczema

8.2. How bad was your/your child's eczema during the past month?

0	1	2	3	4	5	6	7	8	9	10
No eczema										very severe eczema

8.3. How bad was your/your child's eczema during the past 3 months?

0	1	2	3	4	5	6	7	8	9	10
No eczema										very severe eczema

8.4. How bad is your/your child's eczema now?

0	1	2	3	4	5	6	7	8	9	10
No eczema										very severe eczema

8.5. How often do you/your child have outbreaks of eczema?

1☐ Never
2☐ Every day/ all the time
3☐ Every week
4☐ 1-3 times per month
5☐ 4-6 times per year
6☐ 1-3 times per year
7☐ Other: _____

9. LIFE QUALITY

PLEASE REatopic dermatitis THE INSTRUCTIONS BEFORE FILLING OUT THE QUESTIONNAIRE:

The purpose of the following questions is to assess how much your/your child's eczema has affected you/your child DURING THE PAST YEAR.

9.1. During the past year, how itchy, "scratchy", sore or painful was your child's eczema?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.2. During the past year, how embarrassed, self conscious, sad, or upset was your child because of the eczema?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.3. During the past year, how much did your child's eczema affect your child's friendships?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.4. During the past year, how much has your child changed or worn different or special clothes/shoes because of his/her eczema?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.5. During the past year, how much has your child's eczema affected going out, playing or doing hobbies?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.6. During the past year, how much has your child avoided swimming or other sport activities because of his/her eczema?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.7. During the past year how much did the skin symptoms affect your child's school work?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.8. During the past year, how much trouble did your child have because of his/her skin symptoms with other people calling him/her names, teasing bullying, asking questions or avoiding him/her?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.9. During the past year, how much was your child's sleep affected by his/her skin symptoms?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

9.10. During the past year, how much of a problem was the treatment of the skin for your child?
1☐ Very much
2☐ A lot
3☐ A little
4☐ Not at all

10. ATOPIC DERMATITIS, HAY FEVER AND ASTHMA

10.1. Did your child ever have an itching rash that lasted more than 1 day

1☐ No - If no, please go to question 10.5.
2☐ Yes

10.2. How old was your child when the eczema occurred for the first time?

1☐ 0-2 years
2☐ 2-5 years
3☐ 6-10 years
4☐ over 10 years

10.3. Was the eczema located to the skin folds?

"Skin folds" is the anterior part of the elbow, the back of the knee joints, ankles, neck, or around the eyes.

1☐ No
2☐ Yes

10.4. Does your child have dry skin?

1☐ No
2☐ Yes

10.5. Did a doctor ever tell you that your child has asthma?

1☐ No
2☐ Yes

10.6. Did a doctor ever tell you that your child has hay fever?

1☐ No
2☐ Yes

10.7. Did your child ever suffer from any of the below mentioned skin conditions? Please tick one or more options.

1☐ Eczema
2☐ Warts
3☐ Psoriasis
4☐ Atopic eczema
5☐ Acne
6☐ None of the above

11. ANYTHING ELSE ABOUT YOUR CHILD

11.1. In your experience, what will cause or worsen your child's eczema?

1☐ Soap, liquid soap, shampoo, other personal care products
2☐ Detergents and cleaning products

3☐ Handling food

4☐ Contact with water

5☐ Frequent hand wash

6☐ Protective gloves

7☐ Having a cold, fever, influenza, infections, etc.

8☐ Stress, mood changes.

9☐ Menstruation

10☐ Other? Please specify:_____

11.2. Do you/ does your child smoke?

1☐ No, - If no, please go to question 11.5.
2☐ Yes, every day
3☐ Yes, but not every day

11.3. How many years did you/your child smoke?
Number of years _____

11.4. How much do you smoke each day on average?
Number of cigarettes per day_____

11.5. On a scale of 0-10, how is your / your child's mood currently?
0 = terrible
10 = Couldn't be better

0	1	2	3	4	5	6	7	8	9	10
terrible										couldn't be better

11.6. On a scale of 1-10 how is your/your child's general health?
0 = terrible
10 = Couldn't be better

0	1	2	3	4	5	6	7	8	9	10
terrible										couldn't be better

11.7. How tall are you /is your child?

_____ cm

11.8. How much do you/does your child weigh?

_____ kg

12. PARENTS AND SIBLINGS

12.1. Did your /your child's siblings have eczema?

1☐ No
2☐ Yes
3☐ No siblings
4☐ I don't know

12.2. Do your / does your child's siblings have hay fever?

1☐ No
2☐ Yes
3☐ No siblings
4☐ I don't know

12.3. Do your / does your child's siblings have asthma?

1☐ No
2☐ Yes
3☐ No siblings
4☐ I don't know

12.4. Did your parents have eczema/If you are the parent – did you ever have eczema yourself?

	mom	dad
1☐ No	☐	☐
2☐ Yes	☐	☐
3☐ I don't know	☐	☐

12.5. Did your parents have hay fever/If you are the parent – did you ever have hayfever yourself?

	mom	dad
1☐ No	☐	☐
2☐ Yes	☐	☐
3☐ I don't know	☐	☐

12.6. Did your parents have asthma/If you are the parent – did you ever have asthma yourself?
?

	mom	dad
1☐ No	☐	☐
2☐ Yes	☐	☐
3☐ I don't know	☐	☐

12.7. Do you (parents) smoke?

	mom	dad
1☐ No		
2☐ Yes	☐	☐

12.8. Which education do your parents have? If you are the parent: Which education do you have? (sæt ét kryds ved hhv. mom og dad)

	mom	dad
1. Primary school	☐	☐
2. High school	☐	☐
3. Shorter higher education 1-3 years	☐	☐
4. Longer higher education 3-6 years	☐	☐
5. Skilled	☐	☐
6. Unskilled	☐	☐

12.9. Your parents yearly income/If you are the parents: your yearly income:

		mom	dad
1.	<200.000 dkr.	☐	☐
2.	200.000-400.000 dkr.	☐	☐
3.	400.000-600.000 dkr.	☐	☐
4.	600.000-800.000 dkr.	☐	☐
5.	> 800.000 dkr.	☐	☐
6.	I don't know	☐	☐
7.	I do not wish to answer	☐	☐

THANK YOU FOR FILLING OUT THE QUESTIONNAIRE!

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Declaration of co-authorship

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14/12-17	Anne BS	phd-student

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Authors:	Anne Birgitte Simonsen, Jeanne Duus Johansen, Mette Deleuran, Charlotte Gotthard Mørtz, Lone Skov, Mette Sommerlund

The article/manuscript is: Published ☐ Accepted ☒ Submitted ☐ In preparation ☐

If published, state full reference:

If accepted or submitted, state journal: Journal of the European Academy of Dermatology and Venereology

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
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Element	Extent (A-E)
1. Formulation/identification of the scientific problem	C
2. Planning of the experiments and methodology design and development	C D
3. Involvement in the experimental work/clinical studies/data collection	C
4. Interpretation of the results	E
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	E

Signatures of the co-authors

Date	Name	Signature
11/12-17	Lone Skov	Lone Skov

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In case of further co-authors please attach appendix

Date:
11/12-17

Signature of the PhD student

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Declaration of co-authorship

Full name of the PhD student: Anne Birgitte Nørremark Simonsen

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Element	Extent (A-E)
1. Formulation/identification of the scientific problem	C
2. Planning of the experiments and methodology design and development	D
3. Involvement in the experimental work/clinical studies/data collection	C
4. Interpretation of the results	E
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6. Finalization of the manuscript and submission	E

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Date: 14/12 - 17

Signature of the PhD student