Nickel allergy and hand eczema
– epidemiological aspects
To my family
Anna Josefson

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– epidemiological aspects
ABSTRACT


Nickel allergy is the most prevalent contact allergy and has been discussed as a possible risk factor for hand eczema. However, hand eczema is one of the most frequently occurring skin diseases and has multifactorial origin. The aim of this thesis was to study the association between nickel allergy and hand eczema in the general population. There are only a few population-based studies previously published, that include patch testing. In addition, this thesis aimed to evaluate methods to follow the prevalence of nickel allergy.

The study cohort consisted of 908 women who had been patch tested for the occurrence of nickel allergy as schoolgirls. Twenty years later, they were invited to participate in a follow-up questionnaire study. The response rate was 81%. In total, 17.6% of respondents reported hand eczema after the age of 15 years and there was no statistically significant difference in the occurrence of hand eczema between those who were nickel-positive and those who were nickel-negative as schoolgirls. To further investigate possible links, another study was performed, which included a second questionnaire, a clinical investigation and patch testing. All schoolgirls from the baseline study who were still living in the area as adults were invited to participate and the participation rate was 77%. Patch test showed 30.1% nickel-positive individuals. When all participants were included in the analysis, there was no statistically significant difference between nickel-positive and nickel-negative women regarding occurrence of hand eczema. The most important risk factor for hand eczema was childhood eczema. Adjusted prevalence proportion ratio (PPR) for hand eczema after age 15 in relation to nickel patch test results was 1.03 (95% CI 0.71–1.50) and in relation to childhood eczema 3.68 (95% CI 2.45–5.54). When women with and without history of childhood eczema were analyzed separately, the hand eczema risk was doubled in nickel-positive women without history of childhood eczema. In conclusion, the risk of hand eczema in nickel-positive women may previously have been overestimated.

Next, the validity of self-reported nickel allergy was investigated. In the established cohort; two questions regarding nickel allergy were compared with patch test results. The validity of self-reported nickel allergy was low, and the questions regarding nickel allergy overestimated the true prevalence of nickel allergy. The positive predictive values were 59% and 60%. Another method for estimating the prevalence of nickel allergy, namely self-patch testing, was validated in the last study. In total, 191 patients from three different dermatology departments participated. The validity of self-testing for nickel allergy was adequate, with sensitivity 72% and proportion of agreement 86%.

Keywords: childhood eczema, contact allergy, patch test, population-based, predictive value, questionnaire, self-test, sensitivity, specificity, validity, wet work

Anna Josefson, Department of Dermatology, Örebro University Hospital, SE-701 85 Örebro, Sweden. E-mail: anna.josefson@orebroll.se

Den första studien var en uppföljningsstudie av 908 flickor ur normalbefolkningen, vilka i skolåldern lapptestats med nickel. Tjugo år senare skickades en enkät till dessa kvinnor, svarsfrekvensen var hög (81%). Förekomsten av självrapporterat handeksem efter 15 års ålder var 17.6%. Det förelåg ingen signifikant skillnad i förekomst av handeksem mellan de kvinnor som var nickelallergiska som barn jämfört med dem som inte var nickelallergiska. År 2006 utfördes ytterligare en studie, som inkluderade de kvinnor som fortfarande bodde i Örebro län. Studien omfattade en klinisk undersökning av händerna samt ett lapptest. 30% av kvinnorna var positiva för nickel. Det förelåg ingen signifikant skillnad i förekomst av handeksem mellan de som var positiva för nickel och de som var negativa. Vid separat analys av de kvinnor som angav tidigare barneksem jämfört med dem som aldrig hade haft barneksem visade det sig att risken för handeksem var dubbelt så stor hos nickelallergiker i den gruppen som aldrig hade haft barneksem. Båda studierna visade att barneksem var den största riskfaktorn för att få handeksem som vuxen, med en 3-4 gånger ökad risk.

Den tredje studien var en validering av självrapporterad nickelallergi. Överensstämmelsen var låg mellan enkätfrågor gällande nickelallergi och lapptestverifierad nickelallergi. Av dem som själva bedömde sig vara nickelallergiska var endast 59% positiva enligt lapptest. För att följa förekomsten av nickelallergi i befolkningen behövs därför andra metoder. I den fjärde studien utvärderades ett självtest för nickelallergi. 191 patienter från tre olika hudkliniker i Sverige deltog i studien. Validiteten för metoden självtest var tillfredsställande, sensitiviteten var 72% och graden av överensstämmelse var 86%. 
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<tr>
<td>ACD</td>
<td>Allergic contact dermatitis</td>
</tr>
<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>D</td>
<td>Day</td>
</tr>
<tr>
<td>HECSI</td>
<td>Hand Eczema Severity Index</td>
</tr>
<tr>
<td>ICDRG</td>
<td>International Contact Dermatitis Research Group</td>
</tr>
<tr>
<td>IR</td>
<td>Irritant reaction</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>PPR</td>
<td>Prevalence proportion ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:


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Introduction

Contact allergy is frequent in the general population and nickel allergy is the most common of all. Some nickel-sensitized individuals develop allergic contact dermatitis and nickel allergy has been discussed as a risk factor for hand eczema. However, hand eczema is one of the most frequently occurring skin diseases and its aetiology is regarded as multifactorial. Prevention of hand eczema, when possible, is of great importance for society as well as for the individuals. For this reason, studies concerning risk factors for hand eczema are both exciting and valuable. Historically, most studies probing the association between hand eczema and nickel allergy were performed at dermatology departments and thus only included patients with eczema or other skin symptoms. This thesis aimed to further investigate the association between nickel allergy and hand eczema in the general population.

Contact allergy is a field under constant development due to environmental changes over time as new chemicals are introduced in consumer and industrial products and others are phased out. Continuous epidemiological surveillance is necessary to determine the prevalence of contact allergy and to evaluate interventions. In this thesis, tools for estimating the prevalence of nickel allergy have been validated.
BACKGROUND

CONTACT ALLERGY AND PATCH TESTING

History
The first experimental attempts to relate contact dermatitis to a causative agent were made during the nineteenth century. Josef Jadasson (1863–1936), Germany, is acknowledged as the father of patch testing. In 1895, he presented the process of delayed hypersensitivity to simple chemicals. At about the same time a French entomologist, J.-H. Fabre introduced the first steps of patch testing while working on processionary caterpillars. The patch testing methodology with initial standardization spread throughout the world. Poul Bonnevie, professor of Occupational Medicine in Copenhagen, is the author of the first modern textbook on occupational dermatology. He published the list that can be considered as the prototype of baseline series of patch tests. It was built on experience gained at the Finsen Institute in Copenhagen regarding the occurrence of positive reactions to various chemicals among patch-tested patients. Seven of the 21 allergens listed by Bonnevie in 1938 are still present in the baseline series of patch tests used today.

Contact allergy
Contact allergy is a delayed hypersensitivity type of reaction (Type IV) and may develop following repeated or prolonged skin contact with allergens. Briefly, two phases are recognized, an induction phase, when the individual gets sensitized to the allergen, and an effector phase, the elicitation, when the individual is re-exposed to the same allergen, Figure 1. When a contact sensitized individual is re-exposed to an allergen in concentrations that exceed the individual threshold, allergen-specific T-cells migrate to allergen contact sites and release pro-inflammatory mediators. Subsequently the mediators attract various inflammatory cells, which results in the elicitation of an allergic contact dermatitis reaction within 24–72 h.
Figure 1. Immunological events in allergic contact dermatitis with the induction phase (left) and the effector phase (right). The allergen (hapten) triggers migration of the antigen-presenting cells, Langerhans cells (LC) to the lymph node. Allergen-specific T-cells increase in number and memory cells are released into the circulation. Renewed allergen contact triggers effector T-cells to produce proinflammatory cytokines, inflammatory cells are recruited and an eczematos reaction develops within 24-72 hours. (Adapted from Contact Dermatitis, Frosch et al, 4th ed)

The clinical picture varies from erythema, edema, vesicles and weeping in an acute eczema to dryness, fissures and scaling in a chronic allergic dermatitis. The development of contact allergy is dependent on exposure to allergens and ability of the allergens to penetrate the epidermis. Sensitization is increased if the skin is traumatized and by the presence of penetration-enhancing factors. Long exposure time, high frequency of exposure and occlusion all promote penetration of the skin and contribute to sensitization. Sex, age and ethnicity have been discussed as risk factors, but risk is probably more closely related to differences in exposure. Whether atopy increases or decreases the risk of contact allergy is frequently debated. Clinical studies addressing this problem are contradictory. Some studies find a decreased tendency to contact...
sensitization and other studies indicate that atopics seem to have an increased frequency of contact sensitization.

Population-based studies show that the prevalence of contact allergy is about 20% among adult Scandinavians. Among adolescents, Motrz et al. found that the prevalence of contact allergy was 15%. Population-based studies that include patch testing are scarce. Most publications are based on data from patients visiting dermatology clinics – obviously a selected group – and limited information on incidence or prevalence rates in the general population can be derived from such studies. Environmental allergen exposure may vary over time, which leads to different prevalence in different age groups. Contact allergy to a certain allergen can also be more common in specific groups e.g. hairdressers or industrial workers. Thus, when comparing prevalence one should be aware of these pitfalls and of how important it is to define the study population. In the general population in Scandinavia, the most common contact allergen reactions are to nickel, thiomersal and fragrance mix I. Other frequent allergens are cobalt, chromium, and PPD (paraphenylendiamine).

Contact allergy implies true delayed hypersensitivity with an allergic patch test response, but does not say anything about clinical relevance. The clinical definition of allergic contact dermatitis is based on the history of the patient, clinical examination, patch testing and a detailed, often repeated exposure assessment. Among individuals exposed to contact allergens, only a fraction become sensitized, and among these some will develop clinically manifest allergic contact dermatitis.

**Patch testing**

Patch testing is a well established and widely used method of diagnosing contact allergy. Low concentrations of allergens are applied to the upper back in individual square plastic or round aluminium chambers. They are kept in place with adhesive tape and then left in place for 48 hours, Figure 2.

There are 3,700 chemicals described that can cause allergic contact dermatitis, and data on new ones are published every year. However, patch testing is routinely performed by applying a baseline series of the most frequently occurring contact allergens. The European baseline series contains 28 items but some of them are mixes, which means that the number of allergens is greater than 28. National and international contact dermatitis groups evaluate the series regularly. The baseline series detects approximately 75–80% of all contact allergies.
Reading of a patch test is based on morphological criteria and should be performed by an adequately trained patch test reader. It is recommended that two readings are performed whenever possible. Most studies indicate that readings on day 3–4 (D3–4) and on day 7 (D7) give the most reliable results. Late-appearing positive patch test reactions can appear for most allergens and are common for some. These reactions will be missed if only one reading is performed. Table 1 shows the recommended way to score patch test reactions.

Table 1. Recording of patch test reactions according to the International Contact Dermatitis Research Group (ICDRG)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>+?</td>
<td>Doubtful reaction; faint erythema only</td>
</tr>
<tr>
<td>+</td>
<td>Weak positive reaction; erythema, infiltration, possibly papules</td>
</tr>
<tr>
<td>++</td>
<td>Strong positive reaction; erythema, infiltration, papules, vesicles</td>
</tr>
<tr>
<td>+++</td>
<td>Extreme positive reaction; intense erythema and infiltration, coalescing vesicles</td>
</tr>
<tr>
<td>-</td>
<td>Negative reaction</td>
</tr>
<tr>
<td>IR</td>
<td>Irritant reaction</td>
</tr>
</tbody>
</table>

It must be kept in mind that the patch test is a biological provocation test and is accordingly dependent on multiple factors such as the test material, the biological status of the tested person, and the dermatologist's ability to evaluate the test.
Sometimes it is difficult to distinguish allergic reactions from irritant reactions, especially when weak. Thus, if test reactions are doubtful (+?) or weak (+), a repeated test, increased test concentration, serial dilution test or Use test (ROAT) are recommended to better categorize the reaction and distinguish irritant from allergic ones. Evaluating the relevance of a positive reaction is the most difficult part of the patch test procedure. The relevance depends on the patient’s history, symptoms and signs, and exposure assessment.

**Nickel Allergy**

Nickel allergy is the most common contact allergy. The use of nickel has been traced as far back as 3,500 BC, but it was first isolated and classified as a chemical element in 1751 by Axel Fredrik Cronstedt, who initially mistook nickel ore for a copper-containing mineral. Nickel is a metal and since the nineteenth century, it has been widely used in many alloys, particularly in stainless steel. Nickel is also used in alloys with copper, chromium, aluminium, lead, cobalt, silver and gold. Nickel is an important cause of contact allergy, and sensitization is related to exposure. Contact dermatitis from nickel was recognized in 1889 in the plating industry. Exposure to nickel has varied over time and for the past few decades, piercing has been an important factor in sensitization. The prevalence of nickel allergy is higher among women than among men. Also, where nickel allergy is concerned, most studies have been focused on patients with eczema and consequently been based on clinical data from dermatology departments. However, eighteen population-based studies that included patch testing, published during the past 30 years, were reviewed by Thyssen et al. in 2007. The median prevalence of nickel allergy was 17.1% (range 3.9–38.8%) in women versus 3% (range 0.7–6.8%) in men. This gender difference is traditionally ascribed to greater exposure in women, due to direct skin contact with nickel-releasing metals, such as in jewellery, wristwatches and clothing accessories. There are also certain occupational groups with exposure to nickel, such as hairdressers, of whom a majority are women. Thus, exposure to nickel has varied over time and the prevalence of nickel allergy is different in different age groups. Nielsen et al. reported 19.6% positive patch test reactions among women aged 15–34, compared to 7.9% among 35–49 years old (in 1993). However, in a recently published study was found that nickel allergy decreases in the younger age groups. In addition, Bryld et al. showed a higher prevalence of nickel allergy among women 36–45 years old (25.0%) than in those 20–28 years old (20.3%).
Scandinavian studies present a prevalence of 13–14% in adolescent girls and 2.5% in adolescent boys \(^{17,30}\).

Nickel allergy may cause dermatitis and the primary sites where dermatitis develops are those where skin is in direct contact with nickel-releasing metal. Historically, nickel dermatitis was an occupational eczema seen on the hands and forearms of workers in the plating industry. Since then, the cause of sensitization has changed with fashion, from suspenders to buttons in blue jeans and more recently to ear piercing. The secondary sites may develop in particularly sensitive patients as a systemic contact dermatitis through oral intake. Systemic contact dermatitis is symmetrical and may include the face and neck, elbow flexures, hands and ano-genital region \(^{31}\).

Nickel allergy is often associated with reactivity to other metals, which is usually caused by multiple exposure and sensitization rather than by cross-reactivity \(^{32}\).

To prevent nickel sensitization and dermatitis in already nickel-sensitized individuals, legislation was passed in Denmark in 1990 \(^{33}\). A few years later the rest of Europe followed and the European Nickel Directive came into full force in 2001 \(^{34}\). The Directive limits permissible nickel release from items in prolonged contact with the skin, e.g. jewellery, watches, buttons and zippers, Table 2.

It is important to remember that the regulation does not include occupational exposure from tools and from other everyday items such as coins. Epidemiological studies need to be done and it will be of great interest over the coming years to evaluate the effect of the Nickel Directive. Reports from Denmark and Germany have shown a tendency toward decreasing occurrence of nickel allergy in young people \(^{35,36,37}\). These changes might be a consequence of the regulation of skin exposure to nickel.


<table>
<thead>
<tr>
<th>Part</th>
<th>Nickel may not be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In post assemblies to be left in place during the healing of new piercings unless the posts are homogeneous and the concentration of nickel is less than 0.05%.</td>
</tr>
<tr>
<td>2</td>
<td>In products intended to come into direct and prolonged contact with the skin, such as earrings, necklaces, wristwatch cases, watch straps, buttons, tighteners and zippers, if nickel release is greater than 0.5 µg nickel/cm(^2) per week</td>
</tr>
<tr>
<td>3</td>
<td>In coated products in part 2, unless the coating is sufficient to ensure that the nickel release will not exceed 0.5 µg nickel/cm(^2) per week after 2 years of normal use</td>
</tr>
</tbody>
</table>
**Hand eczema**

Hand eczema is one of the most frequent skin diseases in the population and is thus of interest from public health perspective. It often has a chronically relapsing course with poor prognosis, imposing social and economic burden on the individual and society. The aetiology of hand eczema is multifactorial and includes environmental as well as endogenous factors.

**Occurrence**

Epidemiological studies of hand eczema have repeatedly confirmed that the condition is common in the general population, with a 1-year prevalence around 10% and a lifetime prevalence around 15–20% \(^{38-42}\). Studies on the incidence rate of hand eczema in the general population have yielded estimates ranging from 4.4 to 8.8 cases per 1000 person-years \(^{41-44}\). The incidence is highest among young women \(^{41, 45}\). In a Swedish study was also found that hand eczema often started before the age of 20 years \(^{41}\). Early onset of hand eczema as part of atopic dermatitis might be an explanation for some of these cases, but far from all.

Hand eczema is twice as common among women as among men, with the highest prevalence among young women. Enough evidence has not been found for genetic factors as a reason for this difference. Greater exposure of women to wet work, domestically as well as occupationally, is assumed to be the most likely explanation \(^{42, 46, 47}\).

When estimating the 1-year prevalence of self-reported hand eczema, most of the studies mentioned above used the question ‘Have you had hand eczema on any occasion during the past 12 months?’ This question has been validated; its sensitivity was 53–59% and its specificity was 96–99% \(^{48}\). Thus, the question underestimates the true prevalence of hand eczema and the 1-year prevalence might be 30–60% higher, reaching 12–15%.

Most studies of hand eczema in the general population have been performed in Scandinavia. One reason for this might be that the unique personal code number used for administrative purposes in Scandinavian countries facilitates epidemiological studies. Dry air and cold weather have been shown to influence skin irritability \(^{49}\). For this reason, it has been speculated that hand eczema might be particularly common in Scandinavian countries. However, more epidemiological studies of hand eczema in a general population outside Scandinavia are needed to confirm this.
Predictive factors

It is tempting to seek a single cause for chronic hand eczema but the cause is usually a combination of various interacting factors. The aetiology involves both endogenous and exogenous factors and their effects may be cumulative. The multifactorial origin of hand eczema may be responsible for the chronic course of the condition and for its poor response to treatment 50, 51.

General population studies have repeatedly found that history of atopic dermatitis is the most important risk factor for hand eczema 41, 46, 52-54. A recent review article by Diepgen et al. reported that an atopic background was found in 50% of patients with hand eczema 50. In atopic individuals with a tendency to develop asthma or hay fever but without dermatitis, hand eczema is less frequent. However, Meding et al. showed an association between history of asthma/hay fever and hand eczema among individuals whose hand eczema began before they were 30 years old 41. Since the incidence of atopic dermatitis is increasing in western countries, one might expect an increased prevalence of hand eczema in the future. The association between hand eczema and atopic dermatitis is not fully understood. One possible link is weaknesses in the skin barrier, the function of which is important in all types of hand eczema. The filaggrin gene is important for a functional skin barrier. Defects in the filaggrin gene – null mutations –, have been found in about half of those with moderate to severe atopic dermatitis 55, 56.

In Denmark, studies on twins have shown that other hitherto unrecognized hereditary factors might be associated with hand eczema 38, 46, 57. The authors of those papers presume that the genetic risk factors found in the study primarily relate to the risk of acquiring irritant contact dermatitis, since they controlled for atopic dermatitis and contact allergy in their data analysis. Lerbaek et al. 57 also showed that environmental factors explained almost 70% of the variance in liability regarding frequency of eruptions, which underlines the importance of treatment and secondary prevention.

The most common external cause of hand eczema is contact with skin irritants, such as water, detergents and chemicals. This type of hand eczema is usually referred to as irritant contact dermatitis. Exposure to irritants is common in occupational settings but also during housework and in leisure time. In a Swedish study was found that 19% of the general population reported wet exposure of hands more than ½ hour/day or more than 10 times a day at work 58. Wet exposure was more frequent in women than in men and there was also higher exposure at young age. In some studies the occurrence of hand eczema is higher among those with daily occupational exposure to water, detergents, chemicals or dirt, than among those with no exposure 59. However, most studies are cross-sectional observational studies, which makes it difficult to study the
causal relationship between exposure and hand eczema. The frequent exposure of young women to irritants and wet work might contribute to the high prevalence of hand eczema in this group.

Another type of hand eczema is allergic contact dermatitis, which is less common than irritant contact dermatitis, but can be a serious problem for some people. Allergic contact dermatitis occurs in people who have developed contact allergy to a specific substance, such as nickel, chemicals in rubber or acrylates. Theoretically, identifying and eliminating the allergen could cure the allergic hand eczema. However, in clinical practice such cases are rare, because the hand eczema is often due to a combination of endogenous factors and exposure to irritants and contact allergy. Nickel allergy is common and the association between hand eczema and nickel allergy will be described in next section, page 24.

Thus, hand eczema is multifactorial and atopic dermatitis has been shown to be a major risk factor, whereas the role of allergies is overestimated. In studies adjusted for exposure factors, sex and age do not influence the risk of hand eczema. Lifestyle factors such as smoking and alcohol have not been considered as risk factors for hand eczema. However, in a recently published study, an association between heavy smoking and hand eczema was confirmed.

Clinical aspects and morphology
Eczema is the most frequent dermatosis affecting the hands. Hand eczema can vary from mild involvement of a few fingers to a severe condition with blistering eruptions and pain affecting the entire hand and all the fingers. Hand eczema is characterized by signs of erythema, vesicles, papules, fissures, scaling, hyperkeratosis, and by itch and pain. There is usually no correlation between the outward morphology and the aetiology of hand eczema, and the morphology varies over time within the same patient. All types of hand eczema are exacerbated by water, dryness, friction and cold. One way to grade the severity of hand eczema is by the Hand Eczema Severity Index, HECSI, which employs scoring of both the morphology and the extent of the affected area. Other grading methods consider only the extent of the eczematous area.

There is no single universally accepted classification for hand eczema. Most published classifications invoke a combination of aetiological factors, such as irritative, allergic or atopic disease, and morphological features such as pompholyx, vesicular and hyperkeratotic eczema. Due to the multifactorial aetiology of hand eczema it may be difficult to determine the role of atopic dermatitis, contact allergy, and exposure to skin irritants in an individual with hand eczema.
**Prognosis and Consequences**

Hand eczema has a considerable public health impact because it tends to run a chronic relapsing course, with the vast majority of patients experiencing negative psychological consequences. Several studies have shown a mean duration time of hand eczema exceeding 10 years. In an 8-year follow-up almost 68% of cases, still reported hand eczema the previous year. In a fifteen-year follow-up of hand eczema, Meding *et al.* showed a poor long-term prognosis for hand eczema in the general population. Of all cases, two-thirds reported periods of hand eczema during the follow-up period and nearly half reported symptoms during the previous year. For about 5% the consequences were long periods on sick-leave, disability pension or changes of occupation. Meding *et al.* also showed that the main determinant for a poor long-term prognosis is widespread hand dermatitis at the initial examination. Other important factors are low age at onset of hand eczema, history of childhood eczema, and contact allergy. In a Danish study was found that a longer delay before medical attention was associated with poor prognosis.

Chronic hand eczema is associated with significantly lower quality of life, comparable to that of generalized eczema or psoriasis. Hand eczema may constitute a considerable problem for the individual as it may disturb sleep and hamper leisure activities and also – as an occupational skin disease – cause sick leave and sometimes change of occupation. The social stigma associated with a visible skin disease can be a great burden. The hands are important in human communication and expression. Hand eczema may also result in major psychological problems e.g. anxiety, low self-esteem and social phobia.

The high prevalence of hand eczema, its chronically relapsing course, its poor prognosis, its high impact on quality of life, and its tendency to cause disability and economic hardship make hand eczema an important disease to study from an individual and a social perspective.

**Nickel Allergy and Hand Eczema**

Nickel allergy is considered as a possible risk factor for hand eczema. The association has previously been studied in the general population using self-reports of nickel allergy and hand eczema. In these studies hand eczema was reported by 30–43% of the nickel-sensitive individuals. Only a few population-based studies have been published that also include patch testing. A summary of previously published, population-based
studies regarding the association between nickel allergy and hand eczema is shown in Table 3. Mortz et al. reported, in 2002, a doubled risk of hand eczema in nickel-sensitive adolescents. A hand eczema prevalence of 42% (odds ratio 2.95) in nickel-sensitive women was reported by Nielsen et al. in 1990, while in a follow-up study in 1998, this association was not found. In a study among Finnish university students, in 2001, no statistically significant increase in hand eczema was found in nickel-positive individuals. Some of the studies presented in Table 3 include men in the study population. However, owing to the small number of men who are sensitive to nickel, the association with hand eczema is not presented in these studies. In one Swedish study including men, no association between nickel allergy and hand eczema was found. Thus, the association between nickel allergy and hand eczema needs to be addressed further.
Table 3. Previously published population-based studies concerning the association between nickel allergy and hand eczema.

**Nickel allergy by self-reports**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Country</th>
<th>Target population</th>
<th>n</th>
<th>Measure of prevalence</th>
<th>Self-reported nickel allergy</th>
<th>No self-reported nickel allergy</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menné</td>
<td>1982</td>
<td>Denmark</td>
<td>16-99 years (women)</td>
<td>1,976</td>
<td>Lifetime</td>
<td>43</td>
<td>18.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Meding</td>
<td>2001</td>
<td>Sweden</td>
<td>19-80 years</td>
<td>10,950</td>
<td>Lifetime</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stenberg</td>
<td>2010</td>
<td>Sweden</td>
<td>16-84 years</td>
<td>&gt;65,000</td>
<td>1-year</td>
<td>–</td>
<td>–</td>
<td>2.31(2.16-2.47)</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

* multivariate analysis

**Nickel allergy by patch tests**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Country</th>
<th>Target population</th>
<th>n</th>
<th>Measure of prevalence</th>
<th>Nickel-positive</th>
<th>Nickel-negative</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peltonen</td>
<td>1979</td>
<td>Finland</td>
<td>Staff of newspaper, printing plant and hospital workers</td>
<td>980</td>
<td>Lifetime</td>
<td>45</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Meijer</td>
<td>1995</td>
<td>Sweden</td>
<td>Men in military service</td>
<td>520</td>
<td>Lifetime</td>
<td>4.5</td>
<td>6.4</td>
<td>–</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mattila</td>
<td>2001</td>
<td>Finland</td>
<td>University students(women)</td>
<td>188</td>
<td>Point</td>
<td>14</td>
<td>11</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nielsen</td>
<td>2002</td>
<td>Denmark</td>
<td>15-41 years (women) patch tested 1990</td>
<td>154</td>
<td>Lifetime</td>
<td>42.3</td>
<td>21.1</td>
<td>2.95 (1.17-7.74)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15-41 years (women) patch tested 1998</td>
<td>276</td>
<td>Lifetime</td>
<td>31.9</td>
<td>32.6</td>
<td>0.95 (0.48-1.48)</td>
<td>–</td>
</tr>
<tr>
<td>Mortz</td>
<td>2002</td>
<td>Denmark</td>
<td>12-16 years</td>
<td>1,146</td>
<td>Lifetime</td>
<td>22.4</td>
<td>9.4</td>
<td>2.36 (1.39-4.01)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Bryld</td>
<td>2003</td>
<td>Denmark</td>
<td>20-44 years (women, twins)</td>
<td>697</td>
<td>Lifetime</td>
<td>54</td>
<td>41</td>
<td>2.73(1.65-4.51)</td>
<td>–</td>
</tr>
<tr>
<td>Thyssen</td>
<td>2009</td>
<td>Denmark</td>
<td>18-60 years (women)</td>
<td>1843</td>
<td>Lifetime</td>
<td>28.0</td>
<td>24.7</td>
<td>n.s.</td>
<td>–</td>
</tr>
</tbody>
</table>

* adjusted for co-twins, both men and women
– not given
n.s. not significant
Atopic dermatitis (AD) is a chronic and relapsing disease that is affecting a growing number of patients. The lifetime prevalence of AD is estimated to 15–30% in children and 2–10% in adults. An increased incidence has been reported in western countries over the past decades. In 60–70% of AD patients there is a positive family history of atopy. AD is related to allergic rhinitis, allergic conjunctivitis and asthma. It is an inflammatory skin disease with an onset usually before the age of 2, but can also appear for the first time in adulthood. The primary location of the lesions varies depending on age of the patient: cheeks and scalp during infancy, knees and extensor surfaces during crawling stage and joint flexures in adolescents. In adulthood, eyelids, forehead, neck, upper chest, around the wrists and dorsal aspects of hands are classical sites. History of atopic dermatitis is the most important risk factor for hand eczema later in life. This association is discussed further in the section on hand eczema, page 22. In younger patients, the lesions are quite acute, with erythema, blisters and crusts. Later on, more chronic eczema with lichenification and prurigo papules dominate the picture. Severe pruritus and excoriations are common at all ages.

AD is a complex disease. Recent studies in genetics, epidemiology and immunology have provided new important pieces to the mechanism of pathogenesis. The role of genetic factors has been demonstrated in twin studies and furthermore by positive family history being the strongest risk factor for AD. The finding of an association with loss-of-function mutations of the filaggrin gene, which encodes a key protein in terminal differentiation of the epidermis, can be considered as a breakthrough. Skin barrier dysfunction has a central role in AD. Increased transepidermal water loss leads to dry skin, which also may favour the penetration of allergens, bacteria, and viruses. Furthermore, reduced cell-mediated immunity and deficiency in antimicrobial peptides contribute to secondary bacterial and viral infections, which are among the most important complications of AD.

The management of AD remains a clinical challenge, where information and communication is very important. The primary goals are to improve the barrier function, to suppress inflammation, and to control microbial colonization.

In questionnaires, the term ‘childhood eczema’ is often used for assessment of atopic dermatitis. The most common type of eczema in childhood is atopic dermatitis and the question ‘Have you had childhood eczema?‘ has previously been validated.
Several studies concerning hand eczema, atopy, and contact allergy in the past year focus on genetics and filaggrin (FLG) null mutations. Several of those studies have shown that null mutations in the profilaggrin gene are associated with atopic dermatitis. Filaggrin (FLG) is a structural protein and is of importance for the formation of the epidermal skin barrier. Recent reports discuss a possible association between hand eczema and the filaggrin gene. Scharschmidt et al. concluded that the barrier abnormality due to filaggrin deficiency correlates with reduced inflammatory thresholds to topical irritants and haptens. In another study was shown that the filaggrin mutations were associated with increased susceptibility to chronic irritant contact dermatitis. In a Danish study was found that FLG null-mutations were significantly associated with hand eczema in subjects with atopic dermatitis, but no association was found in those without atopic dermatitis.

Whether the FLG null mutations are associated with allergic contact dermatitis or not is unclear. In a study by Novak et al. it was shown that the filaggrin gene null-mutations were positively associated with nickel sensitization. However, in other studies this association could not be verified. FLG mutations have also been shown to be associated with ichthyosis vulgaris. This new and more detailed knowledge about the filaggrin gene is exciting, but concerning its association with contact allergy further studies are required.

Recent discoveries from Germany show that nickel might directly activate a receptor (Toll-like receptor 4) which acts as a gatekeeper of innate immunity. Activating this receptor promotes the inflammation cascade and leads to an allergic reaction to nickel.

Another interesting issue is whether atopy favours contact allergy or not. More recent studies show that allergic contact dermatitis is at least as common in patients with AD as in the general population, if not more so. Since it is known that a majority of atopic patients have a disturbed epidermal barrier function, it has been speculated that this phenomenon increases penetration of allergens and thus promotes sensitization. Some studies present an increased prevalence of allergy to preservatives in atopics, which probably is related to their increased exposure to such substances.
Epidemiological surveillance of contact allergy

Epidemiology can be used to estimate the occurrence of contact allergy. It is also of interest to analyze whether contact allergy is more common in specific groups or if allergy to a specific allergen is increasing or decreasing in the general population. Epidemiological tools can be used to evaluate the results of interventions in specific populations. When estimating the prevalence of contact allergy, reliable and inexpensive epidemiological tools are required. Patch testing is the most reliable method. However, when studying the general population, patch testing is expensive and difficult to perform for logistical reasons.

Validity

The concept of validity concerns the degree to which a measurement or study reaches a correct conclusion. The word ‘valid’ is derived from the Latin validus, meaning strong. Validity of a measurement tool is considered to be the degree to which the tool measures what it claims to measure.

When comparing a test or a method against a reference (‘gold’) standard, the terms sensitivity and specificity are used to describe the validity.

*Sensitivity* is the proportion of persons with the disease of interest who have positive test results.

*Specificity* is the proportion of persons without the disease of interest who have negative test results.

Sensitivity and specificity are descriptors of the accuracy of a test. Although well established, sensitivity and specificity are not ideal for clinical use as they are population measures. These terms summarize the characteristics of the test over a population. *Predictive values* combine the true and false positives (or negatives) into one and are used for estimation of the probability of the presence (or absence) of disease in individuals.

*Positive predictive value (PPV)* is defined as the proportion of persons with positive test results who actually have the disease of interest. Thus, PPV can be used to estimate how likely it is that the disease is present if the test is positive.

*Negative predictive value (NPV)* is defined as the proportion of persons with negative test results who do not have the disease of interest.
True diagnosis
‘gold standard’

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test results</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>False negative</td>
<td>True negative</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{a}{a+c} \)
Specificity = \( \frac{d}{b+d} \)
Positive predictive value = \( \frac{a}{a+b} \)
Negative predictive value = \( \frac{d}{c+d} \)

The predictive value is critically dependent on the population chosen and the prevalence of disease. This means that the positive predictive value may not be transferable from one population to another if the populations have different prevalences of the disease. Sensitivity and specificity are more adequate when comparing different studies.

When comparing two methods of measurement the Proportion of agreement can be used. Proportion of agreement is informative and useful, but taken by itself it is of limited value.
Proportion of agreement = \( \frac{a+d}{a+b+c+d} \)

Questionnaires
In observational studies, especially in large study populations, questionnaires may be useful, provided that the questions are validated. Questionnaires are cost-effective and convenient for both the participant and the investigator. However, very few dermatological questionnaires have been adequately validated. Response rates below 70% are likely to bias the result. In a Swedish study, the use of the self-diagnosis term ‘hand-eczema’ was validated. Furthermore, a question on self-reported hand eczema has been validated, as has the question ‘Have you had childhood eczema?’
It is of special interest to follow the prevalence of nickel allergy to evaluate the effect of the Nickel Directive. Regarding nickel allergy, questions on self-reported metal dermatitis have been validated in a few studies. In a recently published study of Swedish adolescents, the question about metal dermatitis showed low validity in predicting nickel allergy, with a sensitivity of 52%. Two other studies reported a positive predictive value (PPV) of 54% and sensitivity of 65% and 82% respectively, when using questions about skin reactions after contact with metals. Furthermore, Mortz et al. found that only 31% of adolescents with self-reported metal-related eczema were positive in nickel patch test (PPV=31%).

**CE-DUR**

Another approach for epidemiological surveillance is the CE-DUR method that is discussed in studies from Germany and Denmark. The CE-DUR method uses assumptions to estimate the 10-year prevalence of contact allergy, assumptions based on national patch test sales information as well as clinical data. In the German study, the authors concluded that the morbidity data concerning contact allergy were in good accordance with data from population-based epidemiological studies. However, regarding nickel allergy, the 9-year prevalence was 2.3% and 5.5% in different models, which is considerably lower than in population-based studies including patch test. According to the Danish authors, the CE-DUR method requires further validation but may be useful for rapid and inexpensive surveillance of contact allergy in the general population.

**Self-testing**

Tests that can be performed and evaluated by the patients at home have been used in other fields of medicine. The usefulness of self-tests has been studied through population-based surveys in internal medicine and for early detection of cancer. Self-testing has not been used in contact allergy investigations due to the fact that evaluation of a patch test requires an adequately trained patch test reader. However, in areas where dermatological health care resources are scarce or for surveillance of contact allergy in the general population, this method might be useful. Hence, the method has to be validated and evaluated. A self-test kit has recently been introduced on the Swedish market for detection of contact allergy to nickel and fragrance substances. The only previous report concerning contact allergy and self-testing is a conference presentation. That study showed a high accordance between the subjects’
self-reading and the dermatologists’ reading regarding allergy to nickel and fragrance mix.
AIMS OF THE THESIS

The overall aim of this thesis was to study the association between hand eczema and nickel allergy in the general population and to evaluate methods to follow the prevalence of nickel allergy.

The specific aims of the individual studies were:

Study I To investigate the occurrence of self-reported hand eczema after 20 years in women patch tested to nickel as schoolgirls.

Study II To further investigate the relation between nickel allergy and hand eczema in the established cohort of women from the general population, now aged 30–40 years.

Study III To investigate the validity of self-reported nickel allergy.

Study IV To investigate the validity of self-patch testing for nickel allergy.
SUBJECTS AND METHODS

PART I: HAND ECZEMA AND NICKEL ALLERGY (STUDY I–II)

Study population
Study I was a 20-year follow-up, based on a cohort investigated for the occurrence of nickel allergy. In 1982–1983, 958 schoolgirls aged 8, 11 and 15 years and living in two cities in the county of Örebro, in central Sweden, were patch-tested for occurrence of nickel allergy \(^{109}\). The prevalence of nickel allergy was 9\% in total (8\% in the 8-year-olds, 9\% in the 11-year-olds, and 12\% in the 15-year-olds). Another 4\% showed doubtful reactions.

Twenty years later, in 2003, current addresses were found for 908 of these women (now aged 29–36 years). They were invited to participate in a follow-up questionnaire study concerning nickel allergy and hand eczema. After two reminders, the response rate was 80.9\% (n=735).

Study II, in 2006, included a second questionnaire, a clinical investigation and patch testing. Of those in the established cohort from the previous questionnaire study, 478 were still living in Örebro County. For logistical reasons only this group of 478 women were invited to participate in the study. After receiving a letter and a phone call, 369 of the 478 (77.2\%) individuals participated in this study, Figure 3.
Study I
1982–1983
958 patch tested

2003
908 addresses available
81%

Study II
2006–2007
735 answered questionnaire I

478 living in Örebro County in 2006
77%

369 participated
(questionnaire II, clinical investigation, patch test)

Figure 3. Presentation of the study population and the design of the two studies.

Questionnaires
The questionnaire used in 2003 (Questionnaire I) contained 35 questions regarding occurrence of hand eczema, atopy history, nickel sensitivity, occupation, and wet exposure. The main questions are presented in Table 4. Occupations involving wet work or other skin irritant exposure were classified as ‘high-risk’ occupations for hand eczema, in line with a previous classification. ‘High wet exposure’ was defined as occupational skin exposure to water >2 h/day, and/or hand washing >20 times/day, and/or housework >2 h/day.

In 2006 Questionnaire II was used, which consisted of 21 of the questions from Questionnaire I and was answered by the participants immediately before undergoing a clinical investigation and patch testing.
Table 4. The main items in the questionnaires.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had hand eczema after age 15?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Have you had hand eczema on any occasion during the past 12 months?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Have you ever consulted a doctor regarding hand eczema?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Have you had childhood eczema (before age 15)?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Have you ever had hay fever?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Have you ever had asthma?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Are you sensitive/hypersensitive/allergic to nickel?</td>
<td>□ yes, with severe symptoms □ yes, with mild symptoms □ yes, without symptoms when avoiding contact □ no</td>
</tr>
<tr>
<td>Do you get a rash from metal buttons, jewellery, or other metal items</td>
<td></td>
</tr>
<tr>
<td>that come in direct contact with your skin?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>What is your present occupation?</td>
<td>......................................................................</td>
</tr>
<tr>
<td>Have you ever changed job due to hand eczema?</td>
<td>□ yes □ no</td>
</tr>
<tr>
<td>Are your hands, at work, exposed to water and detergents?</td>
<td>□&lt;1/2 h/day □½-2 h/day □&gt;2 h/day</td>
</tr>
<tr>
<td>How many times a day do you wash your hands?</td>
<td>□1-10 times/day □11-20 times/day □&gt;20 times/day</td>
</tr>
</tbody>
</table>
Clinical examination
The clinical investigation took place immediately before the patch test reading in April-May 2006 and October 2006-March 2007, and was performed by the same doctor (A.J.). The participants were interviewed about signs and symptoms of hand eczema and their hands were examined for signs of eczema. Erythema, fissures, scaling and papules/vesicles were registered. Criteria for the diagnosis ‘current hand eczema’ were erythema and papules/vesicles or erythema, scaling and fissures and/or a positive history including these signs during the previous year.

Patch testing
A standard patch test, MekosTest®, (Vitaflo Scandinavia AB, Göteborg, Sweden) was used. The test contains 24 different substances, among them nickel sulphate 0.16 mg/patch. The tests were applied on the upper back and left on for 48 hours. The reaction was read at day (D) 3 to imitate the previous patch test procedure of 1982–1983. The requirements for the result ‘positive reaction’ to nickel sulphate were also congruous with the baseline study in 1982–1983, i.e. erythema, infiltration and papules (++) reaction). Morphological evaluation was performed according to international standard (ICDRG) 24. The reaction was said to be ‘doubtful’ if it was + or weaker. In case of doubtful reaction to nickel sulphate, an additional test was done with a dilution sequence. The dilution procedure is presented in detail in paper II. Individuals with doubtful test reactions to nickel, who did not participate in the dilution test (n=14), were excluded from further analysis. Thus 355 women were eligible for analysis in the second study.

Analyses
To investigate the association between nickel allergy and hand eczema, prevalences were estimated. Chi-square tests were used for comparisons of proportions. The associations of hand eczema comparing individuals with and without nickel allergy were expressed as prevalence proportion ratios (PPRs) supplemented with 95% confidence intervals (CIs) using generalized linear models. This association was also adjusted for childhood eczema and ‘high wet exposure’, all coded as ‘yes’ or ‘no’. Statistical interactions pair-wise between these variables were tested, especially to see if the association between hand eczema and nickel allergy was homogeneous or heterogeneous after stratification for childhood eczema or high wet exposure. Hand eczema was evaluated using three different definitions, namely (a) hand eczema after age 15, (b) hand eczema in the past 12 months, and in the second study also (c) current
hand eczema. STATA (StataCorp, College Station, TX, USA) release 10 was used for
generalized linear models, all other analyses were done in SPSS version 13 and 15 (SPSS
Inc, Chicago, IL, USA).

To investigate possible effects of dropouts on the results, missing value analyses were
performed in both studies. There were 173 non-respondents in study I. Every second
women was chosen for a short telephone interview covering the main questions of the
questionnaire. In the second study, the answers from Questionnaire I and the patch test
results from 1982–1983 were known for all 109 dropouts. A Bernoulli random model
was used to predict the outcome of a new patch test (in dropouts) using probabilities
from the observed relations. The procedure was repeated ten times and p-values were
calculated.

PART II: METHODS FOR EPIDEMIOLOGICAL SURVEILLANCE OF NICKEL ALLERGY (STUDY III–IV)

Validity of self-report by questionnaire (III)

Study population
The population in this study was the same as in Study II, Figure 3. Thus, 369 women
aged 30–40 years, from the general population were participating.

Questionnaire
The participants answered Questionnaire II before undergoing a clinical examination
and patch testing. The two questions regarding nickel sensitivity were: (i) ‘Are you
sensitive/hypersensitive/allergic to nickel?’ and (ii) ‘Do you get a rash from metal
buttons, jewellery or other metal items that come in direct contact with your skin?’ The
response alternatives are shown in Table 4. In the analysis, the answers to question (i)
were simplified to ‘yes’ or ‘no’ and all answers that included ‘yes’ were added together.

Patch testing
A standard patch test, MekosTest® (Vitaflo Scandinavia AB, Göteborg, Sweden) was
used, as described for study II. As also mentioned, to be congruous with the baseline
study the definition of a ‘positive reaction’ to nickel sulphate required erythema,
infiltration and papules (++ reaction). The reaction was said to be ‘doubtful’ if it was +
or weaker.
Validity of self-test (IV)

Study population
This study was performed in three dermatology departments in Sweden. Patients were included consecutively from the clinics when referred to patch testing as part of an eczema investigation. Inclusion and exclusion criteria are shown in Table 5. In total, 191 patients participated, 69% women, and average age was 44 years.

Table 5. Inclusion and exclusion criteria for study IV

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 18–65 years</td>
<td>1. Dermatitis on the test area</td>
</tr>
<tr>
<td>2. Never patch tested before</td>
<td>2. Systemic treatment with corticosteroids, antihistamine or other immunosuppressive treatment</td>
</tr>
<tr>
<td>3. Able to read and understand Swedish</td>
<td>3. Exposure to UV-light the past 14 days</td>
</tr>
<tr>
<td></td>
<td>4. Topical treatment with corticosteroids on the test area the past 14 days</td>
</tr>
<tr>
<td></td>
<td>5. Pregnancy</td>
</tr>
</tbody>
</table>

Patch testing
The patients were tested with nickel sulphate 5% pet. and fragrance mix 8% pet. along with the Swedish baseline series provided by Chemotechnique Diagnostics, Vellinge, Sweden. Patch tests were applied for two days on the back and readings were performed at D3–4 and at D7. For the analysis of data +, ++, and +++ readings were pooled as positive patch test. Positive patch test to nickel sulphate D3 and/or positive patch test D7 is referred to as positive by ‘gold standard’.

Self-testing
Patients received a self-test package on the same day as the patch test on the back was applied. The self-test used in the study, Nixema® (Mekos Laboratories ApS, Hillerød, Denmark), is a medical plaster that incorporates two allergen patches with nickel sulphate 0.16 mg/patch and fragrance mix 0.35 mg/patch, respectively. The test package contained detailed written instructions from the Nixema® supplier, regarding how to apply the test on the upper arm and how to evaluate the result. The patients
applied the self-test on the upper arm on the same day as the patch test was applied on the back. The self-reading was done by the patient on D3–4, before the appointment at the clinic. The patient evaluated him/herself by noting a positive or negative score on a recording sheet, which was delivered to the investigator in a sealed envelope that was not opened until analysis. Patch test reading was then performed both on the back and on the arm by the dermatologist.

**Analyses**

In both study III and IV, the validity was estimated by calculating the sensitivity, specificity and negative/positive predictive values. In addition, proportion of agreement was calculated in study IV. The results from the standardized patch test applied on the upper back and read by a dermatologist were referred to as ‘gold standard’. The proportions were supplemented with 95% confidence intervals. Chi square test was used for comparison of proportions. The data were analyzed using SPSS version 15 (SPSS Inc., Chicago, IL, USA).

**Ethics**

Study I was approved by the Medical Research Ethical Committee of Örebro (220/02) and study II–IV were approved by the Ethics Committee of Uppsala, Sweden (2006/007, 2009/059).
RESULTS

PART I: HAND ECZEMA AND NICKEL ALLERGY (STUDY I–II)

Questionnaire I (in 2003)
Answers from Questionnaire I, a 20-year follow up, are shown in Table 6. Self-reported prevalence concerning occurrence of hand eczema, atopy history, occupation and ‘high wet exposure’ are presented.

Table 6. Study I, in 2003. (n=735)
Descriptive data and prevalence figures from Questionnaire I

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>32 years (range 29–36)</td>
</tr>
<tr>
<td>History of childhood eczema</td>
<td>33.1%</td>
</tr>
<tr>
<td>Hand eczema after age 15</td>
<td>17.6%</td>
</tr>
<tr>
<td>Hand eczema the past 12 months</td>
<td>12.8%</td>
</tr>
<tr>
<td>High-risk occupation</td>
<td>24.4%</td>
</tr>
<tr>
<td>High wet exposure</td>
<td>33.7%</td>
</tr>
<tr>
<td>Children &lt; 4 years of age</td>
<td>39.5%</td>
</tr>
<tr>
<td>Self-reported nickel allergy</td>
<td>38.3%</td>
</tr>
</tbody>
</table>

Questionnaire II (in 2006)
In study II, 369 women answered Questionnaire II before a clinical investigation and patch testing. Results from Questionnaire II concerning hand eczema and possible risk factors for hand eczema are presented in Table 7.

Table 7. Study II, in 2006–2007 (n=369)
Descriptive data and prevalence figures from Questionnaire II

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>35 years (range 31–40)</td>
</tr>
<tr>
<td>History of childhood eczema</td>
<td>35.9%</td>
</tr>
<tr>
<td>Hand eczema after age 15</td>
<td>24.4%</td>
</tr>
<tr>
<td>Hand eczema in the past 12 months</td>
<td>15.0%</td>
</tr>
<tr>
<td>High wet exposure</td>
<td>40.1%</td>
</tr>
<tr>
<td>Self-reported nickel allergy</td>
<td>40%</td>
</tr>
</tbody>
</table>
**Clinical examination and patch testing**

At the clinical examination 53 of 369 (14.4%) were diagnosed as having ‘current hand eczema’, in other words signs and symptoms of eczema during the previous year. The patch test in 2006–2007 gave 30.1% nickel-positive individuals. When comparing the patch test results from 1982–1983 with the results of the re-test in 2006, 74% of the previous positive reactions were verified. Furthermore, 77/111 (69.4%) nickel positive individuals were new cases, Table 8.

**Table 8. Comparison of patch test results for nickel in 1982–1983 and at re-test in 2006.**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
</tr>
<tr>
<td>Negative</td>
<td>77</td>
</tr>
<tr>
<td>Doubtful</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
</tr>
</tbody>
</table>

**Association between nickel allergy and hand eczema**

**Study I (Questionnaire I)**

The prevalence of self-reported hand eczema from Questionnaire I in relation to patch test results 1982-1983 is presented in Table 9. There was no significant difference in the occurrence of hand eczema between those who were nickel-positive in 1982–1983 compared with those who were nickel-negative.

**Table 9. Prevalence of hand eczema according to results from Questionnaire I in relation to patch test results for nickel in 1982–1983.**

<table>
<thead>
<tr>
<th>Nickel patch test in 1982–1983</th>
<th>Hand eczema after age 15 (%)</th>
<th>Hand eczema in the past 12 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n=62)</td>
<td>16.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Negative (n=636)</td>
<td>17.5</td>
<td>12.3</td>
</tr>
<tr>
<td>P-value</td>
<td>0.576</td>
<td>0.559</td>
</tr>
</tbody>
</table>

*Doubtful reactions excluded*
There were 33 individuals with doubtful patch test reaction to nickel in 1982–1983. If all of them were regarded as nickel-positive, still no significant difference was seen in comparison with those who had negative reactions. Regarding self-reported nickel allergy, 276 women (38.3%) in study I gave a positive answer to the question about nickel sensitivity. Hand eczema was reported significantly more often by individuals who considered themselves nickel-sensitive than by the others.

**Study II (Questionnaire II and patch test)**

Study II intended to investigate the relation between nickel allergy and hand eczema further and a repeated patch test was performed. Self-reports concerning hand eczema in Questionnaire II and results from the clinical investigation were compared with patch test results for nickel. Table 10 presents unadjusted and adjusted prevalence proportion ratios (PPRs) for hand eczema, in relation to the nickel patch test result, childhood eczema and ‘high wet exposure’. The three definitions of hand eczema, (a) hand eczema after age 15 years, (b) hand eczema in the past 12 month, and (c) ‘current hand eczema’, are presented separately. There were no statistically significant associations between nickel patch test results in 2006–2007 and any of the definitions of hand eczema in either the unadjusted or the adjusted models.
Table 10. The association between three definitions of hand eczema (a,b,c) and nickel patch test, childhood eczema and ‘high wet exposure’. Results shown by prevalence of hand eczema and unadjusted and adjusted prevalence proportion ratios (PPRs).

(a).

<table>
<thead>
<tr>
<th></th>
<th>Hand eczema after age 15 years</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPR (95% CI)</td>
<td>PPR (95% CI)</td>
</tr>
<tr>
<td>Nickel patch test in 2006–2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=244)</td>
<td>23.0</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Positive (n=111)</td>
<td>25.2</td>
<td>1.10 (0.74–1.63)</td>
<td>1.03 (0.71–1.50)</td>
</tr>
<tr>
<td>Childhood eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=234)</td>
<td>12.4</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=130)</td>
<td>44.3</td>
<td>3.57 (2.42–5.28)</td>
<td>3.68 (2.45–5.54)</td>
</tr>
<tr>
<td>‘High wet exposure’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=219)</td>
<td>22.7</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=147)</td>
<td>25.2</td>
<td>1.11 (0.76–1.60)</td>
<td>1.01 (0.71–1.43)</td>
</tr>
</tbody>
</table>

(b).

<table>
<thead>
<tr>
<th></th>
<th>Hand eczema in the past 12 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPR (95% CI)</td>
<td>PPR (95% CI)</td>
</tr>
<tr>
<td>Nickel patch test in 2006–2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=244)</td>
<td>14.3</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Positive (n=111)</td>
<td>15.5</td>
<td>1.08 (0.63–1.84)</td>
<td>1.09 (0.64–1.84)</td>
</tr>
<tr>
<td>Childhood eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=234)</td>
<td>6.8</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=130)</td>
<td>29.2</td>
<td>4.28 (2.48–7.36)</td>
<td>4.65 (2.60–8.31)</td>
</tr>
<tr>
<td>‘High wet exposure’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=219)</td>
<td>14.2</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=147)</td>
<td>15.6</td>
<td>1.11 (0.67–1.82)</td>
<td>1.02 (0.62–1.67)</td>
</tr>
</tbody>
</table>

(c).

<table>
<thead>
<tr>
<th></th>
<th>‘Current hand eczema’</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPR (95% CI)</td>
<td>PPR (95% CI)</td>
</tr>
<tr>
<td>Nickel patch test in 2006–2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=244)</td>
<td>12.7</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Positive (n=111)</td>
<td>16.2</td>
<td>1.28 (0.75–2.18)</td>
<td>1.28 (0.74–2.20)</td>
</tr>
<tr>
<td>Childhood eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=234)</td>
<td>8.1</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=130)</td>
<td>24.4</td>
<td>3.01 (1.78–5.09)</td>
<td>3.14 (1.80–5.49)</td>
</tr>
<tr>
<td>‘High wet exposure’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=219)</td>
<td>13.6</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes (n=147)</td>
<td>14.3</td>
<td>1.05 (0.62–1.76)</td>
<td>1.03 (0.61–1.74)</td>
</tr>
</tbody>
</table>
An analysis of the relation between nickel allergy and hand eczema was performed separately in women with and women without history of childhood eczema. A doubled hand eczema risk was found in nickel-positive compared with nickel-negative women without history of childhood eczema, Figure 4. PPR (95%CI) was 2.23 (1.10–4.49) In women with a history of childhood eczema no such increased risk was found. PPR was then 0.76 (0.46–1.23).

Figure 4. The association between nickel patch test results and hand eczema, separately in women with and without history of childhood eczema.

Hand eczema and atopic dermatitis

History of childhood eczema more than tripled the prevalence of hand eczema both in study I and study II. Table 11 presents the relationship between reported childhood eczema and hand eczema in study I. The prevalences and PPRs obtained in study II for the three definitions of hand eczema in relation to childhood eczema are shown in Table 10. All associations concerning history of childhood eczema and hand eczema are statistically significant.
Table 11. The occurrence of hand eczema in relation to history of childhood eczema

<table>
<thead>
<tr>
<th>History of childhood eczema</th>
<th>Hand eczema after age 15 (%)</th>
<th>Hand eczema in the past 12 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=242)</td>
<td>31.4</td>
<td>24.0</td>
</tr>
<tr>
<td>No (n=483)</td>
<td>10.6</td>
<td>6.9</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hand eczema and irritant exposure

In Questionnaire I, 24% of the respondents reported high-risk occupations for hand eczema. However, there was no statistically significant difference in the prevalence of hand eczema between women who worked in high-risk occupations and those who did not.

‘High wet exposure’ was reported by 33.7% in Questionnaire I and by 40.1% in Questionnaire II. None of the studies showed any statistically significant difference in the prevalence of hand eczema between those with and those without ‘high wet exposure’.

Missing value analyses

When non-respondents in study I were analyzed, no statistically significant difference was found regarding history of childhood eczema, occurrence of hand eczema, or self-reported nickel allergy. A comparison of participants with non-participants in 2006–2007 showed a statistically significant difference regarding history of childhood eczema. For history of hand eczema and other eczema, no statistically significant difference was found between participants and non-participants. When the estimated outcome of a new nickel patch test for the dropouts was added in the missing value analysis, the estimated prevalence of hand eczema after age 15 was 18.6–22.0% in nickel-positive individuals versus 17.1–18.6% in nickel-negative individuals (p-values were in the range of 0.214–0.994).
PART II: METHODS FOR EPIDEMIOLOGICAL SURVEILLANCE OF NICKEL ALLERGY (STUDY III–IV)

Validity of self-report by questionnaire (III)
The self-reported prevalence of nickel allergy was higher than the occurrence of positive patch test to nickel. In Questionnaire II, 40% (140/348) answered ‘yes’ to question (i) ‘Are you sensitive/hypersensitive/allergic to nickel?’ and 35% (126/354) answered ‘yes’ to question (ii) ‘Do you get a rash from metal buttons, jewellery or other metal items that come in direct contact with your skin?’ Self-reported nickel allergy according to question (i) and question (ii) in relation to patch testing are shown in Table 12. The calculated sensitivity, specificity and positive and negative predictive values for the two different questions are also shown in Table 12.

Table 12. Self-reported nickel allergy in relation to patch test results and calculated validity of questions (i) and (ii).

<table>
<thead>
<tr>
<th>Question (i)</th>
<th></th>
<th></th>
<th>Total</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Patch test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>26</td>
<td>108</td>
<td>76</td>
<td>35</td>
<td>111</td>
</tr>
<tr>
<td>Negative</td>
<td>58</td>
<td>182</td>
<td>240</td>
<td>50</td>
<td>193</td>
<td>243</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>208</td>
<td>348</td>
<td>126</td>
<td>228</td>
<td>354</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>76 (67–84)</td>
<td>82/108</td>
<td>68 (59–77)</td>
</tr>
<tr>
<td>Specificity</td>
<td>76 (70–81)</td>
<td>182/240</td>
<td>79 (74–84)</td>
</tr>
<tr>
<td>PPV</td>
<td>59 (50–67)</td>
<td>82/140</td>
<td>60 (51–69)</td>
</tr>
<tr>
<td>NPV</td>
<td>88 (82–92)</td>
<td>182/208</td>
<td>85 (79–89)</td>
</tr>
</tbody>
</table>

PPV=positive predictive value, NPV= negative predictive value

Positive predictive values for the two questions were 59% and 60% respectively, which means that nickel allergy was verified in 59–60% of the women who had reported nickel allergy. Thus, the questions used overestimate the prevalence of nickel allergy. History of childhood eczema was overrepresented among women with ‘false positive’ self-reported nickel allergy (p=0.008). Neither self-reported hand eczema nor ‘high wet exposure’ influenced the validity.
In total, 108 nickel-sensitive women answered question (i) ‘Are you sensitive/hypersensitive/allergic to nickel?’ The proportion what selected each of the four response alternatives for this question is presented in Figure 5. These women were all patch tested positive to nickel, but only 48/108 (44%) reported symptoms of nickel allergy: 24% answered ‘no’ to question (i) in spite of a positive patch test.

![Figure 5. Answers to question (i) ‘Are you sensitive/hypersensitive/allergic to nickel?’ given by women with a positive patch test for nickel (n=108)](image)

**Validity of self-test (IV)**

Patch test as ‘gold standard’ gave 46/191 (24%) nickel-positive individuals, 41 women and five men. In addition three doubtful (IR or +?) reactions were found. Table 13 shows results read by the patients and results from established patch test method read by dermatologists at D3–4 and after two readings (‘gold standard’). Of the 46 individuals who evaluated the self-test for nickel as positive, 33 were regarded as positive by ‘gold standard’. The calculated sensitivity, specificity, positive/negative predictive values and the proportion of agreement for the self-test are also shown in Table 13.
Table 13. Self-test results read by the patient in relation to patch test results read by the dermatologist and the calculated validity of the self-test.

<table>
<thead>
<tr>
<th></th>
<th>Nickel patch test (dermatologist’s reading, back)</th>
<th>'Gold standard'(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reading D3–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Self-test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(patients’reading, arm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n=46)</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Negative (n=145)</td>
<td>9</td>
<td>136</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>152</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>% (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>77 (61–89)</td>
<td>30/39</td>
<td>72 (57–84)</td>
<td>33/46</td>
</tr>
<tr>
<td>Specificity</td>
<td>89 (83–94)</td>
<td>136/152</td>
<td>91 (85–95)</td>
<td>132/145</td>
</tr>
<tr>
<td>PPV</td>
<td>65 (50–79)</td>
<td>30/46</td>
<td>72 (57–84)</td>
<td>33/46</td>
</tr>
<tr>
<td>NPV</td>
<td>94 (89–97)</td>
<td>136/145</td>
<td>91 (85–95)</td>
<td>132/145</td>
</tr>
<tr>
<td>Proportion of agreement</td>
<td>87 (81–91)</td>
<td>166/191</td>
<td>86 (81–91)</td>
<td>165/191</td>
</tr>
</tbody>
</table>

PPV=positive predictive value, NPV= negative predictive value
\(^a\) ‘Gold standard’ is the conclusion from patch test reading by dermatologist on D3-4 and D7

The sensitivity for the self-test was 72%, when compared with ‘gold standard’ patch test method. The proportion of agreement was 86%. However, the sensitivity of the self-test was higher, 77%, when compared with patch test reading at D3–4 only. Positive predictive value for the self-test was 72% when compared with ‘gold standard’, which means that nickel allergy was verified in 72% of the women who evaluated the self-test as positive. Thirteen individuals reported nickel allergy from self-test, but were nickel negative according to ‘gold standard’ patch test. Among the false positives 54% had a history of atopic dermatitis versus 43% among the group as a whole.

The self-test for fragrance allergy was interpreted as positive by seven individuals whereas the ‘gold standard’ patch test gave nine positive reactions. Due to the low number of fragrance-positive individuals, no further analysis of fragrance allergy was performed.
DISCUSSION AND FUTURE PERSPECTIVES

In this thesis the focus has been on epidemiological aspects of nickel allergy, both its association with hand eczema and validation of epidemiological tools to follow the prevalence of nickel allergy. Previously there are only few population-based studies that focus on the association between nickel allergy and hand eczema and include patch testing. Further knowledge regarding this association can be useful in future prevention work. Questionnaires are sometimes used in epidemiological studies and thus validated questions are required. The new information in this thesis concerning the validity of self-reported and self-tested nickel allergy may be of value for future epidemiological surveillance of nickel allergy.

PART I: HAND ECZEMA AND NICKEL ALLERGY (STUDY I–II)

Hand eczema is common in the general population and it affects occupational as well as private aspects of life. The disease is a burden not only to the patient but also to society, since hand eczema mainly affects young people and thus interferes with their professional career. Prevention of hand eczema is important and hence knowledge about risk factors fundamental.

Nickel allergy and hand eczema

Contact allergy and especially nickel allergy have been generally accepted to be risk factors for the development of hand eczema. Undoubtedly, some people with nickel allergy have severe, chronic hand eczema, but it seems that most of the individuals who are allergic to nickel are asymptomatic (Figure 5). Previous statements that 30–40% of individuals with nickel allergy have hand eczema are based on studies using self-reported nickel allergy or data from patients in dermatology clinics (Table 3 in Background). Population-based studies including patch testing performed over the past 10 years showed no convincing difference in the prevalence of hand eczema between individuals with and without allergy to nickel (Table 3). Likewise, in the present studies there was no statistically significant difference regarding hand eczema between nickel-positive and nickel-negative individuals. Even when doubtful reactions were considered as positive, no statistically significant difference in the prevalence of hand eczema was found. Consequently, the association between nickel allergy and hand eczema might previously have been overestimated.
However, study II revealed a possible relation between nickel allergy and hand eczema in women without history of childhood eczema (Figure 4 in Results). The risk of developing hand eczema was doubled in that group and the same trend was found for all three hand eczema outcomes: hand eczema after 15 years of age, hand eczema in the past 12 months and ‘current hand eczema’. Only the association with hand eczema after age 15 was statistically significant however. This interaction remains enigmatic, but one explanation might be that differences are more visible in smaller groups. In those without childhood eczema, only a few reported hand eczema; 14 women reported hand eczema the past 12 months, whereas 7 of them were positive to nickel. Of those without childhood eczema, who reported hand eczema after 15 years of age (n=27), there were only 14 nickel-positive individuals. The fact that the PPR for hand eczema was considerably higher for history of childhood eczema than for nickel allergy may also have contributed to this observation. Of the women who reported hand eczema, a large proportion also reported history of atopic dermatitis (66%).

The proportion of women who were positive to nickel when patch tested in 2006 was high. Other population-based studies report a similar prevalence of nickel allergy (17–38%) among women of about the same age. A large proportion, almost 70%, of the nickel-positive women had become sensitized only after the patch test in childhood. Women of this age (30–40 years) have been widely exposed to nickel in jewellery, piercing and metal buttons before the European Nickel Directive was introduced. It does not seem probable that the nickel regulations have influenced the results regarding the relation between nickel allergy and hand eczema in this cohort. Many of the women were probably sensitized to nickel before the Directive came into full force in 2001. The directive only includes products used for prolonged contact with the skin, which means that hand exposure to nickel in, for example, tools, metal handles and keys, may still be as great as before the legislation.

Atopic dermatitis and hand eczema
Population-based studies have repeatedly found that history of atopic dermatitis is the most important risk factor for hand eczema. The results from study I and study II in this thesis are in concordance with previous studies. History of childhood eczema more than tripled both the prevalence of hand eczema after age 15 and the 1-year prevalence. The proportion of women reporting childhood eczema was surprisingly high, 33% in study I and 36% in study II. The reason for this is unclear. The analysis of non-responders in study I did not indicate a selection of skin atopics among the respondents, whereas the non-participants in study II showed a smaller proportion of skin atopics, 23%. The question used concerning atopic dermatitis has
previously been validated and found to give some overestimation. Of the 243 women in study I who reported childhood eczema, 37 could remember eczema located on the hands during childhood. Two-thirds of them still had hand eczema after age 15. These findings are in accordance with previous studies concerning predictive factors for hand eczema. Hand eczema during childhood has been shown as an important risk factor for hand eczema in adulthood. Furthermore, in a Swedish population-based study was found that a history of childhood eczema influenced onset of hand eczema before age 30, but had less impact at higher ages.

Skin irritant exposure
Occupational hand eczema is more often due to irritant than to allergic contact dermatitis. ‘High wet exposure’ was reported by a large proportion of the women in the present studies. One possible reason might be their age, 30–40 years, a time when many women have young children and do a lot of housework. Forty percent of the women had at least one child younger than 4 years in the household and hand washing > 20 times per day was reported by 15% and 19% respectively in the two studies. The occurrence of hand eczema was slightly higher in those who reported ‘high wet exposure’, but there was no statistically significant difference compared to those who did not report ‘high wet exposure’. In study I, 24%(178) of the women were in high-risk occupations for hand eczema: 133 in medical and nursing work, 19 in production, and 26 in service occupations. High-risk occupations were classified in line with a previously used classification scheme. However, there was no statistically significant difference in the occurrence of hand eczema between women in high-risk occupations and the rest of the women. Wet work is considered an important risk factor for the development of hand eczema. However, in cross-sectional studies the information about exposure refers to the time of data collection, which might not be the same as onset of hand eczema. Thus, it is difficult to draw conclusions with regard to the relationships between exposure and hand eczema. For such purposes another study-design would be required.

Consequences of hand eczema
Hand eczema is known to have costly consequences, which was confirmed in study I in this thesis. Half of those with hand eczema had consulted a doctor on some occasion and 15.5% reported change of job due to hand eczema. Sixteen of the 20 women who reported that they had changed jobs had a history of childhood eczema and only 3 of 20 were nickel-positive in childhood. Hand eczema in the general
population has a poor long-term prognosis and in a study by Meding et al. was shown that for about 5% the hand eczema had far-reaching consequences 69.

**Methodological aspects in study I–II**
The cohort studied was established in 1982–1983, when schoolgirls in two Swedish cities participated in a study including patch testing to diagnose nickel allergy. Thanks to those records and patch test results, it was possible to perform a prospective study focused on the development of hand eczema and its association with previous patch test results to nickel. Thus, the cohort was recruited from the general population and the response rate was good, 81%. The participation rate at the re-test in study II was also high, 77%. The women were all about the same age, 30–40 years old, which might be a limitation of the study. The missing value analysis showed that the non-participants did not seem to have an effect on the outcome variables. The results can be regarded as representative in both studies.

In the baseline study in 1982–1983, the requirement for a positive patch test reaction was ++ reaction. The proportion of doubtful reactions in the baseline study was then 4.5% (33 individuals). In study II, a dilution series was performed to evaluate doubtful reactions further, and approximately half of the doubtful reactions turned out positive and half of them negative. The patch test readings in 2006–2007 were all performed by the same doctor (A.J.) to minimize variation in the reading of the test. The reading was performed after 72 h to imitate the baseline study in 1982–1983. It is known that by performing only one reading, some of the positive reactions could be missed because of delayed reaction. Generally, there is a risk of false-positive nickel patch tests in atopics 116. This risk was limited by the definition of positive reaction as ++ reaction or more and further limited by the dilution test.

Speculations that people who learn early in life that they have nickel allergy might avoid exposure to skin irritants later appear not to be correct, at least not in this cohort. In Questionnaire I 42% reported ‘high wet exposure’ among those who were positive to nickel in childhood compared to 35% of nickel-negative women (p=0.08). Also, the same proportion of those who were nickel-positive and those who were nickel-negative in childhood had an occupation that entailed a high risk of hand eczema.
PART II: METHODS FOR EPIDEMIOLOGICAL SURVEILLANCE OF NICKEL ALLERGY (STUDY III–IV)

In this thesis work two different methods to follow the prevalence of nickel allergy were validated. Epidemiological surveillance of nickel allergy is important for evaluating interventions such as legislation of nickel release in the EU Directive. It is also of interest to follow the prevalence of nickel allergy in different groups in the general population, for example different occupations or age-groups.

Patch testing
Patch testing as a standardized method with readings performed by a dermatologist on D3–4 and D7 is the most reliable method to investigate the occurrence of contact allergy. This method is used in dermatology departments when investigating patients with eczema. However, because of its costliness and for logistical reasons, patch testing is poorly suited for studies of the general population. When being patch tested, each individual has to visit the dermatology department on several occasions. Consequently, in most population-based studies that include patch testing, only one reading is performed. When reading is done only on D3, 10–15% may be missed due to delayed reactions. The results of study IV were similar, showing that 15% of the positive reactions would have been missed with only one reading on D3. Sometimes patch test readings are performed only on D2, resulting in even more missed reactions to nickel. In a Danish study was found that 18–30% of the positive patch test reactions to nickel may be missed with only one reading on D2. Another study compared patch test results for nickel at D2 and D3 and found that 26.6% of the positive reactions appeared at D3 only, while 3.6% of weak reactions at D2 were not considered allergic at D3.

Questionnaires
Using questionnaires to estimate prevalences of diseases is a cost-effective method and this is often done in population-based surveys. However, the question ‘Are you sensitive/hypersensitive/allergic to nickel?’ has not been validated before and questions concerning metal dermatitis have in the few existing previous studies showed low validity. As a consequence of the European Nickel Directive, questions about metal-related dermatitis will no longer be useful for assessment of symptoms related to nickel allergy, as nickel release from items such as buttons, jewellery, and watches is now restricted. Thus, the validation of question (i) ‘Are you sensitive/hypersensitive/allergic to nickel?’ was given higher priority. The two questions tested for
validity in this thesis did not seem to be useful for estimating the prevalence of nickel allergy, as their validity was low. Nickel allergy was verified in only 59–60% of those who reported nickel allergy. Neither of the questions can be regarded as useful in epidemiological studies as they both strongly overestimate the true prevalence of nickel allergy.

One possible reason for overestimation of self-reported nickel allergy might be that skin irritation from other causes confuses the symptoms of nickel allergy. Women with a history of childhood eczema had a higher proportion of ‘false-positive’ answers about nickel allergy than those without childhood eczema. Of 58 women with ‘false-positive’ answers, 29 (50%) reported a history of childhood eczema. A plausible explanation is that individuals with atopic skin type more easily react with irritant dermatitis when exposed to metal items 116. The proportion with hand eczema was slightly higher in the group of women who gave ‘false-positive’ answers compared to those who gave ‘true negative’ answers, but the difference was not statistically significant (p=0.246). ‘High wet exposure’ did not seem to influence the validity of the questions.

Knowledge about the validity of self-reported nickel allergy is of importance for epidemiological studies and also for clinical situations. It is apparently difficult to determine whether or not a person has contact allergy to nickel on the basis of his/her history.

The different response options for question (i) ‘Are you sensitive/hyper-sensitive/allergic to nickel?’ made it possible to study the severity of the symptoms associated with nickel allergy, Figure 5. Of the nickel-positive women, 24% were not aware of the allergy and 31% reported no symptoms if they avoided contact. Thus, more than half of the women with nickel allergy did not have symptoms and likely many individuals never seek medical advice concerning their nickel allergy. These findings emphasize the importance of population-based studies when following the prevalence of nickel allergy.

**Self-testing**

The use of self-testing for surveillance of contact allergy would be advantageous and convenient both for the investigator and the test persons. Most likely, the method would be cost-effective. In study IV was found that the sensitivity of the self-test regarding nickel allergy was 72%, using standardized patch test method with two readings as ‘gold standard’. Furthermore, PPV was 72% and the proportion of agreement was 86%. Comparison with other studies is difficult as the only previous report is a conference presentation 108, in which sensitivity and proportion of agreement for nickel and fragrance mix are added together.
Thus, the results suggest that self-testing might be a feasible alternative method for estimating nickel sensitivity. A limitation of the self-test is of course that an inexperienced layman is evaluating the test. However, comparison of the patients’ and the dermatologists’ readings of the self-test, gave a proportion of agreement of 92%, which has to be considered as fairly high. Another limitation of the self-test is that only one reading is performed, which probably explains some of the false-negative answers. Furthermore, the area where the patch test is applied might influence the results. The skin of the back is more responsive than that of the arms and thighs, and only the upper back is recommended for routine diagnostic patch testing\textsuperscript{118,119}. However, for practical reasons a self-test has to be applied on the arm.

Thirteen individuals in the study reported nickel allergy from self-test, but were nickel-negative according to ‘gold standard’ patch test. One of the reasons for this may be interpretation of irritant or doubtful reactions as positives by the patient. Of these 13 women with false-positive answers, eight had a history of atopy.

\textit{Methodological aspects in study III}
As previously described, the requirement for a positive patch test reaction was ++ reaction or more to facilitate comparison with the baseline study. However, if + reactions had also been regarded as positive for nickel, the validity still would have been low, with PPV 61% and sensitivity 70%. The validity might not be the same in other age groups or in men. As the prevalence of nickel allergy is high in women of this age group, their knowledge about nickel allergy and its symptoms may also be better than that of other groups. The high proportion of atopics in this cohort (35%) might to some extent contribute to the overestimation of nickel allergy.

\textit{Methodological aspects in study IV}
The proportion of dropouts in study IV was high. In total 243 patients were included but only 191 patients completed the study adequately. Apparently some patients had problems applying the self-test, others had problems reading and understanding the written instructions in the package and some of the patients did not turn up for the second reading. The study was performed at three different dermatology departments, and consequently different dermatologists have performed the patch test readings. This might, of course, influence the result but to minimize that risk, all patch tests were read by specialists in dermatology, and the morphological evaluation was performed according to international standard (ICDRG)\textsuperscript{24}. The fact that this study was performed on patients might also influence the results. The proportion of atopics was higher than
in the general population and the validity might differ in a population-based survey. The positive predictive value may not be transferable from the patient population in the present study to the general population due to differences in prevalence of nickel allergy. To further evaluate the usefulness of the self-test as an epidemiologic tool to follow the prevalence of nickel allergy, a study in the general population is needed.

**Final remarks**

Improved knowledge of the association between nickel allergy and hand eczema may lead to a better understanding of the consequences of nickel allergy and may also contribute to the knowledge about hand eczema. Nickel allergy does not seem to be an important risk factor for hand eczema and in this thesis was found that the majority of individuals with nickel allergy had no or mild symptoms associated with the allergy. Further knowledge regarding risk factors for hand eczema is important for understanding and preventing the condition.

Epidemiological surveillance of contact allergy is important and thus, validated, inexpensive tools are required. This thesis work has discussed methods for estimating the prevalence of nickel allergy and validated self-reported and self-tested nickel allergy. All methods available have limitations and it is important to be aware of these limitations when using the methods in future studies. Patch testing is the most reliable method, but is expensive and 10–15% of positive reactions will be missed with only one reading. Self-reports are not useful at all and self-testing might be a useful method, although further studies in the general population are required.
Conclusions

Referring to the overall aim of this thesis to study the association between hand eczema and nickel allergy, and to evaluate methods for estimating the prevalence of nickel allergy, the following conclusions were drawn:

Contact allergy to nickel in childhood did not influence the occurrence of self-reported hand eczema later in life.

Nickel allergy, verified by patch test, did not seem to be a risk factor for hand eczema in women from the general population, 30–40 years old. However, when the association between hand eczema and nickel allergy was analysed separately in women with and without history of childhood eczema, a doubled risk for hand eczema was found in women without childhood eczema.

The risk of hand eczema in nickel-positive women may previously have been overestimated.

Most women with nickel allergy did not have symptoms associated with the nickel allergy. Thus, conclusions regarding occurrence of nickel allergy cannot be drawn from history.

The present studies confirm previous findings that the most important risk factor for hand eczema is history of childhood eczema.

All methods available for estimation of the occurrence of nickel allergy have limitations.

The validity of self-reported nickel allergy was low. The questions studied strongly overestimate the true prevalence of nickel allergy and questionnaires are thus not useful to follow the prevalence of nickel allergy.

The validity of self-testing for nickel allergy was adequate in the studied population and the method might be useful for following the prevalence of nickel allergy.
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REFERENCES


Publications in the series
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