

Allergic contact sensitization in the general adult population: a population-based study from Northern Norway

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Few studies have so far addressed the prevalence and risk factors for contact sensitization in the general adult population; however, many such studies have been conducted in hospitals. We present the prevalence of contact sensitization in a general adult population and its relationship to potential risk factors like smoking, ear piercing and atopic diseases. 1236 adults (44.2% men and 55.8% women) were randomly selected from a cross-section of the population in Sør-Varanger municipality, Norway, and patch tested with TRUE Test (Pharmacia, Hillerød, Denmark). Contact sensitivity to at least 1 out of 24 allergens was found in 35.4% of the women and in 14.8% of the men. The most common allergens were nickel (17.6%), cobalt (2.8%), thiomersal (1.9%), fragrance mix (1.8%) and colophony (1.2%). All other allergens were observed in 1.0% or less. In women, ear piercing was an important risk factor for nickel sensitization. No such significant correlation was seen in men [in women relative risk (RR) = 3.30, 95% confidence interval (CI) = 2.01–5.43, and in men RR = 1.82, 95% CI = 0.66–5.00], and contact sensitivity was associated with atopic dermatitis (AD) [adjusted odds ratio (OR) = 1.58, 95% CI = 1.04–2.40] and smoking (adjusted OR = 1.42, 95% CI = 1.01–1.99) in women but not in men. The prevalence of contact sensitivity was common in this general population, especially in women. Smoking and AD might be a risk factor for contact sensitization.

Key words: allergic rhinitis; asthma; atopic dermatitis; contact allergy; contact dermatitis; nickel allergy; piercing; smoking. © Blackwell Munksgaard 2007.

Accepted for publication 23 August 2006

Epidemiological studies of contact sensitization have indicated a geographical difference in incidence of sensitivity to a number of contact allergens (1–3), which may partly be due to variability in exposure. Contact sensitization is age related, with declining trend after age of 40 years (4, 5). Nickel sensitivity is the most common form of cutaneous hypersensitivity, especially in women from industrialized parts of the world (4–6). From 70s to the early 90s, increased prevalence of nickel allergy has been reported (1, 4, 6), the main risk factor being ear piercing (4–6). A recent investigation from Denmark found no increased prevalence of nickel allergy, indicating that nickel allergy has reached a plateau (7) or even falling

trend (8). In contrast, positive reactions to perfume were significantly increased in both sexes from 1985–1986 to 1997–1998 (7). From 1997, the sale of nickel-containing products and jewellery has been forbidden by law in the European Union, which may be a crucial step towards an efficient prevention of nickel allergy (7).

The importance of contact allergy in patients with atopic diseases has been debated. Atopic diseases are characterized by immunological abnormalities including tendency to develop immunoglobulin E antibodies (type 1 allergic reaction) and reduced cell-mediated immunity (type 4 allergic reaction) (9). However, earlier publications have reported increased frequency of contact allergy in patients with atopic disease (10, 11). This variation may to some extent reflect the population studied and disease activity (11).

The aim of the present study was to investigate the prevalence of contact sensitization in a general

The study was supported by the Norwegian Ministry of the Environment and the Norwegian Ministry of Health and Social Affairs.

adult population in Northern Norway and its relationship to potential risk factors.

Material and Methods

All adults in Sør-Varanger community in Northern Norway aged 18 to 69 years were invited ($n = 6177$), while a total of 3671 (59.4%) subjects were enrolled in the study. The participants were invited consecutively according to their day of birth, starting with January 1. The people with the same day and month of birth were randomized by alphabetical order. This protocol assured that there was a random sample of participants each day. This study included a 4-page questionnaire and patch testing. Additional details about the study design and methods have been given elsewhere (12). Of the total number of participants, we invited 1561 subjects who attended at certain prespecified days to participate in patch testing. Patch testing with TRUE test (Pharmacia, Hillerød, Denmark) (13) was carried out on 1236 (79.2%) of the invited subjects. They were asked several questions regarding smoking habits, ear piercing, contact dermatitis (e.g. dermatitis under metal items such as jeans buttons, buckles, wrist watches, jewellery and reaction to perfume, rubber, chemicals and leather), atopic dermatitis (AD), asthma, allergic rhinitis (AR) and hand eczema. 'Self-reported' AD was diagnosed if the answer to the following question was positive: 'Have you ever had AD (childhood eczema)?', i.e. reporting an itchy rash lasting more than 4 weeks in 1 or more of the following areas: face, neck, wrist, ankles, hands and elbow/knee flexures (12). Asthma was defined by the question: 'Have you ever had asthma?', and AR was defined according to symptoms involving nose/eyes (i.e. sneezing, stuffy nose, itchy eyes and lacrimation) in response to known or strongly suspected allergen(s).

Allergic contact sensitization is here defined as positive reaction to at least 1 patch test allergen. Atopic diseases were restricted to include the 3 main atopic manifestations, namely, AD, asthma and AR. The term 'cumulative incidence' was used for past and/or present symptoms of the diseases.

The TRUE test is a standardized, ready-to-apply patch test consisting of 2 panels, each with 12 allergens (13). The tests were applied to the upper back for 2 days and read after 3 days. We gave the participants a standardized information sheet. The reaction was classified according to the International Contact Dermatitis Research Group (14). A positive reaction 1+ was defined as at least homogenous erythema and palpable infiltration in the test area, 2+ as erythema and infiltration with papules and vesicles and 3+ as

strong erythema and infiltration with confluent papulovesicles or bullae. Irritant reactions defined as weak, macular erythema without infiltration or as a follicular (pore) pattern restricted to the area covered by the chamber, were recorded but not regarded as a positive test. The majority of patch tests were read by a general practitioner (T. S. S.), who was trained in advance by a dermatologist (L. K. D.). The dermatologist also took part in the first 2 days of the study. To check the level of agreement between the readers, we undertook 2 different inter-observer studies (12). When looking at nickel sulfate only and pooling the positive gradings (1+, 2+ and 3+), the agreement was excellent, i.e. the kappa value was 0.93 (12).

The study was approved by the Ethical Committee of the University of Tromsø, Norway.

Statistical analyses

The results were analysed using the SAS statistical software. Logistic regression was used to separate the effect of age (continuous variable), history of AD, asthma, AR and current smoking. We tested goodness of fit of the models to be satisfactory when compared with the Hosmer–Lemeshow test.

Results

The self-reported, cumulative incidence of atopic diseases, hand eczema, smoking habits and ear piercing in Sør-Varanger is shown in Table 1. The average age of the 1236 patch-tested adults were 43.3 years (men 44.9 years and women 42.1 years).

We found a high cumulative incidence of atopic diseases, i.e. asthma 7.9%, AD 15.5% and AR 28.8%. AD and AR were significantly more frequent in women (Table 1). Self-reported contact dermatitis and hand eczema were twice as prevalent in women as in men (i.e. 43.3% versus 20.0% and 17.4% versus 8.8%, respectively) (Table 1).

Table 1. Self-reported characteristics of the adult study population in Sør-Varanger

	Total ($n = 1236$)	Men ($n = 546$)	Women ($n = 690$)
Age in years (mean $\pm$ standard deviation)	43.3 $\pm$ 14.1	44.9 $\pm$ 13.9	42.1 $\pm$ 14.2
Atopic diseases ^a (%)			
Atopic dermatitis	15.5	11.7	18.4 ^b
Asthma	7.9	7.9	8.0
Allergic rhinitis	28.8	23.6	32.9 ^b
Contact dermatitis ^a (%)	33.0	20.0	43.3 ^b
Hand eczema ^a (%)	13.6	8.8	17.4 ^b
Current smoking (%)	40.9	40.8	40.9
Ear piercing (%)	50.0	5.8	86.9 ^b

^aCumulative incidence.

^b $P < 0.01$ compared with men.

Smoking (40.9%) was equally distributed among men and women, while ear piercing was most common among women (86.9%), with the highest figures in the youngest age group, i.e. 18–29 year old (96.2%). Only 5.8% of the men had had their ears pierced, and of these 70% had only 1 earlobe perforation, whereas 97% of the women had 2 or more perforations in their ears.

At least 1 positive patch test reaction was observed in 35.4% of the women, whereas only 14.8% of the men had a positive test. Table 2 shows the distribution of the allergens tested. Contact sensitization to nickel (17.6%) and cobalt (2.8%) accounted for most of the positive reactions followed by thiomersal (1.9%), fragrance mix (1.8%) and colophony (1.2%). All other allergens were observed in 1% or less of the tested adult population.

Sensitization to perfume showed no sex differences. In contrast, colophony, preservatives and rubber chemicals seemed to be somewhat more common in women than in men (Table 2).

Irritant reactions were frequent; nickel showed irritant reactions in 3.8%, followed by cobalt (2.3%), dichromate (1.9%), fragrance mix (1.8%) and carba mix (1.1%).

We found that 27.5% of the women tested positive for nickel, compared with only 5.1% of the men. Of those with a positive test for nickel, strong reactions (i.e. positive nickel test graded 2+ or 3+) were observed more often in women

than in men (70.0% versus 46.4%), respectively. For women, the prevalence of nickel sensitivity decreased with age; however, such a trend did not apply to men (results not shown).

In women, the risk of sensitization to nickel increased with increasing number of earlobe piercings. If the women had 3 or more piercings, the frequency of nickel allergy was 5 times that of women without earlobe piercings (39.2% versus 8.5%; relative risk (RR) 5.4; confidence interval (CI) 2.6–11.0). There was also a tendency of such a dose–response relationship in men, but this was not considered to be statistically significant (25.0% versus 4.7%; RR 6.1; CI 0.6–66.7).

Table 3 shows the results from logistic regression analyses including age, AD, AR, asthma and current smoking. In women, smoking and AD were connected with contact sensitization. In men, only AD seemed to increase the risk of contact sensitization (adjusted odds ratio = 2.05) but without reaching statistical significance.

Discussion

This general population study showed that at least 1 in 3 women and 1 in 7 men had contact sensitization diagnosed by patch test. These figures are in line with some studies (15, 16) but higher than found in recent population-based study in Denmark (17).

Table 2. Patch test results using TRUE test in the study population in Sør-Varanger

Substances	Concentration (mg/cm ²)	Total (n = 1236)		Men (n = 546)		Women (n = 690)		Irritant reaction	
		n	%	n	%	n	%	n	%
Nickel sulfate	0.20	218	17.6	28	5.1	190	27.5	47	3.8
Cobalt dichloride	0.020	35	2.8	5	0.9	30	4.3	28	2.3
Thiomersal	0.0080	23	1.9	9	1.6	14	2.0	10	0.8
Fragrance mix	0.43	22	1.8	10	1.8	12	1.7	22	1.8
Colophony	0.85	15	1.2	5	0.9	10	1.4	3	0.2
(p-tert) butylphenol formaldehyde resin	0.040	12	1.0	6	1.1	6	0.9	5	0.4
Formaldehyde	0.18	11	0.9	4	0.7	7	1.0	3	0.2
Potassium dichromate	0.023	5	0.8	6	1.1	4	0.6	23	1.9
Thiuram mix	0.025	7	0.6	2	0.4	5	0.7	3	0.2
Carba mix	0.25	8	0.6	2	0.4	6	0.9	13	1.1
Epoxy resin	0.050	7	0.6	5	0.9	2	0.3	3	0.2
Cl+Me-Isothiazolinone	0.0040	8	0.6	2	0.4	6	0.9	1	0.1
Neomycin sulfate	0.23	6	0.5	1	0.2	5	0.7	3	0.2
Balsam of Peru	0.80	5	0.4	1	0.2	4	0.6	1	0.1
Quaternium 15	0.10	5	0.4	3	0.5	2	0.3	4	0.3
Paraphenylenediamine	0.090	4	0.3	2	0.4	2	0.3	0	0
Mercapto mix	0.075	3	0.2	3	0.5	0	0	1	0.1
Quinoline mix	0.19	1	0.1	1	0.2	0	0	7	0.6
Paraben mix	1.00	1	0.1	1	0.2	0	0	3	0.2
Ethylenediamine dichloride	0.050	1	0.1	0	0	1	0.1	3	0.2
Black rubber mix	0.075	1	0.1	0	0	1	0.1	2	0.2
Mercaptobenzothiazole	0.075	1	0.1	1	0.2	0	0	1	0.1
Wool alcohols	1.00	1	0.1	0	0	1	0.1	1	0.1
Caine mix	0.63	1	0.1	0	0	1	0.1	1	0.1
At least 1 positive reaction		325	26.3	81	14.8	244	35.4		

Table 3. OR for contact allergy (at least 1 positive patch test) in relation to self-reported atopic diseases and current smoking^a

	Men ^b		Women ^c	
	OR ^a	95% CI	OR ^a	95% CI
Age (year); continuous variable	1.01	0.99–1.03	1.01	1.00–1.02
Current smoking	0.74	0.42–1.30	1.42	1.01–1.99
Atopic dermatitis	2.05	0.97–4.31	1.58	1.04–2.40
Allergic rhinitis	0.82	0.41–1.63	1.00	0.69–1.44
Asthma	1.05	0.38–2.94	0.62	0.32–1.20

CI, confidence interval; OR, odds ratio.

^aAll covariates adjusted mutually for each other in logistic regression.

^bHosmer–Lemeshow goodness-of-fit test, 8 df: $P = 0.83$.

^cHosmer–Lemeshow goodness-of-fit test, 8 df: $P = 0.46$.

There were some methodological limitations in this study as a retrospective ascertainment derived from questionnaires alone might be affected by bias. We obtained a good participation rate (79.2%), making the investigation representative of the background population, and thus, we believe that selection bias is only a minor problem.

Self-administered questionnaires are predominantly used in population studies and may only be suitable for obtaining a rough estimate of atopic diseases in a study population (18). Recall bias may occur; however, we tried to minimize this bias by obtaining information on wide variety of factors in an attempt to mask our major hypothesis. Moreover, we used questionnaires and a design of the study with little room for interpretation by the subjects. On the other hand, caution has to be exercised to subjects with eczema because they might be more aware of previous symptoms of eczema and thus reported AD more often than the subjects without clinical manifestations of contact dermatitis. Furthermore, some degree of misclassification may have occurred and is present in almost all types of epidemiological studies (19). Episodes of atopic symptoms in early life can, in some cases, have been misunderstood or forgotten by the subjects. The clinical manifestation of eczema in contact allergy share predilections with AD e.g. face, neck, wrist and hands. Confounding is an additional source of errors in epidemiological investigation and may have influenced our observation between risk factors and contact allergy. Thus, the correlation between AD and contact sensitization found in this study should be interpreted with caution.

Nickel accounted for most positive patch test reactions in our study, followed by cobalt, both being more common in women than in men. The other allergens showed a frequency of 2% or less without significant differences between the sexes. Studies from Europe have reported the prevalence

of allergy to fragrance mix and balsam of Peru to be between 2 and 7 times higher than the prevalence found by us (8, 20, 21). In a Danish study comparing contact sensitization to cosmetic from 1990 to 1998, the prevalence increased significantly from 2.4% to 5.8% and is caused mainly by an increasing number of fragrance-mix-sensitive females (17). Another Danish study from 1997/98 reported perfume sensitization in 4.5% of the tested population (e.g. fragrance mix 2.7%, balsam of Peru 1.1% and colophony 1.0%) (22). However, 2 German studies also showed very high prevalence of fragrance mix sensitization; 11.4% and 15.9%, respectively (8, 21). The main causes of primary sensitization to fragrance chemicals are cosmetic products, particularly deodorants and fine perfumes.

The prevalence of sensitivity to an individual allergen depends not only on the intrinsic allergenicity of the compound but also on the level of allergen exposure to the population, which may vary from country to country. For instance, the low prevalence of sensitization to thiomersal and neomycin in our study population may be due to infrequent use of these allergens in Norway. In contrast, thiomersal and neomycin are more common contact allergens in Germany (8, 21). A problem when comparing the results from different studies is that different test panels and different concentrations have often been used.

In our study, allergies to dichromate, preservatives, colophony and rubber chemicals were not common. In Danish studies, about 1.0% or less tested positive to wool alcohols, epoxy resin, (p-tert) butylphenol formaldehyde resin, quaternium 15, neomycin and colophony (17, 23). This indicates that people in Scandinavia are infrequently sensitized to these contact allergens. In Europe, cement that contains dichromate is still a problem among cement workers. Since 1983, ferrous sulfate has been added to cement (i.e. reducing the amount of water-soluble dichromate) in Denmark and lately in Norway, thus overall significant reduction of dichromate sensitization is reported (7, 23). In Nigeria, chromium is 1 of the 3 most important contact allergens causing allergy by the use of leather shoes without stockings (24). In Scandinavia, however, chromium does not seem to be an important contact allergen neither in children nor adult (3, 23).

In the multivariate analyses, we found a significant 42% increased risk of contact sensitization in female smokers. No such correlation was seen in men. In our study, a high prevalence of smoking was observed in both sexes. The influence of smoking on cell-mediated immunity is still obscure. However, a recent Danish study also found a significant association between contact

allergy and smoking, with a dose–response relationship (25). Further investigations into the possible mechanisms of this connection are required.

In Northern Norway, ear piercing is relatively uncommon in men but common in women. The highest ear-piercing rates are reported in young adults. The risk of eliciting nickel allergy appears to be parallel to the number of earlobe perforations in both sexes but only reaching statistical significance in women. Girls in their early teens often use cheap jewellery containing nickel, and this may account for the predominance of nickel allergy in women (6, 10). Norwegian men seldom have more than 1 ear pierced and tend to wear a gold earring, hence they are less susceptible to nickel allergy (10, 12). Since 1997, a statutory order in Norway has limited the permitted release of nickel from metal objects intended for close skin contact, and thus we could expect that nickel allergy will be reduced in adolescents and young adults (26).

Despite the correlation between AD and contact sensitization presented in this study, the importance of this finding in the clinical setting have to be studied further. In general, AD cannot be regarded as a risk factor for contact sensitization as impaired responsiveness in atopic subjects to experimental sensitization with dinitrochlorobenzene has been convincingly demonstrated (27). On the other hand, some studies have shown an equal or higher occurrence of contact allergy in atopic compared with non-atopic subjects (6, 8, 10, 11). A possible explanation may be that subjects with AD have increased allergen penetration through damaged eczematous skin and thus increased risk of sensitization.

Several studies have shown high prevalence of hand eczema (28–30). There are many possible explanations for the high frequency of hand eczema found in recent studies. It is often difficult to distinguish between irritant and allergic contact skin reactions in a clinical setting (31). Thus, the relevance of contact sensitization in hand eczema is still disputed. In fact, most patch tests are negative in patients with hand eczema, but they often have a present or past history of AD (3, 29). This indicates that hereditary factors and particularly AD play a significant role in the development of hand eczema (3, 28, 29). Hand eczema is predominant in women, i.e. the frequency of hand eczema in women was twice that found in men. A similar trend, but with higher figures, was reported in a twin study in Denmark (29).

This may be due to high prevalence of hand eczema among housewife, health care personal and other 'wet workers' who are predominantly female (28, 29).

In contrast, an adult study from England reported a male to female ratio of 0.8, with 24% of the adults having had hand eczema in the previous year (30).

In summary, we found a high prevalence of contact sensitization in this general adult population, especially in female smokers and women with ear piercing. The mechanisms of the relationship between contact sensitivity and smoking is still uncertain, but our study may support the hypothesis that smoking and AD might be a risk factor for contact sensitivity. Hence, further studies are needed to confirm the present findings.

Acknowledgements

We thank Anna-Kirsti Jenssen for applying the patch tests and professor Eiliv Lund for his efforts during this study.

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