

The epidemiology of contact allergy in the general population – prevalence and main findings

JACOB PONTOPPIDAN THYSEN¹, ALLAN LINNEBERG², TORKIL MENNÉ¹ AND JEANNE DUUS JOHANSEN¹

¹National Allergy Research Centre, Department of Dermatology, Gentofte University Hospital, 1. 2820 Gentofte, and ²Research Centre for Prevention and Health, Glostrup University Hospital, 2600 Glostrup, Denmark

A substantial number of studies have investigated the prevalence of contact allergy in the general population and in unselected subgroups of the general population. The aim of this review was to determine a median prevalence and summarize the main findings from studies on contact allergy in the general population. Published research mainly originates from North America and Western Europe. The median prevalence of contact allergy to at least 1 allergen was 21.2% (range 12.5–40.6%), and the weighted average prevalence was 19.5%, based on data collected on all age groups and all countries between 1966 and 2007. The most prevalent contact allergens were nickel, thimerosal, and fragrance mix. The median nickel allergy prevalence was 8.6% (range 0.7–27.8%) and demonstrates that nickel was an important cause of contact allergy in the general population and that it was widespread in both men and women. Numerous studies demonstrated that pierced ears were a significant risk factor for nickel allergy. Nickel was a risk factor for hand eczema in women. Finally, heavy smoking was associated with contact allergy, mostly in women. Population-based epidemiological studies are considered a prerequisite in the surveillance of national and international contact allergy epidemics.

Key words: contact allergy; contact dermatitis; epidemic; healthy; nickel; unselected. © Blackwell Munksgaard, 2007.

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Contact allergy is caused by skin contact with low molecular weight haptens and may evolve to allergic contact dermatitis (ACD) if exposure exceeds the individual threshold (1). ACD can be a distressing skin problem for those who have it and may cause sick leave as well as increase national health expenses. Consequently, there has been substantial focus on contact allergy among patients with eczema (2). However, a substantial number of studies have also investigated the prevalence of contact allergy in the general population and in unselected subgroups of the general population. These studies have demonstrated variations in the prevalences of contact allergy depending on the selected study population and year of investigation. The aim of the present review is to determine a median prevalence and summarize the main findings from studies on contact allergy in the general population. A discussion about a possible association between atopic dermatitis and contact allergy has been left out as it has been previously discussed (3–6).

Materials and Methods

A review of the literature was carried out using Pubmed-Medline and contact dermatitis textbooks. Search terms included: contact allergy, contact sensitization, general population, unselected, healthy, epidemiology, and nickel. Published work on contact allergy and nickel allergy in the general population or unselected subgroups of the population was included. Nickel has traditionally been responsible for a large proportion of contact allergy in the general population (7). Thus, knowledge about contact allergy in the general population can to some extent be generated from studies on nickel. Thimerosal and neomycin are also traditional high-prevalence allergens. However, past epidemiological studies focusing on these allergens have only contributed with contact allergy prevalence estimates, whereas an identification of possible risk factors has not been carried out. Consequently, such studies have been excluded from the review (8–12). The patch test concentration of nickel sulfate was only stated

when it differed from 5% (or 0.20 mg/cm² in the TRUE-test).

A linear regression model was carried out using Statistical Products and Service Solutions package for windows (release 13.0); the year of publication was correlated with the proportion of nickel allergy out of contact allergy to at least 1 allergen (Fig. 1). It was not possible to stratify this regression for sex, as too many studies did not present details about nickel sensitivity stratified for sex. Statistical significance was considered to be present if the *P* value was below 0.05. Furthermore, prevalence estimates from included studies were ranked and the median selected as an average estimate of the prevalence of contact allergy in the general population between 1966 and 2007. Also, a weighted average prevalence was conducted from the studies in Table 1. Odds ratio (OR) or relative risk (RR) was given with confidence intervals (CI) of 95%.

Major Studies on Samples of the General Population

Between 1990 and 1991, a random sample of 793 subjects was invited for a health examination with special emphasis on allergy. A total 567 (71.5%) of these were patch tested (TRUE-test) and furthermore examined with standard prick testing and serum total immunoglobulin (Ig)E measurements (13, 14). Contact allergy was observed in 15.2% (18.8% women versus 11.5% men, *P* < 0.05) and were independent of enhanced IgE responsiveness. No significant difference was observed between the age groups. Nickel allergy was demonstrated in 6.7% and was more prevalent among women than men (11.1% versus 2.2%,

P < 0.0001). The difference was mainly explained by an increased frequency of pierced ears in women compared with men (67.1% versus 12.1%, *P* < 0.0001). In addition, a history of eczema in metal contact sites was more likely in women than men (35.5% versus 8.4%, *P* < 0.0001). Sensitization to cosmetic ingredients included in the TRUE-test (fragrance mix, colophony, myroxylon pereirae (Balsam of Peru), parabens, quarteronium-15, wool alcohols, and isothiazolinones) was observed in 3.7% of the population, whereas thimerosal sensitization was observed in 3.4%. The study demonstrated positive patch test reactions in 20 out of 23 haptens and mixtures of haptens. It also showed that 3% had more than 1 positive patch test reaction (13). Finally, contact allergy (adjusted OR 1.8; CI 1.2–2.9), nickel contact allergy (adjusted OR 2.7; CI 1.4–5.2), and ACD (adjusted OR 3.0; CI 1.5–6.2) were significantly associated with a smoking history of more than 15 pack-years (15). These results could not be explained by socio-economic variables and were independent of age, sex, atopy, and ear piercing. Thus, it was suggested that heavy smoking was a risk factor for the development of contact allergy (15).

During 1997 and 1998, another Glostrup allergy study was performed by the same study group and with the same methods in a new cross-sectional sample (16). A total of 469 subjects aged 15–41 years were patch tested. To investigate the development of contact allergy in the general population, a comparison was made to 290 subjects aged 15–41 years from the 1990 study. It showed that contact allergy increased from 15.9% to 18.6%, mainly as a result of an increase among women from 22.1% to 26.4% (16). The prevalence of nickel allergy decreased from 12.1% in 1990 to 10.8% in 1998, whereas contact allergy to cosmetic haptens increased from 2.4% to 5.8% (OR 2.44; CI 1.04–5.73). Furthermore, all 567 subjects that participated in the 1990 study were re-invited for patch testing in 1998, and 365 (64.4%) persons were examined (17). Contact allergy persisted in 71%, whereas nickel allergy persisted in 79% (17). It was also assessed that 12% subjects had developed 1 or more positive patch test reactions between 1990 and 1998 and that it was mostly caused by nickel (18). A history of ear piercing for men and women was registered in 58.9% in 1990 and 62.4% in 1998. The study showed that the prevalence of self-reported hand eczema increased from 17% in 1990 to 26.6% (CI 1.23–2.56) in 1998 in subjects aged 15–41 years (19). An increased focus on allergic diseases and increased prevalence of atopic dermatitis in the population might have contributed to this

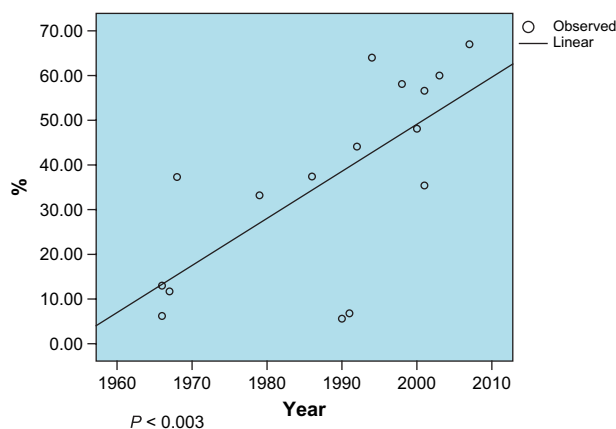


Fig. 1. The proportion of nickel contact allergy prevalence out of the proportion of contact allergy prevalence to at least 1 allergen derived from published studies between 1966 and 2007.

Table 1. Studies on contact allergy in the general population conducted between 1966 and 2007

Author	Year of publication	Country	Population	n	Age (years)	Female/ male (%)	Allergens used for patch testing	Patch test reading performed at day	Positive reaction to at least 1 allergen; total (%)	Positive reaction to at least 1 allergen; women (%)	Positive reaction to at least 1 allergen; man (%)	Positive reaction to nickel; total (%)	3 most common allergens
Röckl	1966	Germany	Children	357	1/12–14 years	—	^a	3 and 4	40.6	—	—	2.5	Chromium, HgCl ₂ , and formaldehyde
Forsbeck	1966	Sweden	Relatives to patients with allergic contact dermatitis	93	x > 10	62.4	Standard series	—	24.7	32.8	11.4	3.2	Nickel, fragrance mix, and Balsam of Peru/formaldehyde/ <i>p</i> -phenylenediamine
Sipos	1967	Hungary	Subjects with intact skin	659	—	—	^b	3	13.7	—	—	1.6	HgCl ₂ , formaldehyde, and nickel/PPD
Forsbeck	1968	Sweden	Twins	202	43–82	83.1	Standard series	3	15.8	20.6	6	5.9	Nickel, chromium, and methyl thiuram disulfide
Magnusson	1979	Sweden	Patients awaiting hip surgery	274	Mean = 65	60	Standard series	3	22	19.5	16.4	7.3	Nickel, Balsam of Peru, and formaldehyde
Weston	1986	USA	Children	314	½–18	47.1	Standard series	3	20.3	23	18	7.6	Neomycin, nickel, and chromium
Seidenari	1990	Italy	Cadets	593	18–28	—	Standard and textile series	3	12.5	—	12.5	0.7	Thimerosal, nickel, and HgCl ₂
Barros	1991	Portugal	School-children	562	5–14	49.6	Standard series	2	13.3	11.8	14.8	0.9	Neomycin, thimerosal, and <i>p</i> -tertiary-butylphenol-formaldehyde
Nielsen.	1992	Denmark	General population	567	15–69	49.2	TRUE-tests	2	15.2	18.8	11.5	6.7	Nickel, thimerosal cobalt/Balsam of Peru
Dotterud	1994	Norway	Schoolchildren	424	7–12	—	Epiquick test	2	23.3	30.3	17.0	14.9	Nickel, cobalt, and MCI/MI
Nielsen	1998	Denmark	General population	469	15–41	58.8	TRUE-tests	2	18.6	26.4	7.3	10.8	Nickel, fragrance mix, and thimerosal
Bruckner	2000	USA	Infants	85	½–5	43.2	TRUE-tests	4 and 5	24.5	11.8	11.8	11.8	Nickel, thimerosal, and MCI/MI
Mortz	2001	Denmark	School-children	1146	12–16	54.1	TRUE-tests	3 ^c	15.2	19.4	10.3	8.6	Nickel, fragrance mix, and thimerosal/colophony/cobalt
Schäfer	2001	Germany	General population	1141	28–78	50.4	Standard series	3	28	—	—	9.9	Nickel, fragrance mix, and thimerosal
Bryld ^d	2003	Denmark	Twins	627	20–44	62.3	TRUE-tests	3	21.4	29.7	7.6	12.8	Thimerosal, nickel, and colophony/fragrance mix
Basketter	2004	Thailand	General population	1178–2545	18–55	49.1–70.7	^e	2	—	—	—	27.8	Nickel, PPD, and chromium
Dotterud	2007	Norway	General population	1236	18–69	55.8	TRUE-tests	3	26.3	35.4	14.8	17.6	Nickel, cobalt, and thimerosal

—, not given; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; PPD, para-phenylenediamine.

^aChromium, nickel (2%), formalin, benzocaine, mercury chloride (HgCl₂), and turpentine.^bHgCl₂, formaldehyde, nickel, chromium, novocaine, PPD, turpentine, and lanoline.^c40 children were not read at D3 but rather on D2, D4, or D7. Some were also read by parents who had been previously instructed.^dCalculations made on subjects without hand eczema.^eNickel, Fragrance, formaldehyde, PPD, MCI/MI, colophonium, and chromate.

increase. In 1990, a strong association was found between hand eczema and both nickel contact allergy (OR 2.95; CI 1.17–7.44) and nickel ACD (i.e. nickel allergy and a history of metal contact dermatitis) (OR 2.99; CI 1.15–7.80) among women but this was not reproduced in 1998. It was speculated whether this finding could be explained by the Danish nickel regulation that was enforced in 1991 and resulted in a decrease of nickel exposure (19).

In 2001 in Augsburg, Germany, Schäfer et al. (20) recruited 1141 random subjects aged 28–78 years for patch testing (standard series). Subjects were selected so that 50% had a positive radioallergosorbent test. Furthermore, 50% within each group should give at least 1 positive answer to questions on asthma attacks, allergic rhinitis, and skin irritation. The interviews showed that 32.3% subjects gave a history of adverse skin reactions to certain substances, and 27.2% reported that a patch test had previously been carried out. Contact allergy to nickel, fragrance mix, thimerosal, turpentine, and cobalt was significantly more common in women than men. The study demonstrated an overall trend of decreasing sensitization with increasing age ($P_{\text{trend}} = 0.09$). For nickel, this trend was strongly significant ($P_{\text{trend}} < 0.0001$), whereas fragrance mix allergy increases with increasing age ($P_{\text{trend}} < 0.003$). Furthermore, nickel allergy was significantly associated with a self-reported history of intolerance to jewellery. Based on an extrapolation of the results from the representative study base, the prevalence of contact allergy was estimated at 28% in the general population. In addition, it was estimated that 11.4% had contact allergy to fragrance mix, 9.9% to nickel, and 3.2% to thimerosal. The study demonstrated a significant decrease of contact allergy with increasing degree of occupational training ($P = 0.023$).

In 2004, patch testing was performed with paraphenyldiamine (PPD), fragrance (isoeugenol, evernia prunastri, and myroxylon pereirae) and formaldehyde in 2545 adult Thais; and with nickel and chromate in 1397 Thais; and finally with methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and colophony in 1178 Thais (21). Patch test readings showed positive reactions to nickel in 27.8%, PPD in 2.7%, chromium in 2.6%, fragrance in 2.5%, colophony in 2.0%, MCI/MI in 1.2%, and formaldehyde in 0.7%. The female–male ratios were 61.5%, 70.7%, and 49.1%, respectively. Contact allergy to nickel, PPD, and fragrance was more common in women than men (33.8% versus 3.9%; 3.2% versus 2.4%; and 2.7% versus 2.1%, respectively). The prevalence of nickel allergy decreased with increasing

age ($P < 0.001$), whereas PPD allergy increased with increasing age ($P < 0.05$). These findings were explained by an increased frequency of multiple ear piercing among young girls and greater exposure to PPD among elderly because of the presence of grey hair.

In a Norwegian study from 2007, a total of 1236 subjects aged 18–69 years of age were tested with TRUE-tests and readings performed at D3 by trained general physicians (7). Contact allergy was observed in 26.3% and nickel allergy accounted for 17.6%, cobalt for 2.8%, thimerosal for 1.9%, fragrance mix for 1.8%, and colophony for 1.2%. Nickel sensitization was common among both women and men (27.5% versus 5.1%). Ear piercing was significantly more prevalent in women than men (86.9% versus 5.8%, $P < 0.01$) and was an important risk factor for nickel allergy (RR 3.30; CI 2.01–5.43). In addition, the risk of nickel sensitization increased with the number of piercing. The study showed an association between contact allergy and smoking in women (OR 1.42; CI 1.01–1.99), whereas this was not the case in men (OR 0.74; CI 0.42–1.30). In addition, self-reported hand eczema was more frequent in women than men (17.4% versus 8.8%, $P < 0.01$).

Studies in Infants, Children and Adolescents

In 1966, Röckl et al. (22) patch tested (Table 1) 357 German children aged between 1 month and 14 years (243 healthy children and 114 children from the Paediatric and Dermatology Department in Munich with other dermatoses than eczema). Some 40.6% were contact sensitized, and a higher prevalence was recorded among the youngest, that is 72.8% among infants aged 4–12 months, 56.4% among children aged 1–3 years, 32.6% among children aged 4–9 years, and 19.7% for children between 10 and 14 years. Nickel allergy was observed in 2.5%, whereas chromium was observed in 29.7%.

In 1986, Weston et al. (23) patch tested (standard series) 314 unselected children from the Denver metropolitan area. Some 41% were between 6 months and 5 years of age; 36% were between 5 and 12 years; and 23% were between 12 and 18 years. Some 20.3% were contact sensitized; 6.6% had a strong reaction (+++/+++). Contact allergy was observed in 20% aged 6 months and 5 years, in 20% aged 5–12 years, and in 21% aged 12–18 years. With regard to strong reactions, the corresponding proportions were 7%, 5%, and 9.8%, respectively. The authors found no significant differences in terms of sex and race. The most common allergies were neomycin (8.1%),

nickel (7.6%), chromium (7.6%), and thimerosal (3.5%). At the time, neomycin was often used for the treatment of minor skin infections and diaper dermatitis, whereas the large proportion of chromium allergy was attributed to leather in shoes.

In 1991, Barros et al. (24) patch tested (standard series) 562 Portuguese schoolchildren aged 5–14 years and found that 13.3% had at least 1 positive reaction, and 2.0% had more than 1 positive reaction. The highest prevalence was observed among the youngest. Prevalent allergens were neomycin (2.8%), thimerosal (2.3%), *p*-tertiary-butylphenol-formaldehyde (2.1%), and fragrance mix (1.8%), whereas nickel was only observed in 0.9%. At the time both neomycin and thimerosal were widely used in non-prescription topical preparations in Portugal (24). Finally, the study demonstrated positive patch test reactions to 14 of 25 allergens.

In 1994, Dotterud et al. (25, 26) patch tested (Epiquick test) 424 Norwegian schoolchildren aged 7–12 years. Contact allergy was observed in 23.3% (30.3% girls versus 17% boys, $P < 0.002$), whereas 16.3% had strong patch reactions (++/+++). Furthermore, 8.5% subjects had more than 1 positive reaction. The most prevalent allergens were nickel (14.9%), cobalt (5.7%), MCI/MI (5.2%), wool alcohols (1.7%), neomycin (1.4%), and chromium (1.2%). Nickel allergy was found more often in girls with ear piercing than in girls without (30.8% versus 16.3%, $P < 0.05$) and significantly more girls than boys had their ears pierced (38.8% versus 4.9%, $P < 0.001$). Finally, metal dermatitis was reported by 18.6% of the children (27.4% girls and 10.8% boys) but was only confirmed by patch testing in 34.2%.

In 2000, Bruckner et al. (27) patch tested (TRUE-test) 85 American infants between 6 months and 5 years of age recruited from paediatric practices in Denver where they presented for routine health examination. Only strong reactions (+++/++) were considered significant. Contact allergy was observed in 24.5%, and 45% of these were <18 months. Nickel allergy was observed in 12.9%, thimerosal allergy in 9.4%, and MCI/MI in 1.2%.

In 2002, Mortz et al. (28) patch tested (TRUE-test) 1146 Danish schoolchildren aged 12–16 years and showed that 15.2% (CI 13.2–17.4%) were contact sensitized (19.4% girls versus 10.3% boys, $P < 0.001$). 2 or more positive patch test reactions were observed in 2.3% subjects. Positive reactions were observed in 20 out of 24 allergens. Nickel allergy was observed in 8.6% (13.7% girls versus 2.5% boys, $P < 0.001$) and was strongly associated with pierced ears (OR 3.18; CI 1.43–7.08,

$P < 0.004$). Individuals, who had their dental braces applied prior to ear piercing, showed a significantly reduced prevalence of nickel allergy (OR 0.07; CI 0.01–0.59, $P < 0.002$) (29). Piercing was observed in 50.8% of the population (81.5% of the girls and 20.7% of the boys). Contact allergy to fragrance mix was observed in 1.6% of the girls and 2.1% of the boys. A significant association was found between hand eczema and nickel contact allergy (OR 2.36; CI 1.39–4.01, $P < 0.002$) (28).

Studies in Other Unselected Subgroups

In 1966, Forsbeck et al. (30) patch tested (standard series) 73 pairs of Swedish monozygotic (MZ) twins, that is twins conceived from the same egg and sperm which split and develop into 2 persons with the same set of genes and 76 pairs of dizygotic (DZ) twins, that is twins developing from 2 fertilized eggs, each with unique genetic makeup, that develop at the same time. The age range was 43–82 years. A total of 15.8% were contact sensitized. Contact allergy to nickel was observed in 5.9%, to perfume in 1.5% and to Balsam of Peru (myroxylon pereirae), PPD, procaine, and formaldehyde in 1% persons, respectively.

In 1967, Sipos (31) examined the prevalence of contact allergy (Table 1) in 5086 Hungarians with 19 different skin disorders. Patch testing was carried with gauze (1 cm²) soaked in allergen and was applied on the lower arm with adhesive plaster for 2 D. In a group of 659 subjects with intact skin, 13.7% were contact sensitized. The most common positive allergens were mercury chloride (HgCl₂ 4.1%), formaldehyde (2.1%), PPD (1.6%), and nickel (1.6%).

In 1968, Forsbeck et al. (32) patch tested (standard series) 93 relatives to patients with ACD and showed that 24.7% were contact sensitized. Contact allergy to nickel and tetramethylthiuramdisulfide (TMTD) was observed in 3.2%, respectively, whereas chromium was demonstrated in 14%. No explanation for the high frequency of chromium was presented.

In 1979, Magnusson et al. (33) patch tested (standard series) 274 Swedish patients (average age 65 years) operated upon or scheduled for total hip arthroplasty. Contact allergy was observed in 21.9% patients, and the most prevalent allergens were nickel (7.3%), Balsam of Peru (myroxylon pereirae) (4.7%), and formaldehyde (2.2%).

In 1990, Seidenari (34) patch tested (standard series) 593 Italian cadets aged 18 to 28 years. Contact allergy was demonstrated in 12.5%. Thimerosal accounted for 4.7%, ammoniated mercury for 1.2%, whereas only 0.7% was positive to

nickel. The high prevalence of thimerosal was explained by recent revaccination in all cadets, whereas contact lens exposure was excluded. Finally, patch testing with allergens from the textile industry was performed in 336 cadets of whom 3.8% had a positive reaction.

In 2003, Bryld et al. (35) performed patch testing (TRUE-test) in 627 Danish twins (same sex MZ and DZ) unlikely to have hand eczema based on questionnaire responses. They found at least 1 positive reaction in 21.4% subjects. Nickel allergy was observed in 12.8% individuals (19.1% women versus 1.3% men) (35). Other prevalent allergens were thimerosal (2.2%), colophony (1.3%), and fragrance mix (1.3%).

Studies on Nickel Allergy

In 1979, Prystowsky et al. (36) patch tested 1158 paid adult Americans with 2.5% nickel, benzocaine, neomycin, and ethylenediamine. They showed that 7.4% persons were contact sensitized and that nickel allergy was demonstrated in 5.8%, neomycine allergy in 1.1%, ethylenediamine allergy in 0.4%, and benzocaine allergy in 0.2%. Nickel allergy was more prevalent among women than men (9%, CI 7–11.4% versus 0.9%, CI 0.24–2.2%). The frequency of nickel allergy was significantly higher among individuals with a positive history of pierced ears, earlobe rash, and jewellery rash. There were no association of contact allergy with race and age in the study.

In 1979, Peltonen (37), nickel tested 980 Finns, including 158 schoolchildren (2.5% nickel), 46 medical students, 51 hospital workers, 39 subjects from a home for elderly, and 686 subjects from a newspaper office. Nickel sensitivity was observed in 4.5% (8% women and 0.8% men, $P < 0.001$) and occurred more often among elder women in comparison with young women ($P < 0.05$). Hand eczema was observed in 4% of the population and was associated with nickel allergy in women but not in men ($P = 0.01$).

In 1982, Boss and Menné (38), nickel tested 53 Danish hairdressers at a school of hairdressers. Positive reactions were observed in 20% subjects of whom all had pierced ears. The authors also performed a larger questionnaire and demonstrated that 98 girls out of 107 (91.6%) had pierced ears.

In 1982, Camarasa et al. (39) performed patch testing with nickel 2.5%, cobalt, chromium, and HgCl_2 in 100 (55 girls and 45 boys) randomized Spanish children with trivial conditions, for example verrucae, naevi, alopecia, and papillomas. Contact allergy was observed in 20% (23.6% girls and 15.5% boys). In detail, HgCl_2 allergy was

observed in 11%, nickel in 9%, cobalt in 4%, and chromate in 4%. Nickel allergy was mainly observed in girls (14.6% girls versus 2.2% boys), and furthermore all nickel positive girls had their ears pierced.

In 1985, Larsson-Stymne and Widström (40) patch tested 960 Swedish schoolgirls aged 8–15 years with cobalt and nickel. Contact allergy to nickel was observed in 9% and the prevalence of ear piercing was 72%. Girls with pierced ears were more likely to be nickel allergic in comparison with girls without pierced ears (13% versus 1%, $P < 0.001$). Upon patch testing, a total of 44 (4.6%) girls had contact allergy to both nickel and cobalt, whereas 7 (0.7%) girls only had contact allergy to cobalt.

In 1988, Feasby et al. (41) nickel (2.5%) patch tested 700 Canadian children aged 5–12 years. Among these, 252 subjects had nickel containing intra-oral appliances. The prevalence of nickel allergy was 8.1% (9.5% girls versus 6.8% boys) and was considerably higher among the youngest children in comparison with older children (10.6% versus 4.5%). Children with nickel containing intra-oral appliances had a non-significant higher prevalence of nickel allergy.

In 1995, Meijer et al. (42) nickel patch tested 520 Swedish recruits and found 3.3% positive reactions. A higher proportion of nickel allergy was observed among men with pierced ears as opposed to men without ears pierced (7.9% versus 2.7%, $P < 0.05$). There were no significant difference in nickel allergy between smokers and non-smokers. Finally, the study showed that nickel allergy was not a risk factor for the development of hand eczema.

In 1996, Kerosuo et al. (43) nickel patch tested 700 Finnish adolescents aged 14–18 years. Out of these, 68% had a history of orthodontic treatment with metallic appliances, whereas 32% contributed as a control group. A total of 19% (30% in girls and 3% in boys, $P < 0.001$) were patch test positive to nickel but the difference in prevalence between the 2 study groups was neglectable. Some 91% of the girls had pierced ears as opposed to 12% of the boys. The frequency of nickel allergy was lower among subjects who had orthodontic treatment prior to ear piercing as opposed to subjects who had ear piercing performed before the onset of orthodontic treatment (20% versus 35%, $P < 0.01$).

In 1999, Smith-Sivertsen et al. (44) investigated the possible effect of local nickel pollution on the prevalence of nickel allergy. They compared 2 study groups from 2 different geographic areas of northern Norway, Tromsø, and Soer-Varanger. The latter is situated near the Russian city of

Table 2. Studies on mainly nickel allergy in the general population conducted between 1979 and 2004

Author	Year of publication	Country	Population	n	Age (year)	Female/male (%)	Patch test reading performed at day	Ear piercing female (%)	Ear piercing male (%)	Positive reaction to nickel: total (%)	Positive reaction to nickel: female (%)	Positive reaction to nickel: male (%)
Prystowsky	1979	USA	General population	1158	x > 18	—	4, 5, and 6	67.3	8.3	5.8	9	0.9
Peltonen	1979	Finland	General population	980	10–74	51.2	4	—	—	4.5	8	0.8
Boss	1982	Denmark	Hairdresser students	53	16–22	100	3 and 4	91.6	—	20	20	—
Camarasa	1982	Spain	Children	100	0.7–11	55	4 and 5	—	—	9	14.6	2.2
Larsson-Stymne	1985	Sweden	School girls	960	8–15	100	3	72	—	9	9	—
Feasby	1988	Canada	Paediatric dental patients	700	5–12	49.7	2	38	—	8.1	9.5	6.8
Nielsen.	1992	Denmark	General population	567	15–69	49.2	2	67.1	12.1	6.7	11.1	2.2
Dotterud	1994	Norway	School children	424	7–12	47.4	2	38.8	4.9	14.9	21.9	8.5
Meijer	1995	Sweden	Recruits	520	18–24	—	2	—	29.2	3.3	—	3.3
Kerosuo	1996	Finland	Adolescents	700	14–18	60	3, 4, or 5	91	12	19	30	3
Nielsen	1998	Denmark	General population	482	15–41	58.8	1	—	—	10.8	17.2	2.1
Smith-Sivertsen	1999	Norway (Soer-Varanger)	General population	1236	18–69	55.8	3	86.9	5.8	17.6	27.5	5.1
Smith-Sivertsen	1999	Norway (Tromsøe)	General population	531	22–75	54.4	3	85.8	7.9	19.2	31.1	5.0
Mattila	2001	Finland	University students	284	18–26	66.2	4	89	16	27	38.8	3
Jensen	2002	Denmark	School girls	305	10–14	100	4	68.9	—	3.9	3.9	—
Jensen	2002	Denmark	High schoolgirls	275	17–22	100	4	86.2	—	17.1	17.1	—
Mortz	2002	Denmark	Schoolchildren	1146	12–16	54.1	3	81.5	20.7	8.6	13.7	2–5
Joehnke	2004	Denmark	Infants	304	0–1½	50.3	2, 3, and 4	—	—	8.6	13.1	4

Nikel where elevated nickel concentrations have been demonstrated in its vegetation and mammals (45). In Soer-Varanger, 1236 subjects were patch tested and their findings have been presented previously in this review (7). In Tromsøe, 531 subjects aged 22–75 years were patch tested, and nickel allergy was demonstrated in 31.1% of the women and 5.0% of the men. In women from both areas, nickel allergy decreased significantly with age ($P_{\text{trend}} < 0.05$). In Tromsøe, 85.8% of the women reported ear piercing in comparison with 7.9% of the men. Women with ear piercing were more likely to be nickel allergic than women without piercing (32.1% versus 8.5%, $P < 0.001$). In addition, the frequency of nickel allergy increased with the number of piercing, that is 3 or more ear piercing led to a fourfold increase. These associations were not observed in men. The authors concluded that the population in Soer-Varanger did not have an increased risk of nickel allergy because of nickel pollution.

In 2001, Mattila et al. (46) nickel patch tested 284 Finnish university students aged 18–26 years. The study was based on 1 group with asthmatic symptoms and 1 sex matched control group. A positive reaction to nickel was observed in 26.8% of the students (38.8% women and 3.1% men, $P < 0.001$). Among women, an increase of nickel allergy was observed from 13% in 1985 to almost 39% in 1995. Skin piercing was observed in 64.1% (89% women and 16% men). Significantly more subjects with skin piercing had a positive reaction to nickel (39.0% versus 4.9%, $P < 0.001$). Current hand eczema was observed in 14% of nickel allergic subjects in comparison with 11% without nickel allergy ($P > 0.05$). Finally, the study showed that female sex independently increased the risk of nickel allergy.

In 2002, Jensen et al. (47) demonstrated a nickel prevalence of 3.9% in 305 Danish schoolgirls aged 10–14 years and a prevalence of 17.1% in 275 high-school girls aged 17–22 years. The frequency of ear piercing was 68.9% and 86.2%, respectively. It was suggested that the significantly lower prevalence of nickel allergy among schoolgirls was a result of the Danish Nickel Regulation as the subjects in the 2 study groups had their ears pierced mainly before and after its implementation, respectively.

In 2004, Joehnke et al. (48) nickel tested 543 Danish infants at birth and after 3, 6, 12, and 18 months. A positive reaction was defined as a reaction that occurred on at least 2 reading days and was present at both 12 and 18 months. Some 304 infants were tested at both 12 and 18 months, and the prevalence of reproducible nickel patch test was 8.6% (13.1% girls and 4.0% in boys,

Table 3. Main findings from epidemiological population-based studies (published between 1966 and 2007) investigating contact allergy in the general population or subgroups of the general population

1. Contact allergy was independent of enhanced IgE responsiveness
2. The median prevalence of contact allergy was 20% (adults 15–69 years)
3. Contact allergy to a wide range of allergens as well as multiple contact allergy was observed in both children and adults
4. Contact allergy was most commonly observed against nickel, fragrances, and thimerosal
5. The proportion of nickel allergy out of contact allergy to at least 1 allergen has been increasing significantly over the past 4 decades
6. The median prevalence of nickel allergy among women was 17.1%
7. A median prevalence of 81.5% women, have pierced ears
8. Pierced ears are a strong risk factor for nickel allergy
9. Nickel contact allergy may be associated with hand eczema in women
10. Heavy smoking may be a risk factor for nickel allergy

$P < 0.05$). It was concluded that most reactions in infants are of non-specific or irritant nature.

Discussion

This review summarizes the main findings from published epidemiological studies on contact allergy in unselected populations (Tables 1–3). The first study was carried out by Röckl (22) in 1966 in Germany, but Table 1 shows that 11 (65%) studies have been performed since 1990. Studies have so far been published from North America (36), Thailand (21), Italy (34), Spain (39), Portugal (24), and Hungary (31), whereas the largest share originates from countries in Scandinavian Europe (7, 13, 42). Thus, our knowledge is mainly based on recently published research from North America and Western Europe. This also means that the findings are not directly applicable in countries outside these geographical areas.

In general, the prevalence of contact allergy against specific allergens differs between various countries (49, 50). In addition, prevalences are not static as they are influenced by changes and developments in the surrounding environment and society. Allergen exposure is mainly determined by for example climate (chromium allergy in Nigeria because of the frequent wearing of leather sandals in warm weather) (51), occupation (contact allergy because of *Parthenium hysterophorus* in workers in India) (52), cultural habits (cheep jewellery and nickel allergy or the use of neomycin for skin infections (24, 44, 50), and legislations (the regulation of nickel in Denmark) (53). Thus, contact allergy prevalences are generally

restricted in time and place as its determinants are constantly evolving.

Before comparison and definite conclusions are made on such heterogenic material, all critical differences should be exposed. Some of the study populations were not entirely unselected, for example in the study by Schäfer et al. (20) 32.3% gave a history of adverse skin reactions, and 27.2% reported that patch testing had previously been carried out. Furthermore, some studies were based on subgroups that were so different that they cannot be directly compared, for example Danish hairdresser students (38) and Italian recruits (34). These 2 studies showed that the frequency of pierced ears and nickel allergy was very high among female hairdresser students, whereas the prevalence of nickel allergy among Italian recruits was very low (and probably also the frequency of pierced ears). However, the information generated from such studies adds to our accumulated knowledge of contact allergy in the general population and were hence included in this review. Finally, the age difference as well as the different female–male ratios in the studies should be taking into account. A total of 23 studies included both men and women and the female–male ratios were above 50% (50.3–83.1%) in 17 (74%) of these.

The diagnosis of contact allergy is mainly determined by the outcome of patch testing. However, a positive test reaction is not necessarily an indicator of clinical disease, that is ACD, as the patch test only measures whether the individual is sensitized or not. It is generally acknowledged that the patch test holds some biological as well as technical limitations. Biological limitations include the occurrence of false-positive and false-negative reactions (2). Despite, the exact sensitivity and sensibility of patch testing is unknown, it has been estimated that the reproducibility is generally high (54, 55). A limited diagnostic performance is mainly suspected when patch testing is carried out in a population with low disease prevalence, that is a low positive predictive value and a high proportion of false-positive reactions (56). In addition, patch test concentrations are not age adjusted and are most likely not equally optimized for the diagnosis of contact allergy in all age groups.

Technical limitations include the different criteria that are used in the definition of a weak positive reaction (57). In the presented studies (Tables 1 and 2), patch test readings were carried out by dermatologists, paediatricians, and trained general physicians (20, 23, 25). As it requires substantial training to correctly differ between allergic and irritative reactions, adequate education is a prerequisite. The anatomical application site

also differed in the studies as 1 study applied patch tests on the arm (37). Regional variations of patch test responses has previously been investigated and shown that reactivity is weaker on the arm than on the back (58). Furthermore, patch test readings were performed at D3 or D4 in most studies, whereas a few studies, for example the Glostrup studies, only performed readings at D2. This has traditionally been a subject of concern as it misses about 5–20% of all positive tests (2, 13, 59, 60). However, D2 readings have been repeatedly chosen for logistic reasons in Glostrup. In addition, the aspect of seasonal variations should be considered as less positive reactions are observed in months of summer (61). The applied patch test material (e.g. TRUE-test, Epiquick or standard test allergens from Hermal and Chemotechnique) differed in the studies as did the concentrations of for example nickel sulfate. This may influence the number of positive patch test reactions and should be accounted for. Finally, our knowledge about antigen reliability of different commercial patch test products is limited.

Main Findings

This review suggests that the median prevalence of contact allergy to at least 1 allergen was 21.2% (range 12.5–40.6%), and that the weighted average prevalence was 19.5%, based on data collected on all age groups and all countries between 1966 and 2007. The median prevalence was 21.8% (range 11.8–35.4%) in women and 12% (range 6–18%) in men. If the calculations were concentrated on subjects between 15 and 69 years, a median prevalence of 20% (range 12.5–28%) was found for all nationalities combined and 21.4% (range 15.2–26.3%) for Scandinavians only. Thus, the overall prevalence estimates turned out similar and do not seem to depend much on age, race (23, 36), or geographic origin of the study group. Furthermore, the median prevalence seems to be a good indicator of the average prevalence of contact allergy in Western Europe and North America. A 9-year prevalence estimate of contact allergy from Germany assessed a prevalence estimate of 16.6% in 2002. Schnuch et al. (50) concluded that between 15% and 20% of the general German population were contact sensitized at the time. Likewise, the results of recent population-based epidemiological studies were close to the median prevalence determined in this review (7, 17, 20, 36). However, a recent Danish 10-year prevalence estimate of contact allergy showed that the prevalence has decreased to 12.9% in Denmark (57).

The prevalence of contact allergy among children and adolescents has previously been addressed. Mortz et al. (62) showed that 13–23% children had positive patch test reactions to standard allergens. However, the results from the current review indicated that the true prevalence of contact allergy in children is difficult to assess. It is conceived that the prevalence of contact sensitization should gradually increase through childhood and adolescence because of an increased environmental exposure to contact allergens. A possible difference in allergen exposure between different age groups should also be taken into consideration. Nevertheless, patch test results demonstrated that contact allergy was highly prevalent among infants and young children: Röckl et al. (22) showed that 72.8% of infants between 4 and 12 months were sensitized; Weston et al. (23) showed that 20% between 6 months and 5 years were sensitized; and Bruckner et al. (27) showed that nearly 50% of all positive reactions in their sample were less than 18 months. Furthermore, several studies demonstrated higher prevalences among the youngest in comparison with older children (22, 24, 27, 41). Thus, it seems legitimate to question the reliability of patch test results from testing in unselected infants and young children. Even when only strong patch test reactions (++/+++) are accepted, high-prevalence estimates were observed (25, 27). An explanation for the high-prevalence estimates could be the occurrence of irritative reactions, which has previously been a subject of concern (23, 27, 48). It is likely that a reasonable prevalence estimate of contact allergy among unselected children is impossible to determine.

The most prevalent contact allergens in the general population were nickel, thimerosal, and fragrance mix. In addition, cobalt, chromium, PPD, and MI/MCI were prevalent allergens in several studies. Table 1 shows that the prevalence of individual allergens was mostly depending on the year of investigation [chromium and HgCl_2 were prevalent in the 1960s whereas nickel has later become increasingly prevalent (Fig. 1)] rather than the country investigated. Multiple contact sensitivity was observed in the general population among adults as well as children (13, 24, 62). Finally, contact allergy was observed against nearly all tested allergens in the patch test material suggesting that contact allergy in the general population was not restricted to a subset of haptens and mixtures of haptens (13, 17, 62).

Thimerosal is a traditional high-prevalence allergen in the general population (13, 24, 34, 35). When used topically as an antimicrobial agent, it is a well-known contact sensitizer (8).

Furthermore, the content of thimerosal in vaccines and contact lens solutions have been associated with a high prevalence of thimerosal allergy in unselected populations (34). However, there are indications that the prevalence in the general population is decreasing in Denmark, probably because of the exclusion of thimerosal in vaccines (13, 17). An expected decrease of thimerosal allergy in the general population in Denmark and other countries will inevitably lead to an overall decrease of the contact allergy prevalence in the future. However, different national approaches to the use of thimerosal may prevent such a decrease in other countries.

The prevalence of cosmetic related allergens was assessed in the 2 Glostrup allergy studies and showed an increase from 2.4% in 1990 to 5.8% in 1998 (13, 17). In the 2001 Augsburg study, it was estimated that 11.4% were contact sensitized to fragrance mix in Germany (20). The German prevalence estimate was extremely high in comparison with estimates from other epidemiological population-based studies in Europe (1.3–2.5%) (7, 13, 35, 62). The high prevalence can partly be explained by the study method itself as a reduction from a population-based study population was carried out to determine the prevalence. However, clinical data from Germany and Denmark also supports a marked difference in the prevalence of fragrance mix allergy in the 2 countries (50, 57). Furthermore, it is possible that allergy to fragrance mix is truly elevated in older individuals (20). The Augsburg study was based on adults aged 28–75 years and showed a significant increase in fragrance mix allergy with increasing age (20). Similar, Magnusson et al. (33) demonstrated that the prevalence of Balsam of Peru (*myroxylon pereirae*) was 4.7% among 65 years old Swedish hip patients. In conclusion, national differences and age differences of the study populations may explain the different prevalences of allergy against fragrances. Among children and adolescents, the prevalence of fragrance mix allergy was nearly 2% in Portugal and Denmark in 1991 and 2002, respectively, and emphasized that fragrance mix allergy is an important sensitizer in all ages (24, 28). Future studies will determine whether the increased focus on fragrance mix can be detected from epidemiological studies in the general population.

The median nickel allergy prevalence based on all studies (Tables 1 and 2) was 8.6% (range 0.7–27.8%). The estimate demonstrates that nickel is an important cause of contact allergy in the general population and that it is widespread in both men and women. In Fig. 1, the proportion of nickel allergy out of the proportion of overall con-

tact allergy in the general population was estimated for the period 1966–2007. It showed that a significant increase ($P < 0.003$) was observed for this proportion during the observation period. It was not possible to stratify for sex but it would have been suspected that regression line would have been steeper for women than for men. However, the regression shows that today, nickel allergy is the primary determinant of the contact allergy prevalence in the general population, both among children and adults. The increase of nickel contact allergy over the decades has mainly been explained by the frequent wearing of blue jeans with metal buttons and zippers in the 1970s (63) as well as the growing popularity of ear piercing in combination with the use of imitation jewellery in the 1980s (38). In 1990 and 1994, respectively, legislations were passed in Denmark and the European Union (EU) in order to diminish the nickel release in consumer products (53, 64). The effect of these regulations has so far been demonstrated in clinical material as well as population-based material (47, 65). It will probably require decades before the decreasing load of nickel allergy can clearly be demonstrated from Fig. 1.

The nickel prevalence was higher among women than men (17.1%, range 3.9–38.8% versus 3%, range 0.7–6.8%). Furthermore, numerous studies demonstrated that pierced ears were a significant risk factor for nickel allergy (7, 26, 40, 46, 47, 62). Thus, the higher prevalence of nickel allergy in women was explained by the higher median prevalence of pierced ears in women in comparison with men (81.5%, range 38–91.6% versus 12%, range 4.9–29.2%). This was also supported by the fact that a history of eczema in metal contact sites was more likely in women than men (7, 13). An association between nickel allergy and age has been investigated in several studies (13, 20, 21, 36, 37, 44). Based on their results, the prevalence of nickel allergy is most likely decreasing with increasing age, probably because of a decrease in exposure to imitation jewellery as well as different frequencies of ear piercing in different generations.

A possible association between nickel allergy and hand eczema in women has been addressed and supported by several population-based studies (19, 29, 37, 42), whereas an association has been questioned in men (19, 37, 42). There are several known mechanism that can cause and aggravate hand eczema among nickel sensitized individuals (66). Occupational exposure to moderate or high concentrations of nickel is known to induce and elicit hand contact dermatitis (67, 68). Furthermore, transcutaneous absorption of nickel from for example imitation jewellery may lead to

vesicular hand eczema (69). Finally, hand eczema, as a part of systemic contact dermatitis, may evolve following oral intake of food with a high nickel content (70). The result emphasize that the combination of nickel allergy and hand eczema is a problem to a higher extent in women than men and hence that the EU nickel regulation (64) probably will lead to a decrease in the morbidity of hand eczema.

It has been speculated whether smoking is associated with nickel allergy (7, 15, 42). Linneberg et al. (15) demonstrated a strong association between both contact allergy, nickel allergy, and nickel ACD, respectively, and smoking. An association between nickel allergy and smoking was supported in women but not in men by Dotterud et al. (7) whereas Meijer et al. (42) did not find any associations among young men. Further studies are warranted to clarify whether this association is causative. The possible mechanism underlying the observations has so far not been elucidated. Finally, 2 studies have suggested that nickel containing metallic orthodontic appliances before ear piercing reduce the likelihood of nickel allergy (29, 43), whereas 1 study has shown that children with nickel containing intra-oral appliances had a non-significant higher prevalence of nickel allergy (41).

Conclusion

In Scandinavian Europe, several population-based epidemiological studies have been carried out recently (7, 17, 20). Besides the important role of contact allergy surveillance, future studies should mainly address possible risk factors such as smoking and socio-economic status. However, only few population-based studies have been published from major parts of Europe and the rest of the world. This is regrettable as such population-based epidemiological studies contribute with important risk data to government agencies, industries, and consumer-oriented groups. The knowledge is essential when the safety and benefits of different consumer goods are balanced against their risk of causing allergic diseases. Other parts of the world cannot rely on published data from Europe and North America. Several cases of contact dermatitis to lidocaine have been reported from Australia, and it is believed that their high share is caused by prevalent over the counter lidocaine containing preparations (71). Similar, benzocaine is a constituent of more than 600 different products in Australia (72). Thus, the prevalence of lidocaine and benzocaine allergy in the general population is probably higher in Australia than in other parts of the world. Such examples emphasize that population-based epidemiological studies are prerequisite in

the surveillance of national and international contact allergy epidemics.

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Address:

Dr Jacob Pontoppidan Thyssen, MD
National Allergy Research Centre
Department of Dermatology
Gentofte University Hospital
Ledreborg Allé 40
1. 2820 Gentofte
Denmark
Tel: +45 3977 7307
Fax: +45 3977 7118
e-mail: jacpth01@geh.regionh.dk