

Review Article

The sex of the individual as a factor in allergic contact dermatitis

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Exogenous and endogenous factors have been implicated in allergic contact dermatitis (ACD); this review explores the sex of the individual as a possible endogenous factor. While there is a clinical impression that women are more skin-reactive than men, upon review this hypothesis appears oversimplified. This review explores sex differences in controlled testing of adult ACD, occupational ACD and juvenile ACD. Further, geographical location and socioeconomic and cultural factors in relation to sex differences in allergic contact dermatitis are discussed. We conclude that female sex could be a factor predisposing to allergic contact dermatitis not so much because of possible differences in intrinsic skin characteristics between the sexes, but more because of different exposure patterns. This conclusion has practical consequences regarding product labelling requirements, occupational risk assessment and legislation.

Key words: age, allergic contact dermatitis, allergy, exposure, gender, men, nickel, occupational, sex, women. © Blackwell Munksgaard, 2004.

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Exogenous and endogenous factors have been implicated in the development of allergic contact dermatitis. Exogenous factors include the allergen's chemical and physical properties; the endogenous are believed to be age, skin and other diseases, genetic background, skin sensitivity, and, the subject of this review, sex. The precise role that sex plays in the development of allergic contact dermatitis remains undefined. While there is a clinical belief that women are more skin-reactive than men, detailed investigation finds that this view is oversimplified. No definitive correlation between female skin and increased frequency of allergic contact dermatitis has been documented.

The role that sex plays in allergic contact dermatitis is important for commercial, legal, judicial and insurance purposes. Sex differences could give rise to specially tailored products (i.e. soaps and fragrances) and additional product-labelling requirements. Further, sex differences could prompt legislation to protect a particularly prone sex from dermatological hazards in the workplace. For example, the National Social Insurance Board of Sweden asserted that women were treated unfairly in the occupational rehabilitation of skin disorders (1), if women have more allergic contact dermatitis, perhaps they should

be given special attention in rehabilitation cases. European governments have proposed and passed laws to protect their population's skin. Denmark (2) and the European Union (3) have passed laws regulating the skin's exposure to industrial nickel. Similarly, in 1996, Germany regulated wet work (4), and the European Union has begun to regulate protective gloves (5) and the labelling of cosmetics (6). An understanding of differences between the sexes could better refine these laws and tailor them to an individual's predisposition. The clinical and practical consequences of sex differences in skin reactivity make understanding sex as an underlying factor in allergic contact dermatitis relevant.

Controlled Adult Testing of Dermatitis: Epidemiological Evidence from Patch Test Clinics

In a much-cited study, Lantinga et al. (7) patch tested 141 individuals who had eczema with potassium dichromate 0.5%, nickel sulfate 5%, cobalt chloride 1%, thiuram mix 1%, *p*-phenylenediamine (PPD) mix 0.6%, epoxy resin 1% and balsam of Peru 25%. A greater percentage of women than men reacted to nickel sulfate and

potassium dichromate. However, men were more reactive to cobalt chloride. The other allergens caused negligible differences in reactivities between the two groups (Table 1).

Under similar conditions to Lantinga et al. (7), Akasya-Hillenbrand and Özkaya-Bayazit (8) patch tested 542 individuals in Turkey who had suspected cases of contact dermatitis, but reported some different results. Just as in the Lantinga et al. study (18), nickel sulfate 5% caused more positive reactions in women than in men. Palladium chloride 0.5%, which Lantinga did not test, also elicited more frequent responses in women than in men (14.8% compared to 2.5%, $P < 0.001$). Carba mix, also not part of the Lantinga study, elicited more reactions in men than in women (9.2% compared to 1.3%, $P < 0.001$). Akasya-Hillenbrand and Özkaya-Bayazit also found interesting results with regard to potassium dichromate 0.5%, thiuram mix 1% and cobalt chloride 1.0%. While Lantinga found potassium dichromate elicited more responses in women than in men, Akasya-Hillenbrand and Özkaya-Bayazit found the opposite, that far more men than women had positive reactions. Regarding thiuram mix, Lantinga found that men and women reacted essentially equally, while Akasya-Hillenbrand and Özkaya-Bayazit found men to have significantly more positive reactions. Lastly, both studies found significant differences between men's and women's reactions to cobalt chloride 1%; however, the relative ratios between the men and women in both studies were different [1.98, $P < 0.001$, men-to-women ratio for Akasya-Hillenbrand and Özkaya-Bayazit and a 7.91, $P = 0.013$ (P value not in original publication) ratio of men-to-women for Lantinga et al.] (Table 1).

Most of the variables, such as patch test method, between Lantinga et al. and Akasya-Hillenbrand and Özkaya-Bayazit were similar. The clearest difference between the studies was geographical. Lantinga's subjects were from southern Sweden, while Akasya-Hillenbrand and Özkaya-Bayazit's subjects were from Turkey. The

geographical locations and associated ethnic and socioeconomic considerations between the two groups may be noteworthy. The comparisons between these two studies make a strong case for believing that factors besides sex are partially responsible for relative skin sensitivity, such as exposure patterns.

Instead of fundamental skin differences women may show more frequent reactivity than men to certain allergens due to differences in skin exposure to allergens between the sexes. The most cited and frequent contact allergen is nickel, an allergen that is seen more frequently in women. Women have greater exposure to nickel through jewellery, especially earrings. Although the numbers vary from paper to paper, women show a commanding lead in incidence of nickel allergy. A 1:8 ($P < 0.001$, P value not in original publication) ratio of men to women has been noted among nickel-sensitive subjects (9), and nickel allergy has been found to affect 15–20% of females while only 2–5% of males (10–13).

Several ways exist to investigate the cause of this increased sensitivity of females. Comparing nickel reactivity among females with different levels of exposure to nickel gives valuable information. In a Danish study (12), Danish girls who had their ears pierced before a Danish law regulated nickel exposure were 3.3 times ($P = 0.0044$) more likely to be nickel-sensitive than girls without pierced ears. Danish girls who had their ears pierced after the regulation were only 1.2 times ($P = 0.52$) more likely to be sensitized to nickel than girls with unpierced ears. This is a statistically insignificant difference. 17.1% of girls whose exposure, for the most part, occurred prior to the regulatory legislation were sensitized to nickel (12). The frequency of sensitization of younger girls, whose exposure occurred mostly after the legislation, was only 3.9% ($P < 0.001$, P value not in original publication). Johansen et al. (13) found a decrease, from 24.8% to 9.2% ($P = 0.0008$), in the occurrence of positive patch tests to nickel between those aged 0–18 in

Table 1. Sex differences in allergic reactions in Turkey and Sweden

	Vehicle	Sex prevalence	Percentage (female-to-male)
Lantinga et al. (7)	Nickel sulfate 5%	Women	26.3 to 6.5 $P = 0.013^*$
	Potassium dichromate 0.5%	Women	7.4 to 4.3 $P = 0.507^*$
	Cobalt chloride 1%	Men	1.1 to 8.7 $P = 0.024^*$
	Thiuram mix 1%	Equal	2.1 to 2.2 $P = 1.00^*$
Akasya-Hillenbrand and Ozkaya-Bayazit (8)	Nickel sulfate 5%	Women	30 to 5.4 $P < 0.001$
	Potassium dichromate 0.5%	Men	3.9 to 21.7 $P < 0.001$
	Cobalt chloride 1%	Men	5.9 to 11.7 $P < 0.001$
	Thiuram mix 1%	Men	2.6 to 14.2 $P < 0.001$

* P value not in original publication.

Denmark before and after the Danish legislation that decreased nickel in jewellery.

Comparing males whose exposure to nickel is similar to that of females also adds to possible insight. Von Hoogstraten et al. (14) found that 21.0% of men aged 35 and younger with pierced ears had nickel allergies, while only 2.7% of men without pierced ears had allergies ($P=0.001$). The observations of Von Hoogstraten et al. (14) on women of the same age range are remarkably similar. 37.9% of the women aged 35 and younger who had pierced ears had positive nickel patch tests, while only 4.8% of those without ear piercings had a positive patch test ($P<0.001$). The data presented for men and women with and without piercings seems to indicate that piercing and not sex is the stronger influence on sensitization.

Closer inspection yields interesting results. Using χ^2 analysis, we compared the rates of positive reactions for men with piercing to women with piercing, 21.0–37.9%, respectively. The P value for this comparison is 0.045, yielding only a slight statistically relevant difference between the sexes. Comparing the frequency of positive patch tests results in men without pierced ears (2.7%) to women without pierced ears (4.8%), we found a P value of 0.365 indicating no statistically relevant difference between the groups. The fact that a similar percentage of men and women with pierced ears are sensitive to nickel suggests that a prominent correlation between nickel allergy and sensitization lies with exposure, and not sex. Ehrlich et al. (15) found that 4.0% of men without piercing, 11.1% of men with one piercing and 14.6% of men with more than one piercing had at least one positive reaction to patch tests with nickel sulfate 2.5%, gold sodium thio-sulfate 0.5%, cobalt chloride 1% and palladium chloride 1%. Using this information, Ehrlich et al. (15) found that the number of piercings can be used as a predictor of metal allergy ($P=0.04$). Note that women typically have more piercings, both on the ear and on other parts of the body, than men. This can help explain why there was a slight statistically significant difference between men and women with pierced ears in the Von Hoogstraten et al. study, but no such significance among those with no ear piercing. A positive correlation between exposure and positive patch test results is found in both sexes.

One area of particular interest is changes in women's reactivity during pregnancy and menstruation. While there have been some indications that women become more prone then to allergic reactions, to date, the data has been inconclusive and with implications that are not clear (16).

Work-Related Contact Dermatitis

In a study done in Germany, female bakers, confectioners and cooks had higher incidence rates of occupational skin diseases, including allergic contact dermatitis, compared to their male counterparts (17). Other studies in Western countries also show that women have more occupational skin diseases than male co-workers (18, 19).

An important factor in allergic contact dermatitis is exposure to irritants such as wet work and detergents (20). Water and detergents associated with wet-work harm the skin barrier, which can then in turn increase the rates of irritant responses by lowering the threshold necessary for elicitation of responses (21). Given that women tend to hold more jobs with exposure to wet work than men, it is thus not surprising that the majority of allergic contact dermatitis cases are seen in women. For example, among the nine careers in Sweden that have the highest relative incidence of occupational skin disease: hairdressers, machine fitters, cooks (two categories), dental assistants, mechanics, cleaners, kitchen assistants and nurses, and females dominate the work force of seven: hairdressers, machine fitters, cooks (one of two categories), dental assistants, cleaning, kitchen assisting and nursing (22).

Hairdressers (23–25), cleaners (26–28), caterers (17, 29) and nurses (30–32) have well-noted and well-researched high incidences of hand eczema in Europe, especially Scandinavia. These professions are female-dominated trades, and so the fact that women comprised 66.7% of eczema cases over a five-year period in Denmark (33) is unsurprising. Meding and Bengtsson (34) found that exposure to wet work was reported as the cause of skin ailments in 50% of documented incidents found in Swedish injury records. Also, at home, women do the majority of wet work, which has been shown to have a positive correlation to incidence of skin disease (27). Note that women in high-risk fields, who do not have dishwashers and who have children under the age of four, all factors associated with increased wet work, have a fourfold increased probability of acquiring hand eczema over women without these risk factors (30).

The above studies (17, 20–34) focused on Scandinavian and Western European countries, and their findings do not necessarily hold true for other populations. Goh and Soh (35) found that in Singapore slightly more women than men had occupational irritant contact dermatitis (71.4% to 61.4%) and slightly more men than women had allergic contact dermatitis (35.7% to 25.0%). Singapore's economic base and job market is

markedly different from Europe's: Singapore is under the process of rapid industrialization. The occupations that provide the greatest source of contact and occupational dermatitis in Singapore were (in order of highest percentage): construction, engineering, electronics, food, transportation, shipyard work, printing, cleansing, optical work and electrical work (35). This is clearly different from the careers in Sweden that were shown to be high-risk fields (22). Such socioeconomic considerations could be at the heart of the different findings with regard to sex differences in allergic contact dermatitis in Singapore and Europe.

Olumide studied contact dermatitis in Nigerian women (36) and men (37). Although women comprise the majority of the work force in cooking and dishwashing in Nigeria, more men than women have incidents of contact dermatitis in these fields (36, 37). Olumide attributes this difference to the early childhood exposure of wet work in women, which after continuing exposure, hardens and desensitizes their hands to irritants.

Olumide's findings on nickel are also interesting. Nickel was the second-most frequent alleged cause of hand allergic contact dermatitis in men and the most common sensitizer in women. This was due to the high rate of individuals working in jobs that have a great deal of exposure to nickel. For women this was mostly dressmaking, while for men it was apparently gate keeping. This points to exposure, and not sex-specific characteristics of skin, as being the main factor in contact dermatitis. Among those patch tested, 28% of women and 16% of men had positive responses to nickel ($P=0.260$, P value not in original publication). Even though women did display more frequent positive reactions, the ratio between the sexes was noteworthy. Using the data available, we found that there was a statistically insignificant 1.75:1 female-to-male ratio ($P=0.260$, P value not in original publication) of frequency of positive reactions between the sexes in Nigeria (36, 37). The findings in other countries were markedly different (Table 2). Cross-cultural differences in female and male reactivity are likely due to different exposure patterns. Note that gate keeping, a common occupation for men in Nigeria,

is no longer common in Europe. In fact, prior to 1930, European men who electroplated for a living were frequently victims of nickel dermatitis (38). As hand plating decreased in Europe, the incidence of nickel dermatitis became associated with women and their personal items of jewellery (38).

Juvenile Difference

The main obstacle to determining conclusively whether women are intrinsically more prone to contact dermatitis than men lies in separating intrinsic differences in the skin from the different skin exposure patterns between the genders. One way to minimize the difference in exposure patterns between the sexes is to focus on juvenile contact dermatitis, assuming that female and male children have relatively similar exposure patterns. As children age, their incidence of contact dermatitis increases and makes a substantial upward shift after age 10, corresponding to increased exposure to allergens (39–50). Although it is impossible to isolate adults from the allergens that they face, looking at the male–female differences in contact dermatitis in children proves to be a useful method.

Dotterud and Falk (51) used 20 allergens to patch test 424 northern Norwegian children between the ages of seven and 12. They found that 17.0% of boys and 30.3% of girls had at least one positive patch test ($P<0.002$). Furthermore, two or more positive patch tests were seen more frequently in girls (11.4%) than boys (5.8%, $P<0.05$). However, cases of self-reported hand eczema showed no statistical difference between the sexes. Similar findings have labelled girls as more reactive and sensitive than boys (40, 41, 49, 50, 52–54). In a study of 562 Portuguese school children aged between five and 14, Barros et al. (55) found that 14.8% of boys and 11.8% of girls had at least one positive reaction to the 20 allergens tested. Running our own binomial test, we found these differences statistically insignificant. Some studies find equal rates of sensitivity and reactivity between female and male juvenile subjects (56, 57). As exposure to allergens increases with age, the various age ranges of the children in the studies is a factor in the differing results. The studies also differed in methods, locations and other aspects, which, again, could be a reason for the differing results.

Romaguera et al. (58) found that 18% of children with positive patch tests had occupational dermatitis. This is particularly noteworthy because none of the subjects tested was older than 14. Balato et al. (54) included a 13-year-old girl working in a beauty parlour who had contracted occupational dermatitis, and Gonçalo et al. (41) found

Table 2. Nickel sensitization by region

Region	Female : male nickel sensitization ratio
Nigeria (36, 37)	1.75 : 1 $P=0.260^*$
Sweden (7)	4.04 : 1 $P=0.013^*$
Turkey (8)	5.56 : 1 $P<0.001$
Scotland (9)	8 : 1 $P<0.001^*$

* P value not in original publication.

7% of subjects, all 13 or 14 years old, had occupational allergic contact dermatitis. These findings show that even juveniles studied are not always entirely free from differences in skin exposure to irritants and allergens between sexes. Therefore, studies of children, whose age ranges incorporate gender-partial exposure, can give faulty and deceiving results.

Meding and Järholm (59) found that the incidence of hand eczema is not related to age in men but are in women. This supports the hypothesis that, as women tend to have more sex-related exposure to irritants, their incidence of eczema increases. Wantke et al. (53) found that, while the frequency of positive reactions among females changes with age, the frequency of positive reactions among male children between the age of eight and 14 and male adults are the same. Another study found that girls after the age of 10 have more reactive skin than boys (50).

Studies that focus on nickel allergies and patch testing give rise to interesting observations. Although, in general, females have significantly more positive reactions to nickel than men do, this is not the case at all ages. A shift in female dominance of nickel allergy usually takes place after the age of 12 (40, 41, 47, 56, 60); before the age of 12 boys have been found to have more nickel allergy (41, 50). Note that in the above studies after the age of 12 females begin to have more reactions. This period of transition takes place during both the physical and social maturation of females. Generally, near the age of 12 girls undergo puberty, increasing their levels of female sex hormones. Similarly, it is at this age that girls begin to copy adult fashion. Girls understandably wear more earrings and other jewellery items after the age of 12. So the question remains: is the leap seen in nickel allergy in females after the age of 12 because of puberty or because of increased exposure? Some studies (12–15) found that exposure to nickel was responsible for the high rates of nickel allergy among females. Furthermore, when looking at schoolgirls ages 8, 11 and 15, all approximately at or past puberty, Larsson-Stymne and Widstrom (61) found that 13% of girls with pierced ears had nickel allergy while only 1% of those without pierced ears had nickel allergy ($P < 0.001$).

Other shifts between the sexes have been noted. In Singapore, seven- and 12-year-old boys have a greater ratio of atopic dermatitis than girls (1.18:1 and 1.19:1, respectively). But at the age of 16, girls had more frequent atopic dermatitis than boys with a ratio of 1.57:1 (62). This finding points to exposure as being the culprit in increased female sensitivity. A study done in Växjö, southern Sweden (63), showed that between the ages of 16 and 18 there was a significant increase in the incidence of hand dermatosis in females (12.4–15.7%, $P = 0.029$) and an insignificant decrease in hand dermatosis in males (6.7% to 5.1%). Noteworthy is that the difference between the sexes is insignificant at age 16, but significant at the age of 18. The authors infer that this relative change could likely be permanent and not the product of a short-lived fluctuation. The turning points observed in Singapore (62) and Sweden (63) correlate with females' increased exposure through work or home to wet work, and are far past any ages where the shift could be attributed to physiological changes (Table 3).

Conclusion

We find no definite consensus on whether sex is indeed an endogenous factor in allergic contact dermatitis. There are purportedly more than 3700 contact allergens (64). To say with certainty that women collectively have more sensitive skin than men would be to assume that they displayed more reactivity than men to all 3700 allergens, clearly this is unlikely to be the case. It is impossible to ascertain if even one allergen is universally more inclined to elicit responses in one sex. Most likely, the reported increase in female sensitivity to allergens is due to an increased exposure to the allergen itself, or to wet work and other irritants. Exposure seems to play the central role in determining the reactivity of the skin. The distinct mechanisms and phenomenology of the role of the sex of the individual in allergic contact dermatitis are yet to be fully understood (65). Subtle, but possibly important, endogenous sex differences in such immunologic reactivity await further definition.

Table 3. Observed turning points towards female dominance

Study	Subject	Turning point
Rudzki and Rebandel (40), Gonçalo et al. (41), Sevilá et al. (47), Rademaker and Forsyth (56), and Veien et al. (60)	Nickel allergy	After age 12
Tay et al. (62)	Atopic dermatitis	Age 16
Yngveson et al. (63)	Hand dermatosis	Between ages 16 and 18

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