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NICKEL ALLERGY AND HAND DERMATITIS IN A STRATIFIED SAMPLE OF THE DANISH FEMALE POPULATION: AN EPIDEMIOLOGICAL STUDY INCLUDING A STATISTIC APPENDIX

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Abstract. The occurrence of nickel allergy and hand eczema has been investigated in a stratified sample (2 500) of the Danish female population by an interview technique. The incidence density (allergy intensity) has been estimated by standard maximum likelihood methods. The age-specific prevalence rates have been calculated by life table techniques. The incidence density has doubled in all age groups from 1948 to 1973. The highest prevalence rate of nickel allergy was found in the 45-year-olds (0.189 ±0.023). The possible interaction between nickel allergy and hand eczema was analysed by a Markov chain model. Compared with non-nickel-sensitive women, a woman who has become nickel sensitized ran an increased risk of developing hand eczema. And those who had first developed a hand eczema ran an increased risk of subsequently developing nickel allergy. In future efforts to reduce direct skin contact with nickel, the close relation between nickel allergy and hand eczema should be the main argument. Statistical methods based on the incidence density will be useful in the evaluation of these efforts.

Key words: Epidemiology of nickel allergy; Nickel allergy–hand eczema

Since the first epidemiological data on allergic contact dermatitis appeared in the 'thirties (1) nickel has been the top allergen in women. The primary site for sensitization has shifted, from suspenders to pierced ear lobes and metal buttons in blue jeans (3, 13, 2).

Recent investigations in San Francisco, Finland and Denmark have shown that the number of nickel-sensitive women in the general population approximates 10% (14, 17, 18).

As an isolated phenomenon, nickel allergy is harmless. It is only when hand dermatitis develops that the condition becomes a threat to the patient's working ability. In Denmark, nickel hand eczema is the most common skin disease which leads to permanent disability. In the period 1970–76 a total of 96 cases were registered (16). To analyse the occurrence of nickel sensitivity in different cohorts and its possible relationship to hand eczema we have investigated a representative sample of the whole Danish female population. Statistical models are presented which will make it possible to produce reliable comparable results.

MATERIAL

Since 1974 the Danish National Institute of Social Research has, in collaboration with The Central Statistical Office of Denmark, made questionnaire investigations of the Danish population three times a year. The sample of the population is stratified by using the Central Person Register. In the actual investigation the primary sample consisted of 2 552 women between the ages of 16 and 99. The sample is representative of the general population regarding age, geographical distribution and occupational structure.

Interview and questionnaire

After a preceding mailed appointment the selected women were interviewed in their homes. The non-medical interviewers are trained and before each new investigation they are specially instructed in the particular questions.

The data were collected from the 3rd to the 20th of October, 1978. Questions 1, 3 and 5 could be answered by either 'Yes' or 'No'. Questions 2, 4 and 6 could be answered with the appropriate age.

1. Have you ever had a rash related to suspenders, metal buttons, fasteners, or costume jewelry?
2. How old were you when the rash first appeared? 0–9, 10–19, . . ., 50–59 or more than 60 years?
3. Have you ever had eczema of the hands?
4. How old were you when you first noticed eczema on the hands?
5. Have you ever had small water blisters on the hands?
6. How old were you when you first noticed the water blisters on the hands?

STATISTICAL MODELS AND METHODS

A woman of age x has a probability of $\lambda(x)\Delta x$ of developing nickel allergy for the first time in the small age span

Table I. *Women with a history of nickel allergy in a stratified sample of the whole Danish population (total: 286 out of 1976)*

Age of onset	Age of interview									Total
	16–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–97	
0–9	2	6	6	1	1	0	1	0	0	17
10–19	14	40	30	19	7	3	1	0	0	114
20–29	–	18	22	15	4	7	4	0	0	70
30–39	–	–	8	12	10	3	3	1	0	37
40–49	–	–	–	6	5	3	4	1	0	19
50–59	–	–	–	–	6	6	3	0	0	15
60	–	–	–	–	–	6	2	1	0	9
No information	0	1	0	2	1	1	0	0	0	5
Total	16	65	66	55	34	29	18	3	0	286
Population sample	139	351	383	289	308	239	188	75	4	1 976

from x to $x+\Delta x$. Thus, $\lambda(x)$ is the incidence density, or the allergy intensity. In the analysis we assume that $\lambda(x)$ is constant over each of the age intervals shown in question 2. Estimates of the values of the incidence density on these intervals may be found by standard maximum likelihood methods along with estimates for their standard deviations. Furthermore, age-specific prevalence rates may be computed by life-table methods. (For details, see the Appendix.)

The study of the possible interaction between nickel sensitivity and hand eczema is based on the Markov chain model given in Fig. 1. A woman is born in the box labelled 1. If she becomes sensitized she moves to the box labelled 3. If she then develops hand eczema she moves on to box 4.

If hand eczema is the primary event and is followed by sensitization, the route in the box diagram in Fig. 1 will be from 1 to 2 to 4. The incidence density for a healthy woman of age x for developing hand eczema is $\mu(x)$ and the incidence density for a nickel-sensitized woman of developing hand eczema is $\varrho\mu(x)$. Thus, the quantity ϱ measures the relative increase in the incidence density for a woman with a nickel allergy, of developing hand eczema.

Similar interpretations are valid for θ and $\nu(x)$, given in Fig. 1. If nickel allergy and hand eczema are independent events in the life history of a woman, θ and ϱ will both be equal to one. If there is a relation between nickel allergy and hand eczema, at least one of them will differ from one. By estimating θ and ϱ and testing for possible deviations from unity, the relationship between hand eczema and nickel allergy can be analysed. In the analysis we have also taken into account that $\mu(x)$ and $\nu(x)$ change from cohort to cohort (for details, see the statistical Appendix).

RESULTS

2552 women were selected for investigation; 1976 (77.4%) participated. The number with a history of nickel allergy in the different age groups is given in Table I. A total of 286 of the 1976 answered 'Yes' to question 1. The total prevalence rate of a history of nickel allergy is 286/1976=0.145. The calculated age-specific prevalence rate is given in Fig. 2 for different cohorts with one standard deviation. The prevalence rate is greater in the younger cohorts than in the older ones.

Fig. 3 shows the incidence density (ID) with one standard deviation of developing nickel allergy at different time periods depending on age. In the younger age group there has been a steady increase in the ID from 1948 to 1973. In the most recent years (1968–78) the ID is higher than in all previous periods.

A preliminary analysis has shown a close correlation between the occurrence of hand eczema and small water blisters on the hands. Therefore, hand eczema in the following analyses was defined as an affirmative answer to either question 3, 5, or both in

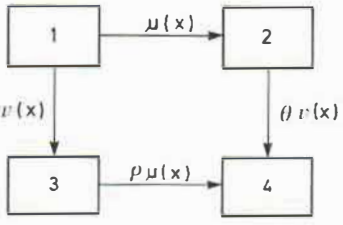

Fig. 1. The Markov chain model. 1: Disease-free woman. 2: Woman with hand eczema. 3: Woman with nickel sensitivity. 4: Woman with both nickel sensitivity and hand eczema.

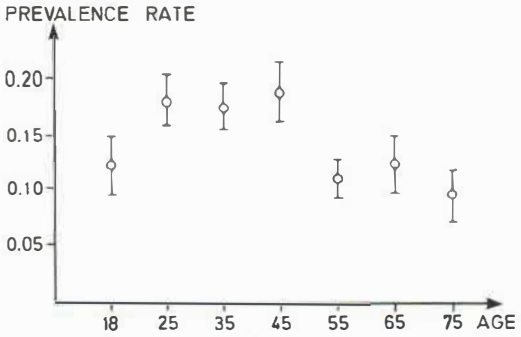

Fig. 2. Age-specific prevalence rate of a history of nickel allergy for different cohorts with one standard deviation.

the questionnaire. The lowest age at onset reported in questions 4 and 6 was used.

In Fig. 4 the data on nickel allergy and hand eczema for the 1961 who gave information about age at onset for both nickel allergy and hand eczema have been summarized. In 1366 (70%) of 1961, neither nickel allergy nor hand eczema occurred. A total of 435 developed hand eczema. 279 became nickel sensitive, and 119 of those (43%) reported hand eczema. Of the 1682 without nickel allergy, 316 (18.8%) reported hand eczema. In 77, hand eczema and nickel allergy occurred within the same 10-year interval, and it is impossible to determine which of the two events was the primary one.

The value of ϱ in Fig. 1 has been estimated to 2.26, with a standard deviation of 0.49, while the estimated value of θ is 3.01, with a standard deviation of 0.62. A 95% confidence region for the parameters is given in Fig. 5. Since the lines $\varrho=1$ and $\theta=1$ do not intersect the ellipse, both values are significantly different from 1 on the 5% level.

DISCUSSION

Man has always been exposed to nickel in his natural environment. Because of its inherent properties, nickel is widely used in metal alloys and chemical processes (11). The world production of nickel ore has increased from 2.8×10^5 tons in 1960 to 6.9×10^5 tons in 1978 (19, 20). The sensitization hazard of the increased amount of nickel in the environment is difficult to evaluate. More important for nickel sensitization is the daily use of nickel-plated metal objects used in direct skin contact. The import of bijoutery minus the export in Denmark has risen from 52 tons (mean value, range 27–67) per year in 1959 to 1963 to 72 tons (mean value, range 46–113) per year in 1975 to 1979 (7).

While the exposure to, for instance, epoxy is limited to a relatively small part of the population, nearly every woman is exposed to nickel. In the present study we intended to analyse the consequences of this exposure on a stratified sample of the female population. Earlier studies which have evaluated the occurrence of nickel allergy in the general population have been made on partly selected materials (14, 17, 18). The only realistic way to obtain data on such a large and geographically widespread population is by interview. The drawback of such an investigation may be the quality of the data obtained. A woman may forget an earlier episode of dermatitis in relation to nickel objects or

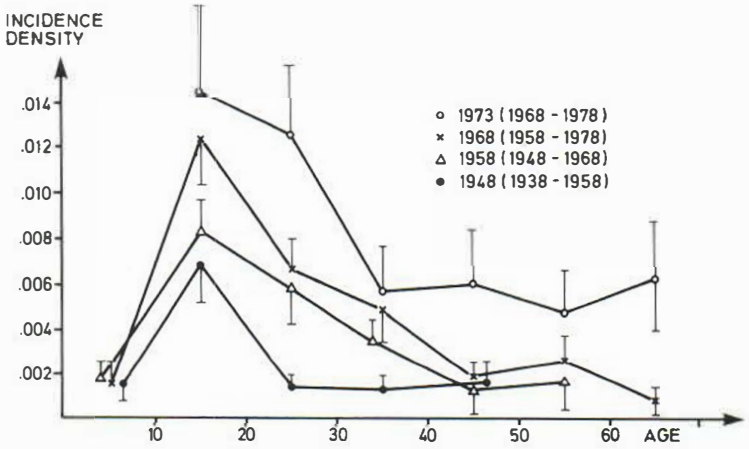

Fig. 3. The incidence density with one standard deviation of developing nickel allergy, at different time periods, depending on age.

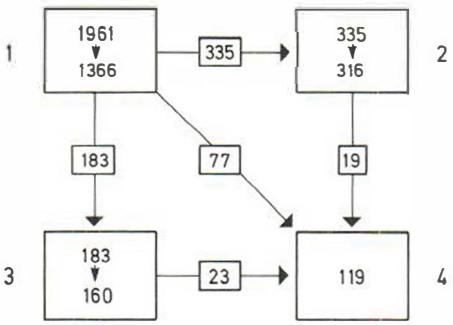

Fig.4. Development of nickel allergy and hand eczema in a population of 1961 women. See caption to Fig. 1. for explanation of abbreviations 1, 2, 3 and 4.

she may not recall the correct age at onset. It is also possible that different age groups will give unequal proportions of false answers. From a study of 50–70-year-old twins we know that 62 of 88 who reported a positive history of nickel allergy had a positive patch test, and 4 of 67 with a negative history had a positive patch test (15). Thus the data obtained by diagnosing nickel allergy just by questionnaire seem to be reasonably reliable, at least in the age group from 50 to 70 years.

In the present study 23% would not agree to participate in the investigation. Two factors were important, namely that the interviews took place during a school holiday in the autumn. And in the same period the Central Person Register, from where the population sample was drawn, was debated in the press. These factors for non-responding are not correlated to either hand eczema or nickel allergy. Because of this, and since age is taken explicitly into account in the analysis, the high percentage of non-responders should not introduce bias in the results.

Much has been done to make epidemiological studies on contact dermatitis comparable. The Scandinavian and, later, the International Contact Dermatitis Research Group have standardized patch testing (8, 10). Wilkinson has emphasized the importance of sex, occupation, hand eczema, and leg ulcers, the MOHL index (21).

Another important factor which often is not handled adequately is the age structure of the material. With for instance cement dermatitis we know that it often appears after a long exposure period (9). If we compare two groups of patients with cement dermatitis without taking the age structure into account the results may be quite misleading. Even with a similar median or medium age, the age distribution in two materials may be different.

The methods applied in the present paper may serve as a model to achieve comparable results in future studies on the epidemiology of contact dermatitis. In the calculation, both the age at investigation and the age of onset of the nickel allergy have been taken into account. This is important, as a woman is no longer in the risk population when she is first sensitized. With the calculation of the incidence density the risk of becoming sensitized in different populations can be compared, as the results are independent of the age structure.

From Fig. 3 it appears that the incidence density from 1948 to 1973 has more than doubled in all age groups. Earlier Marcussen found a rise in the number of nickel-sensitive patients at the Finsen Institute after the Second World War (12).

The prevalence rate is highest in the younger age groups and declines after the age of 50. In the population study in San Francisco (18) the prevalence of a positive patch test to nickel was 11.5% in those less than 24 years of age, and 7.2% in those above 35. But in Finland, Peltonen found the highest prevalence in the elderly. In a study among unselected Danish twins one of us (T. M.) has found a prevalence near 10% in the 50–70-year-olds, which is similar to the figures in the present study. The high prevalence in the young age group in this study could indicate that nickel sensitivity is a growing problem, but it is impossible to draw reliable conclusions from retrospectively collected data.

One of the everyday clinical problems in the

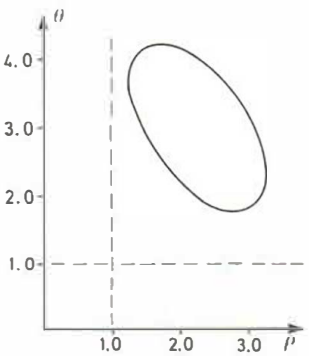

Fig. 5. The 95% confidence region for the parameters ϱ and θ given in Fig. 1.

handling of patients with allergic contact dermatitis is the possible relevance of positive patch tests. From figures from dermatological departments we know that hand eczema occurs with a frequency of 20–60% in nickel-sensitive patients (3, 4, 5, 13). As patients are often referred to the departments not because of a nickel allergy, but because of persistent hand eczema, the observed correlation may be due to a sampling bias. Because of the observation of the high prevalence of nickel allergy in the general population, this problem has become even more relevant, as emphasized by Cronin (6). In the earlier mentioned population studies from Finland and Denmark (14, 17) nearly 40% of the nickel-sensitive have or have had hand eczema. Both studies lacked a control group sampled in the same manner.

In the present study we have some nickel-sensitive and some non-nickel-sensitive subjects collected in the same way and stratified according to age, geography, and occupation. The reporting of hand eczema by questionnaire will contain errors. Therefore the relative incidence density is more interesting than the absolute figures. Our results demonstrate that the nickel-sensitive woman runs a considerably increased risk of developing hand eczema during her lifetime. The analysis of the data by the Markov chain model (Fig. 1) discloses a new interesting point. It indicates that persons who have developed hand eczema have a statistically significant increase in the risk of developing nickel allergy as compared with healthy individuals. This supports the general opinion that persons who already have an ongoing dermatitis run an increased risk of developing secondary sensitivities.

Our data have been reported with 10-year intervals for the age of onset. If we had had the exact ages for the onset of nickel allergy and hand eczema, the use of the Markov chain model (Fig. 1) would have provided us with more detailed information on the relation between nickel allergy and hand eczema.

As nickel hand eczema often is a troublesome and persistent condition the observed increased risk for a nickel-sensitive woman of developing hand eczema should be the main argument against the widespread nickel exposure for the female population. The illustrated statistical models can be used propectively to measure the effect of a general regulation forbidding the use of nickel-releasing alloys designed for direct contact with the skin.

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STATISTICAL APPENDIX

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The methods presented in this Appendix are applications of principles well known to research workers in the fields of biometry, demography and actuarial mathematics (1, 3).

In the actual study the data consist of retrospectively collected records of each woman's disease history. Since nickel allergy and hand eczema have no influence on mortaility, one can thus analyse the data as if death is not possible (2).

Consider first a homogeneous group of n women, e.g. a cohort, and assume that the allergy intensity or incidence density $\lambda(x)$ is constant in each of K age intervals. Denote its constant value on the kth interval by λ_k. For a woman, indexed by j, who is y_j years at the time of the interview, let U_{kj} be her observed lifetime without allergy in age interval number k if she is not observed to contract allergy during that interval; $U_{kj}=0$ otherwise. Moreover, let V_{kj} denote her observed lifetime in the kth interval if she gets an allergy in that interval; $V_{kj}=0$ otherwise. Then the conditional likelihood for woman number j, given her age at interview, is

$$L_j = \exp\left\{-\sum_{k=1}^{K}\lambda_k U_{kj}\right\} \times\left\{1-\exp\left(-\sum_{k=1}^{K}\lambda_k V_{kj}\right)\right\}. \quad (A)$$

According to the sampling scheme adopted in the present study, the ages at interview may be considered as independent replications of a random variable with distribution function corresponding to the age distribution in the actual group of women at October 1978. Hence, one obtains the likelihood for the jth woman by multiplying (A) by the density function of this age distribution. The overall likelihood is given as a product of such terms. Now, the age distribution is functionally independent of the λ_ks, and the maximum likelihood estimators $\hat{\lambda}_1, \hat{\lambda}_2, \ldots, \hat{\lambda}_K$ are found by maximizing

$$L = L_1 \times L_2 \times \ldots \times L_n \quad (B)$$

numerically. Moreover, it follows by standard maximum likelihood theory that the $\hat{\lambda}_k$s are asymptotically independent and normally distributed with the proper expectations and with asymptotic variance

$$-1/nE\frac{\partial^2 \ln L_j}{\partial\lambda_k^2} \quad \text{for} \quad \hat{\lambda}_k.$$

This asymptotic variance may be estimated by its empirical counterpart

$$-1/\frac{\partial^2 \ln L}{\partial\lambda_k^2}(\hat{\lambda}_k).$$

Since allergy does not influence mortality, $1-\exp(\int_0^x \lambda(u)\,du)$ is the probability that a woman has had allergy, given that she is alive at age x. Hence, an estimate for the age-specific prevalence rate for an age x in the kth interval is given by

$$1-\exp\left\{-\sum_{i=1}^{k-1}\hat{\lambda}_i l_i - \hat{\lambda}_k\left(x-\sum_{i=1}^{k-1} l_i\right)\right\},$$

where l_i is the duration of the ith interval. The asymptotic variance may be found by linearizing.

The analysis of the interaction between nickel allergy and hand eczema is based on the Markov model given in Fig. 1 in the paper. In the actual analysis it is also taken into account that one does not have a homogeneous population, since $\mu(x)$ and $\nu(x)$ in Fig. 1 may vary from cohort to cohort. To deal with this problem it is assumed that $\mu(x)$ and $\nu(x)$, for a woman who is y years at the time of the

interview, are given as $\mu^0(x)\exp\{\beta_1(y-40)\}$ and $\nu^0(x)\exp\{\beta_2(y-40)\}$, respectively. The "underlying intensities" $\mu^0(x)$ and $\nu^0(x)$, as well as θ and ϱ, are the same for all women. Moreover, $\mu^0(x)$ and $\nu^0(x)$ are assumed to be constant for each of K age intervals, the constant values on the kth interval being denoted as μ_k^0 and ν_k^0. (If one wants to, one may consider the assumptions on $\mu(x)$ and $\nu(x)$ as a form of efficient "internal standardization" for age.)

Let the total observed lifetime of woman no. j (irrespective of in which state) in the kth interval be denoted by T_{kj}. Furthermore, let N_{kj}^{ih} equal 1 if woman no. j is in state i at the start of the kth interval and in state h when she was "last seen" in that interval; $N_{kj}^{ih}=0$ otherwise. Then the likelihood of the jth woman, given her age at interview is

$$L_j = \prod_{k=1}^{K} \prod_{i,h=1}^{4} P_{ih}(x_k, x_k + T_{kj})^{N_{kj}^{ih}}, \qquad \text{(C)}$$

were $P_{ih}(x,z)$ is the probability that a woman in state i at age x will be in state h at an age $z>x$, and x_k is the left endpoint of the kth age interval. (Here Π is the product sign and 0^0 is interpreted as 1.) Now the $\{P_{ih}(x_k, x_k+T_{kj})\}$ are relatively simple functions of the parameters $\mu_k^0, \nu_k^0, \theta, \varrho, \beta_1$, and β_2 (we omit the explicit expressions here), and by an argument similar to the one given above, it follows that the maximum likelihood estimators $\hat{\mu}_k^0, \hat{\nu}_k^0, \hat{\theta}, \hat{\varrho}, \hat{\beta}_1$, and $\hat{\beta}_2$ are found by maximizing (B) numerically, where L_j is now given by (C). The estimators are asymptotically multinormally distributed with the proper expectations and with a covariance matrix that may be estimated by

$$\left\{ -\frac{\partial^2 \ln L}{\partial\gamma_i \partial\gamma_j}(\hat{\gamma}) \right\}^{-1},$$

where

$$\gamma = (\mu_1^0, \ldots, \mu_K^0, \nu_1^0, \ldots, \nu_K^0, \varrho, \theta, \beta_1, \beta_2).$$

The values of $\hat{\varrho}$ and $\hat{\theta}$ are given in the paper. Moreover, the values of $\hat{\beta}_1$ and $\hat{\beta}_2$ were found to be -0.055 ± 0.004 and -0.039 ± 0.005, respectively. The negative value of $\hat{\beta}_2$ again illustrates the rise in the allergy intensity found in the younger cohorts (cf. Fig. 3).

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