

Letters to the Editor

Chronic fatigue syndrome and nickel allergy

Dear Sir

Recently, Marcusson et al. (1) reported a significantly higher prevalence of nickel sensitivity, especially in women, in a group of patients with chronic fatigue syndrome (CFS), compared to healthy controls; this interesting finding was discussed as a possible result of neuroimmunological abnormalities. However, particularly in the case of epidemiological findings not (yet) supported by experimental or clinical data, careful consideration should be given to the possibility of (i) chance (ii) bias or (iii) faults in the study design, which might explain such results.

Multiple testing without Bonferroni or similar adjustment may have compromised the validity of statistical analysis in the study, i.e., chance can possibly not be ruled out as having led to the impression of a significant association. However, much more importantly, the 3rd possibility seems to hold true for this small case-control study. While no mention was made concerning the exclusion of persons with a "history of metal allergy" in the case group, i.e., these persons will have implicitly been *included*, this particular subset was explicitly *excluded* in the control group (p. 269).

There is, however, no doubt that a history of metal intolerance is the most important (albeit neither fully sensitive nor specific (2)) clinical sign of nickel allergy, which is often acquired by the wearing of imitation jewelry – and thus most often found in young women (3). Therefore, a strong artifactual difference between the proportion of

nickel-allergic persons was introduced between case and control groups *by design*, which does not allow any conclusion to be drawn.

Furthermore, the lack of a significant difference in the prevalence of other metal allergies noted by Marcusson et al. (1) could be explained by the fact that these are not as strongly, or not at all, associated with a history of metal intolerance (3), which means that the pre-selection process had no (strong) effect on the prevalence in the control group – and thus no seeming association to CFS was observed.

Yours sincerely

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References

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2. Kieffer M. Nickel sensitivity: relationship between history and patch test reaction. *Contact Dermatitis* 1979; 5: 398–401.
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Reply

Dear Sir

When we wrote the paper on nickel allergy and chronic fatigue syndrome (CFS) (1) and interpreted our results, we were quite aware of the

pitfalls with regard to chance and bias. In the discussion, however, we chose to focus on the possible implications of our results rather than dwelling on methodology.

The prevalence of nickel allergy in the control group was 19% in the actual paper (1), which should be compared with the prevalence of 17% in a previous study (2). The latter control group consisted of patients having undergone patch testing due to various dermatological conditions, and the former control group consisted of healthy unrelated subjects recruited by the CFS patients and hospital staff.

As can be seen, the difference between the 2 control groups is negligible. The control subjects have been recruited from the same area of Stockholm but on different occasions. Therefore, we do not think that the control group has influenced our results that much.

Design of the study and the statistics can be discussed indefinitely, but we think that the best way to get further is to perform a similar study at another centre.

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