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Letter

Response to the Critics by Pekkanen et al

Our original study entitled "Moist and mold exposure is associated with high prevalence of neurological symptoms and multiple chemical sensitivity (MCS) in a Finnish hospital workers cohort" has raised a lot of interest. It has been criticized by our Finnish colleagues [1]. In fact, this critic toward our work depicts the current situation in Finland. Opinions different from the official guidance have been censored during the recent years.

Here, we defend our results and conclusions. *The claims of Pekkanen et al* are cited in italics and ours are in the following paragraphs.

Authors were able to contact only 13% of the personnel working at the hospital.

Pekkanen et al are right. The management of the hospital responded negatively to our request to study symptoms of the Obstetric hospital personnel. Therefore, we were able to contact only a small fraction of the exposed cohort. The first author of the article (S.H.) recommended authorities to do the study based on severe adverse health problems reported by the occupants, but this request was denied.

The hospital in question has attracted a lot of attention in the national media and there are also ongoing litigations, which is likely to affect the self-reported symptoms.

No, it is quite the opposite. Hospital personnel experienced symptoms, but their symptoms were ignored and the exposure to dampness microbiota persisted. In Finland, symptoms and diseases caused by moist and mold are explained by a nocebo effect making prevention almost impossible. The hospital was shut down after the long exposure due to serious mold and moisture damage and the pressure form the media.

All persons from the hospitals were female, but only half of the control group.

Correct, a male midwife is a rarity. Recruitment of the control cohort was very difficult. Finally, we were able to recruit office workers of both genders. This control group was used in two studies. Our article describing morbidity in the Finnish policemen ended up with similar results [2]. The comparison of the risk ratios (RRs) in predominantly female and male cohorts is shown in Table 1. The table shows that the risks are not gender related. We also have data on children from a mold infested school, and the symptoms of the school children are similar.

There are also many problems with the statistical analyses. The methods promise a test for the confounding effect of gender, but it is not reported in the results.

The answer from our statistician:

Confounding factors

Two possible major confounding factors were recognized. First, the numbers of doctor-diagnosed diseases were different between the groups. At least 2 diagnoses were 69% vs. 27% in the study cohort and control cohort, respectively. Second, the gender distribution was very different, as 100% vs. 55% were women. It was not possible to estimate the main effect or the confounding effect of gender using multivariable statistical methods, that is, to include gender as a covariate in analysis such as in logistic regression or log-binomial regression, or in the Mantel–Haenszel method because the study cohort consisted of 100% of women. Thus, of those two confounding factors, only the number of diagnoses was the only variable to include as a covariate in statistical analysis. However, different gender distributions were not forgotten. The possible bias caused by different gender distribution was considered in subgroup analyses including only female participants.

Statistical methods

Logistic regression may overestimate risk estimates when the prevalence of the condition in question is high (>10%). The prevalences of primary symptoms were as high as 40–80% among nurses and midwives. The log-binomial regression analysis was a valid method to estimate the adjusted RRs. However, the Mantel–Haenszel method was chosen because it is much easier to understand. The log-binomial regression method is still very rarely mentioned in the basic textbooks. In the Mantel–Haenszel method, the participants were divided into two strata (0-1 diagnoses and ≥2 diagnoses). And, as described earlier, the same procedure with gender was not possible. Section 2.4 Data analysis describes what was really carried out.

Incorrect text of logistic regression

'The results are presented in Table 1. The logistic regression analysis shows a significant difference between the cohorts in the prevalence of central nervous system (CNS) symptoms RR: 4.94 (95% confidence interval (CI): 2.72-6.91, $p < 0.001$), autonomous nervous system, that is, numbness of limbs, tongue, or face; tetanus; or weakness of muscles RR: 4.36 ($p < 0.001$), arrhythmia RR: 19.75 ($p < 0.001$), fatigue RR: 3.05 ($p < 0.001$), and MCS RR: 3.44 ($p < 0.01$).

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Table 1
Symptoms reported by predominantly female and male cohorts of occupants in workplaces infested by dampness microbiota

Symptom/disease	symptom prevalence midwives/policemen	prevalence controls	RR midwives/policemen	95% CI	*p*-value
CNS symptoms	56/90 (62%) 35/115 (30%)	5/44 (11%)	4.94 2.85	2.72-6.91 1.19-6.85	<0.001
Symptoms of autonomous nervous/peripheral nervous system	45/90 (50%) 23/115 (20%)	4/44 (20%)	4.36 2.57	1.90-7.41 0.95-6.95	0.001 0.06
Asthma	51/90 (57%) 35/116 (30%)	9/45 (20%)	1.86 1.56	0.86-3.13 0.81-3.00	0.11 0.18
Multiple chemical sensitivity	36/90 (40%) 25/114 (225)	4/43 (9%)	3.44 2.81	1.39-6.44 1.06-7.46	0.01 0.04
Fatigue	69/90 (77%) 67/113 (59%)	10/42 (24%)	3.05 2.82	2.19-3.64 1.55-5.11	<0.001 0.001
Muscle or joint pain	46/90 (51%) 29/103 (28%)	9/41 (22%)	2.02 1.50	1.11-3.02 0.75-3.00	0.02 0.25
Respiratory symptoms	72/90 (80%) 79/111 (71%)	12/42 (29%)	2.56 2.66	1.84-3.04 1.58-4.48	<0.001 <0.001
Cardiac arrhythmia	51/90 (57%) 23/101 (23%)	1/41 (2%)	19.75 9.58	4.47-36.30 1.33-68.81	<0.001 0.02

RR = risk ratio. The comparison was carried out to the same control healthy cohort.

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We admit that the mention of logistic regression in the Results section was mentioned incorrectly. However, in the Materials and methods, the detailed description of the methods has been presented. We admit also that in the footnote under Table 1, the explanation of the RRs was dropped out, probably due to a technical mistake. Unfortunately, these minor mistakes have not been noticed despite careful manuscript proof reading. However, as they say, one should see a forest behind the trees. The calculated RRs inarguably demonstrate higher morbidity in the exposed individuals than unexposed. These RRs were statistically significant. The results of this study corroborated the results presented in another study [2], where we tested different statistical approaches, but the results remained unchanged.

There were no objective markers of health status and little, if any, exposure assessment.

This study reports only the symptoms. Pekkanen et al know very well that indeed there are no validated biomarkers to assess the exposure to indoor air dampness microbiota. The exposure assessment was mentioned in the article using the official reports of the microbial work-up. Toxicological investigation in the building was not performed despite suggestions from the first author (S.H.).

Taken together, the low response rate (a common problem with questionnaire studies and a problem of reaching the occupants), *likely high selection bias* (selection bias has been mentioned as a limitation of the study. Symptomatic individuals are more eager to participate, even in the control cohort) *and reporting bias* (no reporting bias, all participants were enrolled in the study), *missing exposure assessment* (reported in the article) *and unclear and missing statistical adjustments* (refer explanations in the following paragraphs) *make the empirical results of the paper quite unreliable* (conclusions were confirmed in another study [2]. Table 1.)

In their review of literature, the paper completely neglects the majority of the literature on multiple chemical sensitivity and only concentrates on papers supporting the authors' unidirectional toxicological interpretations. Current knowledge supports the biopsychosocial origin of environmental intolerance, e.g., multiple chemical sensitivity, which is not due to exposure.

Pekkanen et al cite the publications they have selected. These articles do not deal with health effects caused by moist and mold milieu. Using this selection, Pekkanen et al try to convince the readers about the biopsychological nature of the symptoms. However, irreversible symptoms were not relieved by psychological treatment [3], thus undermining the proposed hypothesis of Pekkanen et al. We, being the authors of the original article, have full rights to cite any article that supports our findings.

Thus, the relationship between microbes and nonspecific symptoms presented in this paper should be interpreted with considerable caution.

We admit that it might have been too strong to mention causality. Nonetheless, from study to study, we obtain similar results (refer Table 1) of higher morbidity in toxic compared with healthy environment. These observations allowed us to apply deduction: when the same phenomenon is reproduced, the chance for a pure incidence becomes improbable.

We are thankful to the Editor for providing the platform of this journal to make a debate and hope that the readers will make their own conclusions whether our arguments are convincing. Pekkanen et al being representatives of the Finnish health authorities should be concerned about public health in moist environments and do their best to prevent health damage instead of downplaying the problem. Our endeavor to investigate how to diagnose mold-related illness will continue without any prejudices.

Conflict of interest

The authors declare no conflict of interests.

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