

# Teachers' work-related non-literature-known building-related symptoms are also connected to indoor toxicity: A cross-sectional study

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## Abstract

A previous study showed that classical building-related symptoms (BRS) were related to indoor dust and microbial toxicity via boar sperm motility assay, a sensitive method for measuring mitochondrial toxicity. In this cross-sectional study, we analyzed whether teachers' most common work-related non-literature-known BRS (nBRS) were also associated with dust or microbial toxicity. Teachers from 15 schools in Finland completed a questionnaire evaluating 20 nBRS including general, eye, respiratory, hearing, sleep, and mental symptoms. Boar sperm motility assay was used to measure the toxicity of extracts from wiped dust and microbial fallout samples collected from teachers' classrooms. 231 teachers answered a questionnaire and their classroom toxicity data were recorded. A negative binomial mixed model showed that teachers' work-related nBRS were 2.9-fold (95% CI: 1.2-7.3) higher in classrooms with highly toxic dust samples compared to classrooms with non-toxic dust samples ( $p = 0.024$ ). The RR of work-related nBRS was 1.8 (95% CI: 1.1-2.9) for toxic microbial samples ( $p = 0.022$ ). Teachers' BRS appeared to be broader than reported in the literature, and the work-related nBRS were associated with toxic dusts and microbes in classrooms.

## KEYWORDS

building-related symptoms, indoor toxicity, microbial toxins, mitochondrial dysfunction, mitochondrial toxicity, sick building syndrome

## Practical implications

- The boar sperm motility inhibition assay, a sensitive method for detecting mitochondrial toxicity, is a promising approach to assess the risk of adverse indoor health effects.
- In toxic classrooms, teachers' building-related symptoms are more diverse than thus far reported.

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## 1 | INTRODUCTION

According to the World Health Organization, healthy indoor air is a human right.<sup>1</sup> However, poor indoor air quality is common, and building-related symptoms (BRS) have been reported worldwide for decades in different types of buildings.<sup>2</sup> Known BRS affect several organ systems, including the eyes, nose, skin, respiratory, and central nervous systems; poor indoor air quality can also cause general and mental health symptoms.<sup>2-4</sup> Microbial toxins indoors in moisture and mold-damaged buildings are suspected to cause some BRS.<sup>5</sup>

In some reports of *in vitro* toxicity, differences have been found between moisture-damaged buildings and reference buildings. In schools with high levels of BRS, the inflammatory potential of deposited dust in human lung epithelial cell line A549 assay was statistically significantly higher than in control schools.<sup>6</sup> In offices, the inflammatory potential of the dusts above the floor in lung epithelial cell A549 assay was associated with central nervous system symptoms but not mucosal or skin symptoms.<sup>7</sup> In two moisture-damaged schools, inflammatory potential of indoor air particles and bioaerosols were examined before and after building renovation<sup>8</sup>; in one school, a clear decrease in both TNF- $\alpha$  and IL-6 levels was observed via the mouse RAW264.7 macrophage assay; in another school no differences in inflammatory potential were observed. In more recent work, the inflammatory potential of indoor air particles in mouse RAW264.7 macrophage assay was significantly lower as measured by TNF- $\alpha$  and IL-6 after extensive renovation of a moisture-damaged school.<sup>9</sup> In the same study, inflammatory markers in teachers' nasal lavage samples were also lower after renovation, as were microbial concentrations in air samples. In a multicenter study in different climatic areas in Finland, the Netherlands and Spain, the inflammatory potential of school deposition dust was studied with mouse RAW264.7 macrophage cells.<sup>10</sup> Significant differences were found between countries, and in the pooled data, moisture-damaged schools had slightly higher, but not statistically significant, inflammatory potentials compared to reference schools. The toxicity of actively collected particle samples in the mouse RAW264.7 macrophage test did not differ significantly between moisture-damaged and control schools.<sup>11</sup>

Boar sperm motility assay has been used to detect toxic microbes and dusts in moisture- and mold-damaged buildings associated with health complaints.<sup>12-21</sup> In a recent study, a clear temporal association was found between heavy occupational exposure to sperm-toxic dust, during renovation of a water-damaged building, and a cluster of 21 new occupational asthma cases.<sup>22</sup>

We previously showed that 20 literature-known BRS were associated with sperm-toxic dust and airborne microbes in teachers' working environments.<sup>23</sup> In the present study, we investigated whether teachers' other work-related non-literature-known BRS (nBRS) are also linked to dust and microbial toxicity.

## 2 | MATERIALS AND METHODS

### 2.1 | Schools

A more detailed description of material and methods was previously published.<sup>23</sup> The Real Estate Department of Helsinki City chose 15 schools that represented different decades of construction, building technologies, and ventilation systems, some of which had been renovated. These schools are described more detailed earlier.<sup>23</sup> The schools were built between 1924 and 2004. Fourteen schools were between 2400 and 8300 m<sup>2</sup> and one school was 474 m<sup>2</sup>. Concrete was the main structural material for all the schools. Thirteen schools had a mechanical exhaust air system, while eight schools additionally had a mechanical supply air system. One building was renovated in 2009. Several moisture damage and indoor air studies had been conducted in eight schools, one study in one school, and no concerns about indoor air quality or moisture damage had been identified in six schools. These building-level data were not available to the research team during the research project.

### 2.2 | Teachers

Teacher eligibility for the study was based on working at least seven hours per week in the study school and for at least one year in the same principal classroom. Further, there had to be information available on his/her workplace and participants could not be pregnant at the time of survey. The symptoms of pupils in these schools were not studied.

We sent a questionnaire to all teachers in the 15 schools. The questionnaire asked whether symptoms were present in the last 12 months, whether they were related to the workplace, and whether they were alleviated during holidays and aggravated during the school year. Demographic data included age, sex, smoking habits and the presence of atopy. The 20 most common work-related nBRS—symptoms which has not been published as building-related—were selected for further investigation. According to the Ethics Committee of Helsinki University Hospital, official approval was not required for this type of anonymous survey.

### 2.3 | Testing indoor samples with boar spermatozoa as biosensors

Two types of indoor samples (wiped dust and airborne microbes) were collected from each teacher's principal classroom. First team collected and analyzed health data, second team collected samples as previously described.<sup>23</sup> Dust samples were collected between March 17 and June 11 in 2011. Microbial fallout samples were collected during lessons between May 9 and June 1 in 2011. Cotton balls were used to wipe dust samples from horizontal surfaces of lamps and cupboards, which had cleaned 8-12 months before sampling. Airborne microbial propagules were collected by allowing

them to fall onto malt extract agar plates for a 1 h sampling time. Plates were incubated for 4-6 weeks, and all growing microbial biomasses were harvested. No colony-forming units were counted and no identification of species was performed. To process these two different types of samples, the wiped dust and microbial biomasses were extracted separately into ethanol and evaporated to dryness at 62°C. Then, the residues were re-dissolved in ethanol to a concentration of 10 mg dry weight per ml.<sup>12</sup> Next, boar spermatozoa were exposed to the extracts of wiped dust and microbial biomass samples for 3 days.<sup>23</sup> Then, we determined the lowest sample extract concentration at which  $\geq 50\%$  of the spermatozoa had lost motility in comparison with control vehicle (ethanol).<sup>12,23</sup> The half maximal effective concentration ( $EC_{50}$ ) indicated the degree of toxicity (ie, the lower the  $EC_{50}$ , the higher the toxicity).

## 2.4 | Statistical analysis

Measurement endpoints are expressed as the median and 25th to 75th percentiles, unless otherwise stated. The number of work-related nBRS and the number of nBRS that were alleviated during school holidays were used as the dependent variables in negative binomial mixed models with school ( $n = 15$ ) used as a random effect. Two different adjustment sets were used when evaluating the effect of sample toxicity on the recorded number of symptoms: (1) Age, sex, current smoking status, and atopy-adjusted model, and (2) exposure time (in quartiles) -adjusted model. The results of negative binomial models are given as rate ratios (RRs) with 95% confidence intervals (95% CIs), which indicate the relative difference in the number of symptoms between groups. The relationship between dust and microbial toxicities was determined with a Spearman's rank correlation analysis. Two-tailed  $p$  values are reported. All analyses were performed with SAS (version 9.4, SAS Institute Inc.).

## 3 | RESULTS

The questionnaire was sent by email to all teachers at the 15 schools ( $n = 630$ ); 464 recipients (74%) responded.<sup>23</sup> Of those, 231 teachers met the inclusion criteria with a complete questionnaire and at least one type of toxicity result (200 responders had microbial toxicity results and 169 responders had dust toxicity results). Table 1 shows the summary of the study population. The median age of responders was 43 years, 81.8% were women, 9.5% were current smokers, and 10.4% had atopy. Their median working time at the primary workplace was 22 hours per week. The median age of survey drop-outs was 44 years, 77.7% of them were women (missing data 3.9%), 9.4% were smokers, and 10.3% had atopy. Their median number of hours spent at the primary workplace was 20 h per week (missing data 41.2%).

Table 2 shows the prevalence of the most common (prevalence over 5%) work-related symptoms in this dataset. In addition, the

TABLE 1 Summary data of study population of 231 teachers

Variable	
Age	43 (34-50)
Female sex, <sup>a</sup> $n$ (%)	189 (81.8)
Current smoking, $n$ (%)	22 (9.5)
Atopy, $n$ (%)	24 (10.4)
Working in primary classroom, hours per week	22 (17-26)
Median number of work-related nBRS	1 (0-3)
Teachers having at least one work-related nBRS, $n$ (%)	121 (52.4)
Teachers having at least five work-related nBRS, $n$ (%)	32 (13.9)

Note: The values are presented as medians with 25th-75th percentiles unless otherwise stated.

<sup>a</sup>One person in the study group lacked information about gender. The maximum possible score for work-related nBRS (non-literature-known building-related symptoms) was 20 points.

table indicates whether the symptom is reported in the literature as building-related (literature-known BRS) or not (non-literature-known BRS, nBRS). Table 2 does not include work-related literature-known BRS analyzed in previous work<sup>23</sup> with a prevalence of less than 5% in this dataset (fever, nose irritation, wheezing, exanthema, swollen eyelids, and difficulty concentrating). The 20 most common work-related nBRS included the following: three general symptoms (repeated or prolonged generalized feeling of sickness, decreased physical condition or performance, and indefinite feeling of thermoregulation failure); three throat symptoms (throat mucus and need to clear the throat, itching in the throat, and globus sensation); two other respiratory symptoms (sensation of pressure in the cheek or forehead, and getting out of breath easily); two eye symptoms (redness in the whites of the eyes, and eye discharge); three hearing symptoms (hearing impaired, difficulty distinguishing speech in noisy environments, and hypersensitivity to sound); three sleep symptoms (insomnia, difficulty falling asleep, and increased need for sleep); and four mental symptoms (depressiveness, irritability, anxiety, and decreased stress resistance). The median number of work-related nBRS per teacher was one symptom. Among the 231 teachers, 121 (52.4%) had at least one work-related nBRS and 32 (13.9%) had at least five work-related nBRS.

Dust toxicity was divided into three categories, and microbial toxicity was divided into two categories. The distribution of toxicities is shown in Table 3. There was no correlation between dust and microbial toxicities (Spearman's  $\rho = 0.087$ ,  $p = 0.31$ ).

According to the negative binomial mixed model adjusted for age, gender, smoking status, and atopy (Model 1), the number of teachers' work-related nBRS was 2.9-fold higher ( $p = 0.024$ ) when the dust sample  $EC_{50}$  was 6  $\mu\text{g}/\text{ml}$ , compared to symptoms in non-toxic classrooms (dust with  $EC_{50}$  of 25  $\mu\text{g}/\text{ml}$  or higher; Table 3). Moreover, according to Model 1, the RR of teachers' work-related nBRS was 1.8 ( $p = 0.022$ ), when the  $EC_{50}$  of fallout propagules was  $\leq 12$   $\mu\text{g}/\text{ml}$ , compared to an  $EC_{50} > 12$   $\mu\text{g}/\text{ml}$ .

Table 4 shows the negative binomial mixed model adjusted for time spent in the primary workspace (Model 2), with results paralleling those in Model 1.

Teachers had more nBRS, which were alleviated during school holidays in classrooms with highly toxic samples compared to those in classrooms with less-toxic samples: according to Model 1 the RR

**TABLE 2** Prevalence of work-related symptoms among 231 teachers divided into literature-known BRS and non-literature-known BRS

	Prevalence, n (%)
Literature-known BRS	
Fatigue	65 (28.1)
Nose stuffiness	64 (27.7)
Hoarseness	62 (26.8)
Nose dryness	52 (22.5)
Headache	46 (19.9)
Dry eyes	45 (19.5)
Dry cough	40 (17.3)
Eye irritation	39 (16.9)
Sneezing	39 (16.9)
Running nose	37 (16.0)
Mouth dryness	30 (13.0)
Sore throat	27 (11.7)
Skin dryness	20 (8.7)
Chills	19 (8.2)
Bloody nasal mucus	16 (6.9)
Wet eyes	15 (6.5)
Shortness of breath	12 (5.2)
Skin itching	12 (5.2)
Non-literature-known BRS	
Throat mucus and need to clear the throat	50 (21.6)
Generalized feeling of sickness	46 (19.9)
Throat itching	35 (15.2)
Decreased physical condition	27 (11.7)
Difficulty hearing speech in background noise	27 (11.7)
Insomnia	25 (10.8)
Irritability	22 (9.5)
Sensation of pressure in the cheek or forehead	22 (9.5)
Difficulty falling asleep	21 (9.1)
Globus sensation	19 (8.2)
Indefinite feeling of thermoregulation failure	19 (8.2)
Decreased stress resistance	18 (7.8)
Increased need for sleep	18 (7.8)
Red eyes	18 (7.8)
Anxiety	14 (6.1)
Eye discharge	14 (6.1)
Hypersensitivity to sound	14 (6.1)
Getting out of breath easily	13 (5.6)
Depressiveness	12 (5.2)
Hearing impaired	12 (5.2)

was 3.3 (95% CI: 1.2-9.2,  $p = 0.024$ ) when classroom dust samples had an  $EC_{50} \leq 6 \mu\text{g/ml}$  compared to classroom samples with an  $EC_{50} \geq 25 \mu\text{g/ml}$ , while the RR was 1.4 (95% CI: 0.8-2.5;  $p = 0.22$ ) when classrooms microbial samples had an  $EC_{50} \leq 12 \mu\text{g/ml}$  compared to microbial samples with an  $EC_{50} > 12 \mu\text{g/ml}$ .

**TABLE 3** Negative binomial mixed model 1 results show the relative ratios (RRs) of work-related non-literature-known BRS, in teachers exposed to materials with different toxicities, compared to those exposed to a reference material

$EC_{50}$ ( $\mu\text{g dry weight/ml}$ ) <sup>a</sup>	Number of teachers N (%)	RR	95% CI	$p$ Value
Surface-wiped dust				
6	15 (8.9)	2.90	1.16 to 7.29	0.024
12	42 (25.0)	0.82	0.44 to 1.54	0.54
25	111 (66.1)	1.00	(reference)	
All	168 (100)			
Cultured fallout propagules				
$\leq 12$	81 (40.7)	1.76	1.09 to 2.83	0.022
$> 12$	118 (59.3)	1.00	(reference)	
All	199 (100)			

Note: RRs are adjusted for age, gender, smoking, and atopy; schools were used as a random effect.

<sup>a</sup> $EC_{50}$  was calculated as the concentration of ethanol-soluble sampled material ( $\mu\text{g dry weight/ml}$ ) that induced loss of motility in  $\geq 50\%$  of exposed sperm cells. Lower  $EC_{50}$  values indicate higher toxicity.

**TABLE 4** Negative binomial mixed model 2 results show the relative ratios (RRs) of work-related non-literature-known BRS, in teachers exposed to materials with different toxicities, compared to those exposed to a reference material

$EC_{50}$ ( $\mu\text{g dry weight/ml}$ ) <sup>a</sup>	Number of teachers N (%)	RR	95% CI	$p$ Value
Surface-wiped dust				
6	15 (9.1)	2.67	1.08 to 6.61	0.034
12	43 (26.1)	0.84	0.46 to 1.56	0.58
25	107 (64.8)	1.00	(reference)	
All	165 (100)			
Cultured fallout propagules				
$\leq 12$	79 (40.9)	1.70	1.05 to 2.73	0.030
$> 12$	114 (59.1)	1.00	(reference)	
All	193 (100)			

Note: RRs are adjusted for exposure time in the studied classroom; schools were used as a random effect.

<sup>a</sup> $EC_{50}$  was calculated as the concentration of ethanol-soluble sampled material ( $\mu\text{g dry weight/ml}$ ) that induced loss of motility in  $\geq 50\%$  of exposed sperm cells. Lower  $EC_{50}$  values indicate higher toxicity.

## 4 | DISCUSSION

Our results show that teachers' work-related non-literature-known BRS were linked to dust and microbial toxicity. This finding suggested that the spectrum of BRS is much broader than expected.

We evaluated the statistical effect of dust and microbial toxicity on teachers' 20 nBRS with a negative binomial mixed model adjusted for age, gender, smoking, and atopy (Model 1) or exposure time in the primary workplace (Model 2). We focused on collecting and analyzing individual and workstation-specific data instead of construction- and group-level data, and schools was used as a random effect in the mixed models. These symptoms, which we have called nBRS, have not been earlier linked to BRS. We found that the number of teachers' non-literature-known symptoms was significantly higher in the more toxic classrooms. When we earlier explored teachers' classroom toxicity and 20 literature-known BRS (like cough, wheezing, itchy eyes, stuffy nose, fatigue, headache) using Poisson regression, the RR values for work-related BRS were 2.8 for dust toxicity and 1.8 for microbial toxicity.<sup>23</sup> When the relationship between teachers' classroom toxicity and the presence of work-related nBRS were analyzed in this study using the negative binomial mixed model, the corresponding RR values were 2.9 for dust toxicity and 1.8 for microbial toxicity.

It was interesting to note that also teachers in toxic classrooms had significantly more nBRS that were alleviated during school holidays compared to teachers in less-toxic classrooms, when toxicity was analyzed using two different sampling methods. The same phenomenon was observed earlier in the relationship between toxic classrooms and literature-known BRS.<sup>23</sup>

In this population, some of the teachers spent a relatively short period of time (minimum time 4 h per week although at least seven hours at school according to the inclusion criteria) in their primary classroom. However, when we used the exposure time (hours per week) in the measured classroom (Model 2), or the interaction of exposure time and toxicity, to adjust the negative binomial mixed model, the results were still similar.

Recently, severe occupational asthma patients have been reported who prior to asthma diagnosis had a high-level, prolonged exposure to dust that showed toxicity in the boar sperm assay.<sup>22</sup> During an eight-month renovation period, a majority of asthma patients' workplace dust samples were markedly toxic; 21% were highly sperm-toxic ( $EC_{50} \leq 6 \mu\text{g/ml}$ ) and 53% were clearly toxic ( $EC_{50}$  7-12  $\mu\text{g/ml}$ ). After one year, in most cases, severe or moderate asthma persisted, even though the individuals had moved to another workplace. Those authors concluded that heavy, long-lasting toxic exposure (months) probably produced permanent consequences. It is important to note that toxic exposure was different in our present study. First, the exposure time was relatively short (workdays were less than 4.5 h, on average); second, the classrooms were tidy, without visible dust; and third, based on the boar sperm assay, the dust toxicity was clearly milder in classrooms (35% with  $EC_{50} \leq 12 \mu\text{g/ml}$ ), compared to the environment tested in the asthma cases (74% with  $EC_{50} \leq 12 \mu\text{g/ml}$ ).<sup>22</sup> These differences might explain why the

teachers' symptoms were reversible (alleviated during vacations), while the work-related asthma symptoms persisted even two years later (20/21 patients [95%] requiring regular asthma medication).

Motility of boar spermatozoa is dependent on the energy produced by mitochondria, and boar sperm motility inhibition assay is a sensitive response-based method for detecting mitochondrial toxicants.<sup>20,24,25</sup> This method is suitable for large-scale field work and has been actively used for decades to detect toxigenic microbes and unknown toxins in moisture-damaged buildings.<sup>14,25</sup> Various toxins produced by microbes isolated from damaged buildings, including valinomycin, cereulide, amyloisin, stephacidin A and B, fusaricidins, several peptaibols, ophiobolins, chaetoglobosins, and communesins, are known to inhibit boar sperm motility.<sup>12-19,21</sup> In addition to microbial toxins, environmental pollutants, consumer chemicals, tobacco smoke, and particulate matter are known to impair mitochondrial function.<sup>26-29</sup>

Normal mitochondrial function and signaling are prerequisites for undisturbed physiological processes in humans, and mitochondrial dysfunction has been found to be associated with the pathophysiology of many common diseases, as well as aging.<sup>30,31</sup> In asthma and chronic obstructive pulmonary disease (COPD), dysfunction of the airway mucosa and smooth muscle mitochondria has been found to be central to pathophysiology.<sup>32-34</sup> Mitochondrial damage causes local and systemic inflammation through both innate and adaptive immunity.<sup>35-37</sup> The above findings have raised suspicion that environmental mitochondrial toxic exposure is one of the major causes of these lung diseases.<sup>38,39</sup> These findings also generate a hypothesis that in addition to asthma,<sup>22</sup> also known BRS and thus far unknown BRS may be associated with environmental mitochondrial toxic exposures.

Our two different sampling methods most likely reflected different sources of toxicity. The surface-wiped dust samples directly showed the presence of harmful substances, but the microbial samples represented an indirect approach, because toxicity was measured after the cultivation of airborne propagules. Moreover, the dust that accumulated on horizontal surfaces over months reflected potential long-term exposure, but the microbial samples potentially reflected only short-term exposure (1 h collection time). The origin of the dust toxicity (biological or chemical agents) could not be determined. However, indoor settled dust has been previously found to contain a massive amount of different toxic chemicals such as phthalates and other plasticizers, flame retardants, organotin, phenols, heavy metals, polycyclic aromatic hydrocarbons, and different biocides.<sup>40</sup> On the other hand, the microbial toxicity is originated from viable toxigenic microbes in indoor air. The toxicities of the dust and microbial samples were not correlated, which further supported the idea that they represented different phenomena.

Our study had some limitations. Of the 630 teachers in the original study population, 74% responded and 50% dropped out for different reasons.<sup>23</sup> In addition, data related to exposure in other areas visited by the study participants (eg, school, home, previous work places) were not available. Furthermore, an inherent limitation of our study design was that it was not possible to

estimate the exact amount of teacher exposure using our sampling methods. We were also unable to assess the effect of ventilation differences on exposure and symptoms. However, we noted that, although we only tested the teachers' present principal classrooms, we found a significant association between the symptoms and the measured toxicity in settled dust and airborne microbial biomass.

## 5 | CONCLUSIONS

The spectrum of teachers' work-related BRS appeared to be broader than generally thought. The frequency of work-related non-literature-known BRS, which were alleviated during school holidays, was markedly higher among teachers exposed to classrooms containing toxic dusts or microbes compared to participants who worked in classrooms with non-toxic samples. Non-literature-known BRS were almost as common compared to literature-known BRS.

Work-related symptoms were strongly associated with indoor toxicity measured as inhibition of boar sperm motility, a sensitive detector of mitochondrial toxicity. Thus, further studies are needed to clarify whether there is an association between BRS and mitochondrial function of people exposed to sources of indoor toxicity.

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## CONFLICTS OF INTEREST

JS owns 3% of company shares in Inspector Sec Ltd. PO and HS declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

JS, PO, and HS: Contributed to conceptualization, investigation, methodology, resources, validation, writing—original draft, and writing—review and editing; JS and PO: Involved in data curation, formal analysis, and software; JS: Involved in funding acquisition; HS: Involved in project administration and supervision.

## DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Individual-level deidentified participant data (including toxicity data, symptom score, age, gender, smoking status, atopy, school number) are available upon request from the correspondence author if colleagues wish to verify statistical analyses.

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