Indoor Environmental Pollutants and Their Association with Sick House Syndrome among Adults and Children in Elementary School

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Abstract

Sick house syndrome (SHS) derived from sick building syndrome (SBS) is used to describe symptoms that inhabitants experience due to indoor environment and personal factors, and children might be more susceptible to the effects of SHS than adults. However, there have been no comprehensive studies on effects of indoor pollutants exposure in relation to SHS. Thus, the aim of this study is to examine the association between indoor pollutants and SHS in children and adults who live in the same dwelling. This is a cross-sectional study on 184 elementary school children and 273 adults/adolescents in Sapporo, Japan. Indoor pollutants were measured in air and dust collected from 128 dwellings. Results showed children (20.6%) have higher prevalence of any symptoms than adults/adolescents (15.1%). Among SHS, mucosal symptoms were the most common in both children and adults /adolescents. Doctor diagnosed allergies, building age, dampness, and ventilation system showed significant association with prevalence of SHS. Formaldehyde, di(isobutyl) phthalate (DiBP), di(2-ethylhexyl) phthalate (DEHP), di(isononyl) phthalate (DiNP), endotoxin, and β-glucan were detected in all dwellings. Any symptoms and mucosal symptoms were significantly associated with the exposure to 2-ethyl-1-hexanol (2E1H). Floor dust DiNP, multi-surface dust Tris(2-butoxyethyl) phosphate with mucosal symptoms and endotoxin with dermal symptoms were inversely associated in adults/adolescent. Multi-surface dust DiBP also showed inverse association with mucosal symptoms in children. 2E1H emission increased

with dampness in the dwellings thus, eliminating dampness in the dwellings may reduce the emissions of 2E1H and the risk of SHS in residents.

Keywords

Sick house syndrome, Indoor chemicals, Biological factors, Dampness, Dwelling.

1. Introduction

Sick house syndrome (SHS) is originally derived from sick building syndrome (SBS) that describes the situations in which building occupants experience health problems such as a headache, fatigue, irritation of eyes, nose, and throat, and dry/ itchy skin, when they spend time in indoor environment [1-3]. The severity of the symptoms tends to increase in the house and improve over time or even disappear after leaving the house [2]. These health impairments are often related to poor indoor air quality, caused by a variety of factors including indoor chemicals, microbial contaminants, building airtightness, and the dampness in the house [3-5]. Adverse public health effects including SHS have attracted attention to indoor environmental pollution in recent years [1,2,6].

Environmental pollutants in indoor air and dust samples have been detected worldwide include volatile organic compounds (VOCs) [6,7], semi-VOCs (SVOCs) [8-11] and

microbial VOCs (MVOCs) [12,13]. In addition, studies reported that exposure to these pollutants increases the personal vulnerability risk of asthma, allergies and SHS in residents [9,14-18]. For instance, formaldehyde and MVOCs such as 1-octen-3-ol were associated with mucosal and atopic dermatitis symptoms [7,10,13,16] and semi-VOCs such as phthalates and tributyl phosphate (TBP) showed associations with mucosal symptoms [1]. Domestic exposure to β(1→3) D glucans also showed an increase in peak expiratory flow variability in school children [17].

Children and women are more susceptible to the effects of indoor environmental pollution because they spend more time in the home environment [19]. Children might particularly be vulnerable because of their smaller, immature, and developing organs [6]. However, there have been no comprehensive studies on the effects of exposure to indoor pollutants in relation to SHS in children and adults who live in the same dwelling. Therefore, the objectives of this study are: (1) to analyse the levels of several indoor pollutants such as formaldehyde, VOCs, MVOCs, phthalates, phosphorus flame retardants (PFRs), and biological contaminants in indoor air and dust samples in dwellings, and (2) to investigate and compare the association of these indoor environmental pollutants with SHS in children and adults, who live in the same dwelling.

2. Materials and methods

2.1. Study design and population

This cross-sectional study solicits health and environmental information regarding elementary school children and their families in Sapporo, Japan. The study population consisted of two groups who live in the same dwelling, 184 elementary school children under 12 years old and their 283 family members (≥ 13 years old; father, mother, and siblings), which will be referred to as “adults/adolescent” hereafter. The detailed description of the study design was described elsewhere [8]. Briefly, in 2008, a total of 6,393 baseline questionnaires were distributed to children in 12 elementary schools in Sapporo. Responses were obtained from 4,408 students corresponding to a 68.9% response rate and the parents of 951 children in 832 dwellings agreed to a home visit. After excluding those respondents who sent back incomplete questionnaires, those who graduated from elementary school, or those for whom the home visit could not be arranged; participants from 128 dwellings with a completed home visit were included in this study. Home visits were conducted in October and November of 2009 and 2010 for the environmental exposure measurements along with the health surveys.

The study protocol was approved by the ethical board for epidemiological studies at Hokkaido University Graduate School of Medicine. All participants and parents of children under 12 years old provided their written informed consent before this study has started.

2.2. Questionnaire

All inhabitants received questionnaires that included questions about SHS, demographics, lifestyle, and household characteristics per dwelling. Parents were asked to respond to the questionnaires for participants ≤ 12 years old elementary school children, while participants over 13 years old (adults/adolescents) answered the questionnaires by themselves.

2.2.1. Sick house syndrome (SHS) questionnaires

We used the Japanese-translated standardized MM questionnaires designed for the epidemiologic assessment of SBS symptoms by the Department of Occupational and Environmental Medicine in Orebro, Sweden [20-22]. MM is an abbreviation of the Swedish word “Miljo Medicine” (Environmental Medicine). Separate MM questionnaires; MM 080 School for children and MM 040 EA for adults/adolescents were used to define SHS. [20-22]. For children, the MM 080 School questionnaire includes ten sub-symptoms categorized as dermal symptoms (dry/or itching hands, dry facial skin, and itchy/ or flaky scalp), mucosal symptoms (irritation of the eye, runny nose, and cough), and general symptoms (fatigue, headache, sleeping problems, and stomach ache). For adults, the MM 040 EA questionnaire includes 12 sub-symptoms categorized as dermal symptoms (dry/or itching hands, dry facial skin, and itchy/ or flaking scalp), mucosal symptoms (irritation of the eyes, runny nose, cough, and dry throat), and general symptoms (fatigue, headache,

sleeping problems, feeling heavy-headed, nausea and lack of concentration). Any symptoms is positive if at least one of the sub-symptoms are positive. Each question has three alternative answers: “Yes, every week”, “Yes, sometimes”, and “No, never” for the past three months. For this study, we only used the responses “Yes, every week” to define the robust cases. There was an additional question “if Yes, do you believe that it is due to the home environment?” Thus, SHS is defined as a symptom that occurs every week and that is attributed to the home environment by the respondents.

2.2.2. Household, Demographics and lifestyle questionnaires

The household characteristics questionnaire includes questions on building structure (wood or concrete), building age, home renovation within 5 years, floor materials (PVC, compressed wood, wall-to-wall carpet and tatami/tiles/natural wood), wall materials (PVC or other), condensation (any window, wall, both or other) in the dwelling ever (Yes/No), mould odour (Yes/No), visible mould (Yes/No), water leakage (Yes/No), high humidity in the bathroom with slow drying wet towels (Yes/No), ETS (Environmental Tobacco Smoke) (Yes/No), furry pets (dog, cat, hamster) at home (Yes/No), mechanical ventilation in all rooms (Yes/No), weekly cleaning of the living room, and annual household income.

Data on demographics and lifestyle information such as gender, age, time spent at home, any doctor-diagnosed allergies ever (asthma, rhino-conjunctivitis, or atopic dermatitis), and

parental history of allergies (both the mother or father of the child) were also collected.

2.3. Environmental exposure measurements

Indoor air and settled dust samples from 128 dwellings were collected for the exposure assessment. Analytical approach, and assessment of quality control and quality assurance (QA/QC) for the measurement of chemicals are described in previous papers [1,8,16] and appendix.

2.3.1. Air Samples

Indoor air samples were collected over a period of 48 hours in the living room. Samples were collected onto diffusive air samplers (DSD-DNPH for aldehydes and VOC-SD for VOCs and MVOCs, both from Sigma–Aldrich Co., St. Louis, MO, USA) at 150 cm above the floor level.

Aldehydes, VOCs, and MVOCs: Full details of the chemical analysis and schematic representations of the analytical procedures are described elsewhere [7,16,23]. The analysis of aldehydes, VOCs, and MVOCs were conducted at Osaka Occupational Health Service part of the Japan Industrial Safety and Health Association in Tokyo, Japan. The effect of individual VOCs has not yet been established. Hence, in this study, we used the sum of 34 targeted VOCs as a single indoor air pollutant, denoted hereafter as TVOC.

2.3.2. Dust samples

Dust samples were collected using a hand-held vacuum cleaner equipped with a paper dust bag. To avoid cross-contamination between the samples, vacuum nozzles were washed in an ultrasound bath and vacuum cleaners were wiped with ethanol after each sample was collected. Dust samples were collected from two areas of the living room, “floor dust” from the floor and any surface less than 35 cm above the floor level and “multi-surface dust” from any surface higher than 35 cm above the floor level such as shelves, mouldings, TV sets, and interior materials such as wallpaper and the ceiling. Full description of dust sampling and sample preparation has been described elsewhere [1,8].

Phthalates and phosphorus flame retardants*:* The analysis methods and quality assurance procedures have been given in details in our previous studies [1,8,11]. Gas chromatography/mass spectrometry (GC-MS) in selective ion mode (SIM) was used to analyze the concentrations of phthalates in the floor and multi-surface dust samples, and PFRs in multi-surface dust samples. The targeted compounds include phthalate esters, di(isobutyl) phthalate (DiBP), di(n-butyl) phthalate (DnBP), butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), di(isononyl) phthalate (DiNP), and di(2-ethylhexyl) adipate (DEHA). PFRs include tripropyl phosphate (TPP), tributyl phosphate (TBP), tris(2-chloro-iso-propyl) phosphate (TCIPP), tris(2-chloroethyl) phosphate (TCEP), tris(2-butoxyethyl) phosphate (TBEP), and triphenyl phosphate (TPHP). These analyses

were carried out at the Tokyo Metropolitan Institute of Public Health in Tokyo, Japan and the Osaka Occupational Health Service Center, Japan Industrial Safety and Health Association.

Endotoxin, β(1→3)-glucan, and mite allergens*:* Floor dust was used to measure these biological factors. Limulus ES-2 single test and Toxinometer ET-5000 from Wako Pure Chemical Industries, Ltd. were used to measure the levels of endotoxins. The microplate-kinetic assay by BGstar KIT from Wako Pure Chemical Industries, Ltd. was used to measure the levels of β (1→3)-glucan. Both endotoxin and β (1→3)-glucan measurements were conducted at Wako Pure Chemical Industries, Osaka, Japan. To avoid contamination, all glassware and stainless-steel materials were sterilized at 250 °C for 2 hours. New empty dust bags were sent to Wako laboratory to measure background level of endotoxin and β (1 → 3)-glucan and the results were in ignorable levels. The levels of mite allergens (*Dermatophagoides pteronyssinus* (Der p1) and *Dermatophagoides farinae* (Der f1)) in sieved floor dust were measured by enzyme-linked immunosorbent assay (ELISA) kits (Nichinichi Pharmaceutical Co., Ltd., Mie, Japan). Polyethylene dust bags were provided by Nichinichi Pharmaceutical to collect samples for measurement of dust mite allergens. We used the sum of Der p1 and Der f1 as a variable, denoted by Der 1.

2.4. Statistical analysis

The analyses of indoor pollutants in air and dust were conducted for all 128 visited homes. The concentrations of the pollutants were not normally distributed; thus, the results are presented as box plot quartiles (minimum, 25^{th}, median, 75^{th} and maximum). The Yes/No answers were assigned a score of 1/0 for condensation in the dwelling, mouldy odour, visible mould, water leakage, and high humidity in the bathroom, and the scores were summed up to calculate the dampness index (0-5) [2]. The chi-square test and t-test were used to analyse the distribution of SHS symptoms with respect to personal and dwelling characteristics. The Mann-Whitney *U*-test was used for non-parametric variables. Personal and building characteristics were introduced into a regression model to further analyse their association with SHS. Multivariate logistic regression was used on $\log_{10}$-transformed variables to assess the potential association between indoor environmental pollutants and health outcomes. We selected the covariates based on the potential confounders age and gender, and the findings of previous studies. Age (continuous), gender (male/female), any doctor diagnosed allergies ever (yes/no), parental history of allergies (yes/no), dampness index (0-5) and environmental tobacco smoke (ETS) were controlled as confounders in the adjusted model. The parental history of allergies was omitted from the multivariate analysis for adults/adolescents. The results are presented as the odds ratio (OR) with 95% confidence interval (95% CI). All analyses were performed using JMP Clinical 6.0 software from SAS.

3. Results

3.1. Personal and dwelling characteristics

Table 1 shows the personal characteristics of the elementary school children and adults/adolescents with mean ages of 9.2 and 37.7 respectively. Both children and adults/adolescents groups spend a similar amount of time in the house per day. The most common SHS symptoms was mucosal symptoms with a prevalence of 17.4% in children and 12.3% in adults/adolescents, and more than half of the responders in both groups have at least one or more doctor-diagnosed allergies. Children have a higher prevalence in all groups of SHS than adults/adolescents. In this study, since a very small number of participants (seven children and four adults/adolescents) have general symptoms, we excluded it from the analysis.

Table 2 shows the characteristics of 128 visited households. The structure of dwellings in this study are wooden and reinforced concrete with a median age of 10.5 years. More than 80% of the dwellings use compressed wood as the flooring material, followed by PVC (8.6%), wall-to-wall carpet (8.6%), and others (2.3%). PVC wall material was used in most (88.2%) houses. Visible mould (76.5%) and condensation (71.1%) were the most common indicators of the dampness in the dwellings even though almost 50% of the dwellings have mechanical ventilation in all rooms.

3.2. Concentration of indoor pollutants

The distribution of indoor pollutants with detection percentage of more than 36% is summarized in figure 1 and supplemental table 1. Formaldehyde in indoor air; DEHP, DiNP, endotoxin, and β-glucan in floor dust; and DiBP and DiNP in multi-surface dust were detected in all dwellings. The median concentrations of formaldehyde and TVOC in indoor air were 28.6 μg/m^3 and 134.2 μg/m^3, respectively. The concentrations of all 34 targeted VOCs are provided in Supplemental Table 2. The concentrations of phthalates and PFRs in indoor dust ranged from <LOD (limit of detection) to 43,961 μg/g dust. The median levels of biological factors, endotoxin, β-glucan, and Der 1 were 3,604 EU/g dust, 332.7 ng/g dust, and 1.60 μg/g fine dust, respectively.

3.3. Association of indoor pollutants with SHS

Table 3 shows the adjusted model for the association between the levels of indoor environmental pollutants and SHS in residents. Significant associations between the exposure of 2E1H with any symptoms (OR = 4.60; 95% CI = 1.42−15.4) and mucosal symptoms (OR = 4.42; 95% CI = 1.27−15.9) were observed in adults/adolescents. Significant inverse relationships were observed in mucosal symptoms with multi-surface dust DiBP with (OR = 0.06; 95% CI = 0.01−0.50) in children, floor dust DiNP (OR = 0.34; 95% CI = 0.12−0.91), TBEP (OR = 0.33; 95% CI = 0.17−0.60) and any symptoms (OR =

0.41; 95% CI = 0.23−0.70) in adults/adolescents. Among the measured biological factors, endotoxin showed a significant inverse relation with dermal symptoms (OR = 0.03; 95% CI = 0.00−0.34) in adults/adolescents.

Table 4 shows the distribution of indoor pollutants significantly associated with SHS in different building characteristics. The concentration of 2E1H was significantly higher in dwellings with dampness and in houses that use PVC as a building material. Similarly, dwellings with PVC wall material have a higher concentration of DiBP in the indoor multi-surface dust.

4. Discussion

This study focused on households with elementary school children. The prevalence of several indoor environmental pollutants and their association with SHS were evaluated separately for children and adults/adolescents who live in the same dwelling. In general, the concentrations of indoor pollutants in this study were lower than or comparable to those in previous studies and the prevalence of SHS was higher in children than adults/adolescents. The present study is the first to examine 2E1H in dwellings in relation to SHS and the result showed significant association with any symptoms and mucosal symptoms in adults/adolescents.

4.1. Prevalence of SHS with personal and building characteristics

The prevalence of SHS was higher in children than in adults/adolescents. Considering the prevalence of SHS and personal characteristics, boys showed a higher prevalence of SHS than girls although both spend approximately the same amount of time in the house (Supplemental table 3). The opposite was true for the adults/adolescents group, 20.8% females showed a higher prevalence of SHS symptoms than 8.0% males (p value=0.003). This attributed to the significant differences in the amount of time they spend in the house (17 and 11 hours/day on average, respectively) (data not shown). However, the data available was insufficient to be conclusive for the gender-specific effects of indoor pollutants; thus, further studies are needed on this subject. In addition, participants who have any doctor-diagnosed allergies ever showed a higher prevalence of SHS and doctor-diagnosed allergies were significantly associated with SHS in both children and adults/adolescents. (Supplemental Table 4). Moreover, we conducted correlation analysis between SHS and doctor diagnosed allergic symptoms. The result showed having one or more allergic symptoms was significantly correlated with experiencing one or more SHS symptoms in both children and adults/adolescents (data not shown). Our study result is consistent with Sahlberg et al. [24] (2012) that reported biomarkers of allergy and inflammation as the independent predictor for incidence of building-related symptoms. This elucidate higher prevalence of SHS in participants with allergies. This indicates

allergies and SHS may share similar symptoms and indoor environmental factors such as indoor chemicals, ETS, dampness, etc. that trigger symptoms. Future studies needing to investigate these correlations may assist to better understand the pathology of SHS symptoms.

Regarding the relationship between SHS and building characteristics, participants with SHS were more likely to live in wooden houses with dampness, and no mechanical ventilation in all rooms (Supplemental Table 5). These results were consistent with our previous study [1,2]. Although frequent cleaning of the house reported to decrease the levels of biological factors such as β-(1→3)-glucan [25] and lower health problem [8]. In this study, increased cleaning habit was observed in inhabitants with SHS (Supplemental Table 5), this may be due to chemicals in cleaning products triggering symptoms [8].

4.2. Chemicals in indoor air and SHS

In general, the measured concentrations of indoor air chemicals in this study were lower than or comparable to the results of the previous studies [6,26,27]. Formaldehyde, acetaldehyde, acetone, and 2E1H were detected in more than 90% of the visited homes. The dwellings in this study were built before or after the implementation of indoor air pollution guidelines by the Ministry of Health, Labour, and Welfare of Japan but the median concentrations of formaldehyde and TVOC were lower than the recommended

levels of 100 μg/m^3 and 400 μg/m^3, respectively, in all dwellings [28]. Although one previous study reported declining emission rates of indoor formaldehyde from wood-based materials [29], our study measured significantly higher concentrations of formaldehyde in wooden houses, indicating higher formaldehyde emissions from wooden dwellings than concrete ones with median concentration (35.5 vs 27.8 μg/m^3 respectively, p-value=0.004). One of the VOCs analysed in this study, 2E1H, is produced by the hydrolysis of DEHP in a damp environment. Thus, the common (>80%) use of PVC in wall materials and dampness in dwellings might contribute to the emissions of 2E1H (Table 4).

Among chemicals in air 2E1H was associated with any symptoms and mucosal symptoms in this study. The health risk factor of 2E1H was examined in experimental and epidemiological studies that reported its relationship with asthma, ocular and nasal symptoms, and decreased tear film stability [30-32]. A study that used biomarkers indicated that elevated 2E1H concentrations in the air increase the lysosomal secretion from nasal mucosa and decrease olfactory sensation resulting ocular and nasal symptoms [32]. A study from Sweden also reported PVC flooring in combination with dampness was associated with increased prevalence of symptoms [3], which is similar to exposure source of 2E1H. On the other hand, experimental studies in humans showed an increased eye blink rate and nose/eye discomfort due to the exposure to 2E1H concentrations ranging from 1 ppb to 1 ppm for 2 to 4 hours [33,34]. The differences between the experimental and environmental

exposure to indoor air pollutants were described in an article by Ernstgard et al. 2010 [33]. Environmental exposure involves longer exposure times with lower levels of 2E1H than short-term experimental exposure studies. The results of the current study provide new evidence that 2E1H is associated with SHS in residents even at very low concentration. Further studies are needed to evaluate the adverse health effects of environmental exposure to 2E1H.

4.3. Semi-Volatile Organic Compounds (SVOCs) in dust and SHS

The concentrations of both floor and multi-surface dust phthalates and PFRs in the dwellings were lower than or similar to the previous studies conducted in Japan [1,9,14], Germany [35] and Bulgaria [18], except for DEHP. Compared to the floor dust, the multi-surface dust had significantly higher concentrations of phthalates. The detail concentration of SVOCs are reported in [8,11]

In this study, among measured phthalates floor dust DiNP in adults/adolescents and multi-surface dust DiBP in children showed an inverse relation with mucosal symptoms. To our knowledge, no prior studies have revealed the association of SHS with DiNP and DiBP. Other chemicals that have association with SHS are PFRs, which are added to treat potentially flammable building materials, including textiles and plastics. The present study found a significant inverse association of TBEP with any symptoms and mucosal symptoms

in adult/adolescents. Although not significant this result was consistent with our previous study that reported inverse relation of TBEP with mucosal symptoms [1]. The inverse association of indoor chemicals (DINP, DiBP, and TBEP) to SHS, may be due to other factors such as building characteristics that increase the level of these chemicals but have a protective effect to SHS.

4.4. Biological factors in dust and SHS

Regarding the biological factors, the median levels of dust mites in this study were lower than the minimum concentration of 2 μg/g for the prevention of sensitization [36] and the findings of some previous studies [22,37], but higher than the levels reported in studies conducted in Croatia [38] and Germany [39]. The indoor levels of endotoxin and β(1→3)-glucan were also lower than the other studies [17,25,40]. Our results were consistent with the findings from a study in German; increased levels of β(1→3)-glucan was observed in houses with carpet and keeping furry pets [25]. The same German study reported that cleaning the house less frequently is attributed to higher levels of β(1→3)-glucan. Thus, frequent cleaning of 3.9 times/week could explain the lower concentrations of biological factors in this study dwellings (Table 2).

Although, exposure to mite allergens has been shown to induce subjective allergic symptoms [22,37], no significant association was observed between SHS and biological factors Der 1

and β (1→3)-glucan in children or adults/adolescents (Table 4). Exposure to endotoxin showed a significant inverse relation with dermal symptoms in adults/adolescents. A similar protective (inverse) association between endotoxin and allergies was observed in a previous study conducted in Germany [41] and in Malaysia [42], likely due to the protective effects of endotoxin in the development of atopic immune response that induces respiratory symptoms [43]. However, caution should be taken with this interpretation due to lack of evidence.

4.5. Correlation among pollutants and relation with SHS

Furthermore, we assessed the overall relation among chemicals in air, SVOCs and biological factors in dust, the result showed significant correlation within each category. This result is predictable as it might be due to similar indoor factors (temperature, humidity, PVC materials) affect pollutants emission within each category [14,27,44]. However, no correlation was observed between different categories; chemicals in air, SVOCs and biological factors in dust. (data not shown). Moreover, analysis for the combined interaction effect of chemicals in air, SVOCs, and biological factors in dust showed no interaction with prevalence of SHS (Supplemental table 6). This result is supported by EU 2012 report of interaction effect is less likely to occur at low level of pollutants [45], indicating the concentration of pollutants in our study is low to show adverse health effect. However, this risk assessment of chemical mixture approach should be considered with caution as individual chemicals/pollutants may have different pathway or etiology and act as

independent factor on the development of SHS [7].

4.6. Children and SHS

Although children are more vulnerable to home environmental exposures than adults/adolescent due to their immature and developing organs [6,19], in this study we did not find any significant positive association between indoor pollutants and SHS in children. We have no clear explanation for this result. Thus, further studies are needed to elucidate these findings.

Additionally, we conducted a sensitivity analysis by excluding junior high school children from the adult/adolescent group. Although significant associations remained the same except for DiBP, the ORs increased or decreased while excluding adolescents from adults/adolescents group (data not shown). This may be attributed to the behavioural characteristics of junior high school students such as spending much less time in the house or in the living room than older adults (12.5 versus 15.5 hours/day) respectively (data not shown).

4.7. *Strengths and limitations of the study*

Strengths of our study include the following: (1) Samples of indoor air, floor dust, and multi-surface dust allowed us to explore various exposure factors. (2) The short period (October-November) of environmental sampling limited the seasonal variations and

eliminated the effect of pollen allergy season. Limitations of this study can be summarised as follows: (1) Due to the small sample number the statistical power of the analysis might be low, resulting wide confidence interval. (2) Numerous statistical analysis could also result significant findings by chance. (3) Since health-conscious parents are more enthusiastic to participate in such studies, selection bias may occur; most (75%) of the children participated in this study reported a parental history of allergies. (4) SHS symptoms in children <12 years old were defined based on parental reports; therefore, misclassifications may occur in the results. (5) Due to immature body development, children often exhibit symptoms that are similar to that of SHS, but not necessarily caused by it. (6) The study design is cross-sectional; thus, causal relationships cannot be provided.

5. Conclusions

The concentrations of indoor chemicals and biological factors in this study are relatively lower than those reported in previous studies. The prevalence of SHS was higher in children than in adults/adolescents. However, indoor pollutants in this study were only associated with SHS in adults/adolescents. The results of 2E1H provide new evidence of the positive association of SHS symptoms in adults/adolescents with lower 2E1H concentrations than those in previous studies. Since 2E1H concentrations was significantly correlated with

dampness, eliminating dampness in the dwellings may reduce the emissions of 2E1H and lower the risk of SHS symptoms in building occupants.

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Conflict of interest statement

The authors declare that they have no conflict of interests.

References

[1] A. Kanazawa, I. Saito, A. Araki, M. Takeda, M. Ma, Y. Saijo, R. Kishi, Association between indoor exposure to semi-volatile organic compounds and building-related symptoms among the occupants of residential dwellings, Indoor Air 20 (2010) 72–84.

[2] R. Kishi, Y. Saijo, A. Kanazawa, M. Tanaka, T. Yoshimura, H. Chikara, Regional differences in residential environments and the association of dwellings and residential factors with the sick house syndrome: a nationwide cross-sectional questionnaire study in Japan, Indoor Air 19 (2009) 243–254.

[3] WHO (World Health Organization), Indoor Air Pollutants: Exposure and health effects. EURO Reports and studies, No. 78. Copenhagen: WHO Regional Office for Europe (1983).

[4] C.G. Bornehag, J. Sundell, L. Hagerhed-Engman, T. Sigsggard, S. Janson, N. Aberg, The DBH Study Group. Dampness at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study, Indoor Air 15 (Suppl 10) (2005) 48–55.

[5] S. Gupta, M. Khare, R. Goyal, Sick building syndrome-A case study in a multistory centrally air-conditioned building in the Delhi City, Build Environ. 42 (2007) 2797–2809.

[6] L. Zhai, J. Zhao, B. Xu, Y. Deng, Z. Xu, Influence of indoor formaldehyde pollution on respiratory system health in the urban area of Shenyang, China, Afr. Health Sci. 13 (2013) 137–143.

[7] T. Takigawa, B.L. Wang, Y. Saijo, K. Morimoto, K. Nakayama, M. Tanaka, Relationship between indoor chemical concentrations and subjective symptoms associated with sick building syndrome in newly built houses in Japan, Int. Arch. Occup. Environ. Health 83 (2010) 225–235.

[8] Y. Ait Bamai, A. Araki, T. Kawai, T. Tsuboi, I. Saito, E. Yoshioka, A. Kanazawa, S. Tajima, C. Shi, A. Tamakoshi, R. Kishi, Associations of phthalate concentrations in floor dust and multi-surface dust with the interior materials in Japanese dwellings, Sci. Total Environ. 468–469 (2013)147–157.

[9] A. Araki, I. Saito, A. Kanazawa, K. Morimoto, K. Nakayama, E. Shibata, M. Tanaka, T. Takigawa, T. Yoshimura, H. Chikara, Y. Saijo, R. Kishi, Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants, Indoor Air 24 (2014) 3–15.

[10] C.G. Bornehag, J. Sundell, C.J. Weschler, T. Sigsggard, B. Lundgren, M. Hasselgren, L. Hagerhed-Engman, The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study, Environ. Health Perspect.112

(2004) 1393–1397.

[11] S. Tajima, A. Araki, T. Kawai, T. Tsuboi, Y. Ait Bamai, E. Yoshioka, A. Kanazawa, S. Cong, R. Kishi, Detection and intake assessment of organophosphate flame retardants in house dust in Japanese dwellings, Sci. Total Environ. 478 (2014) 190–199.

[12] A. Araki, T. Kawai, Y. Eitaki, A. Kanazawa, K. Morimoto, K. Nakayama, E. Shibata, M. Tanaka, T. Takigawa, T. Yoshimura, H. Chikara, Y. Saijo, R Kishi, Relationship between selected indoor volatile organic compounds, so-called microbial voc, and the prevalence of mucous membrane symptoms in single family homes, Sci. Total Environ. 408 (2010) 2208–2215.

[13] B. Sahlberg, M. Gunnbjornsdottir, A. Soon, R. Jogi, T. Gislason, G. Wieslander, C. Janson, D. Norback, Airborne molds and bacteria, microbial volatile organic compounds (MVOC), plasticizers and formaldehyde in dwellings in three North European cities in relation to sick building syndrome (SBS), Sci. Total Environ. 444 (2013) 433–440.

[14] Y. Ait Bamai, E. Shibata, I. Saito, A. Araki, A. Kanazawa, K. Morimoto, K. Nakayama, M. Tanaka, T. Takigawa, T. Yoshimura, H. Chikara, Y. Saijo, R. Kishi, Exposure to house dust phthalates in relation to asthma and allergies in both children and adults, Sci. Total Environ. 485–486 (2014) 153–163.

[15] Y. Ait Bamai, A. Araki, T. Kawai, T. Tsuboi, I. Saito, E. Yoshioka, S. Cong, R. Kishi,

Exposure to phthalates in house dust and associated allergies in children aged 6–12 years, Environ. Int. 96 (2016) 6–23.

[16] A. Araki, A. Kanazawa, T. Kawai, Y. Eitaki, K. Morimoto, K. Nakayama, et al, The relationship between exposure to microbial volatile organic compound and allergy prevalence in single-family homes, Sci. Total Environ. 423 (2012) 8–26.

[17] J. Douwes, A. Zuidhof, G. Doekes, S. van der Zee, I. Wouters, H.M. Boezen, B. Brunekreef, (1→3)-β-D-glucan and endotoxin in house dust and peak flow variability in children, Am J. Respir. Crit. Care Med. 162 (2000) 1348–1354.

[18] B. Kolarik, K. Naydenov, M. Larsson, C.G. Bornehag, J. Sundell, The association between phthalates in dust and allergic diseases among Bulgarian children, Environ. Health Perspect. 116 (2008) 98–103.

[19] A. Davis, Home environmental health risks, Online J. Issues Nurs. 12 (2007) 4.

[20] K Andersson, Epidemiological approach to indoor air problems, Indoor Air 4 (1998) 32–39.

[21] T. Mizoue, K. Reijula, K. Andersson, Environmental tobacco smoke exposure and overtime work as risk factors for sick building syndrome in Japan, Am. J. Epidemiol. 154 (2001) 803–808.

[22] Y. Saijo, A. Kanazawa, A. Araki, K. Morimoto, K. Nakayama, T. Takigawa, Relationships between mite allergen levels, mold concentrations, and sick building syndrome symptoms in newly built dwellings in Japan, Indoor Air 21 (2011) 253–263.

[23] A. Araki, Y. Eitaki, T. Kawai, A. Kanazawa, M. Takeda, R. Kishi, Diffusive sampling and measurement of microbial volatile organic compounds in indoor air, Indoor Air 19 (2009) 421–432.

[24] B. Sahlberg, D. Norback, G. Wieslander, T. Gislason, C. Janson, Onset of mucosal, dermal, and general symptoms in relation to biomarkers and exposures in the dwelling: a cohort study from 1992 to 2002, Indoor Air 22 (2012) 331–338.

[25] U. Gehring, J. Douwes, G. Doekes, A. Koch, W. Bischof, B. Fahlbusch, K. Richter, H.E. Wichmann, J. Heinrich, Beta (1→3)-glucan in house dust of German homes: housing characteristics, occupant behavior, and relations with endotoxins, allergens, and molds. Environ. Health Perspect. 109(2) (2001) 139–144.

[26] M. Takeda, Y. saijo, M. Yuasa, A. Kanazawa, A. Araki, R. Kishi, Relationship between sick building syndrome and indoor environmental factors in newly built Japanese dwellings. Int. Arch. Occup. Environ. Health 82 (2009) 583–593.

[27] S, Takeuchi, T. Tanaka-Kagawa, I. Saito, H. Kojima, K. Jin, M. Satoh, S. Kobayashi, H Jinno, Differential determination of plasticizers and organophosphorus flame retardants

in residential indoor air in Japan, Environ. Sci. Pollut. Res. (2015) 1–8.

[28] Ministry of Health, Labour and Welfare of Japan. Committee on Sick House Syndrome, 2002. Indoor Air Pollution Progress Report No. 4. Tokyo. http://www.nihs.go.jp/mhlw/chemical/situnai/kentoukai/rep-eng4.pdf (accessed 10 February 2017).

[29] T, Salthammer, S, Mentese, R, Marutzky, Formaldehyde in the Indoor Environment, Chem. Rev. 110 (2010) 2536–2572.

[30] D. Norback, G. Wieslander, K. Nordstrom, R. Walinder, Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air, Int. J. Tuberc. Lung Dis. 4(11) (2000)1016–1025.

[31] G. Wieslander, K. Anders, D. Norback, Dampness and 2-Ethyl-1-hexanol in Floor Construction of Rehabilitation Center: Health Effects in Staff, Arch. Environ. Occup. Health 65 (2010) 3–11.

[32] G. Wieslander, D. Norbäck, K. Nordström, R. Wålinder, P. Venge, Nasal and ocular symptoms, tear film stability and biomarkers in nasal lavage, in relation to building-dampness and building design in hospitals, Int. Arch. Occup. Environ. Health 72 (1999) 451–461.

[33] L. Ernstgard, D. Norbacck, T. Nordquist, G. Wieslander, R. Walinder, G. Johanson, Acute effects of exposure to 1 mg/m3 of vaporized 2-ethyl-1-hexanol in humans, Indoor Air 20 (2010) 168–175.

[34] E. Kiesswetter, C. van Thriel, M. Schäper, M. Blaszkewicz, A. Seeber, Eye blinks as an indicator for sensory irritation during constant and peak exposures to 2-ethylhexanol, Environ. Toxicol. Pharmacol. 19 (2005) 531–541.

[35] M. Abb, T. Heinrich, E. Sorkau, W. Lorenz, Phthalates in house dust, Environ. Int. 35 (2009) 65– 970

[36] J. Kuehr, T. Frischner, R. Meinert, R. Barth, J. Forster, S. Schraub, R. Urbanek, W. Karmaus, Mite allergen exposure is a risk for the incidence of specific sensitization, J. Allergy Clin. Immonol. 94 (1994) 44–52.

[37] M. Trakultivakorn, S. Krudtong, House dust mite allergen levels in Chiang Mai homes, Asian Pac. J. Allergy Immunol. 22 (2004) 1–6.

[38] L. Prester, I. Brcic Karaconji, J, Macan, Determination of mite allergens in house dust using the enzyme immunoassay, Arh. Hig. Rada. Toksikol. 58 (2007) 413–419.

[39] S. Lau, S. Illi, C. Sommerfeld, B. Niggemann, R. Bergmann, E. von Mutius, U. Wahn, Early exposure to house-dust mite and cat allergens and development of childhood

asthma: a cohort study, Lancet 356 (2000) 1392–1397.

[40] C.R. Brooks, R. Siebers, J. Crane, I. Noss, I.M. Wouters, I. Sander, M. Raulf-Heimsoth, P.S. Thorne, N. Metwali, J. Douwes, Measurement of beta-(1,3)-glucan in household dust samples using Limulus amebocyte assay and enzyme immunoassays: an inter-laboratory comparison, Environ. Sci. Process Impacts 15 (2013) 405–411.

[41] U. Gehring, W. Bischof, G. Schlenvoigt, K. Richter, B. Fahlbusch, H.E. Wichmann, J. Heinrich, Exposure to house dust endotoxin and allergic sensitization in adults, Allergy 59 (2004) 946–952.

[42] D. Norbäck, J. Hisham, P. Markowicz, C. Gui-Hong, Z. Hashim, F. Ali, L. Larsson, Endotoxin, ergosterol, muramic acid and fungal DNA in dust from schools in Johor Bahru, Malaysia -Associations with rhinitis and sick building syndrome (SBS) in junior high school students, Sci. Total Environ. 545–546 (2016) 95–103.

[43] J. Douwes, N. Pearce, D. Heederik, Does environmental endotoxin exposure prevent asthma? Thorax 57 (2002) 86–90.

[44] V. Polizzi, A. Adams, A.M. Picco, E. Adriaens, J. Lenoir, C. Van-Peteghem, De Saeger, N. De Kimpe, Influence of environmental conditions on production of volatiles by Trichoderma atroviride in relation with the sick building syndrome, Build. Environ. 46 (2011) 945–954.

[45] European Union, 2012. Toxicity and Assessment of Chemical Mixtures. doi: 10.2772/21444. (Accessed 12 March 2018)

Appendix

Analytical approach, and assessment of quality control and quality assurance (QA/QC)

Aldehydes, VOCs and MVOC

Air samples were collected onto diffusive air samplers. The samplers for the aldehydes were DSD-DNPH passive sampling device from Sigma-Aldrich, USA. HPLC equipped with an ultraviolet detector (HPLC/UV; Hitachi D-7100) (Hitachi, Ltd., Tokyo, Japan) was used for the analysis of formaldehyde, acetaldehyde, and acetone. A one-milliliter sample was injected, and chromatic separation was performed using a solvent gradient elution at a flow rate of 0.3 mL/ min in an analytical column (Supelco Ascentis, semi-micro column, 250 mm × 2.1 mm × 5 μm; Sigma Aldrich Co., St. Louis, MO, USA). The mobile phase was distilled water: tetrahydrofuran (5:1) and acetonitrile (55:45). The temperature of the column was 35 °C. The detection wavelength was 360 nm.

For VOCs and MVOCs, a Supelco VOC-SD diffusive air sampler was used. Hewlett Packard Agilent gas chromatograph with mass spectrometry GC6890/ MSD 5973N (GC-MS; Agilent Technologies Inc., Alto, CA, USA) equipped with DB-1 (60 m × 0.25 mm i.d. × 1.5 μm: J & W Scientific, Folsom, CA, USA) was used for analysis. The column temperature was 40 °C (13 min), followed by a temperature rise of 7 °C min/1 to 260 °C (2 min). The temperature of the injector, the MS ion source, and the interface was set at 250 °C, 230 °C and 220 °C, respectively. Helium was used as the carrier gas, with a constant flow rate of 1.2 mL/min. 1μL sample was injected in the split mode (5:1). Electron impact ionization was 70 eV for MS analysis. Compounds were analyzed by the selected ion monitoring (SIM) mode. Along with samples 7 travel blanks (TB) and 3 sample blanks (SB) were sent to the laboratories

these pollutants measured. Due to detection of TB and SB higher than VOC's LOD (0.5 μg/m$^{3)}$ in 5 compounds; Chloroform 2 μg/m^3, n-Heptane 8 μg/m^3, n-Decane 7 μg/m^3, pDCB 4 μg/m^{3,} and n-Dodecane 2 μg/m^3 were set as LOD accordingly (Supplemental Table 2).

Phthalates and Phosphorus flame retardants (PFRs)

An Agilent 5890 Series II GC connected with Agilent 5971A mass spectrometry was used for analysis of the phthalates and PFRs using an ultra-1 (50 m x 0.20 mm x 0.33 μm) column. The column temperatures were 60 °C (2 min), followed by 20 °C/min to 180 °C (10 min), then 15 °C /min to 240 °C (10 min), finally 20 °C/min to 300 °C (20 min). Helium was used as carrier gas with constant 70 kPa pressure mode. The injector was operated in the split less mode at 280 °C (2 μL injection volume). The detector was operated in the SIM mode at a temperature of 280 °C. [3] The limit of detection (LOD) was defined as the absolute amount of analytes that yielded a signal-to-noise ratio of 3 (n = 6). Recovery tests were performed by using wool, cotton, and man-made fiber that imitated dust samples. After 50 ng of each phthalate and PFR was individually added to 50-mg samples, the air-dried samples were extracted with 1mL of acetone and analyzed by gas chromatography/mass spectrometry (GC/MS) (n = 5). The recovery rates for phthalates ranged from 97% (DMP, man-made fiber) to 121.7% (DEHP, man-made fiber) and for PFRs 86.7%(trimethyl phosphate [TMP], wool) to 117.5% (TDCIPP, cotton. Empty glass bottles were sent to the laboratories as travel blank and the levels were <LOD or ignorable level.

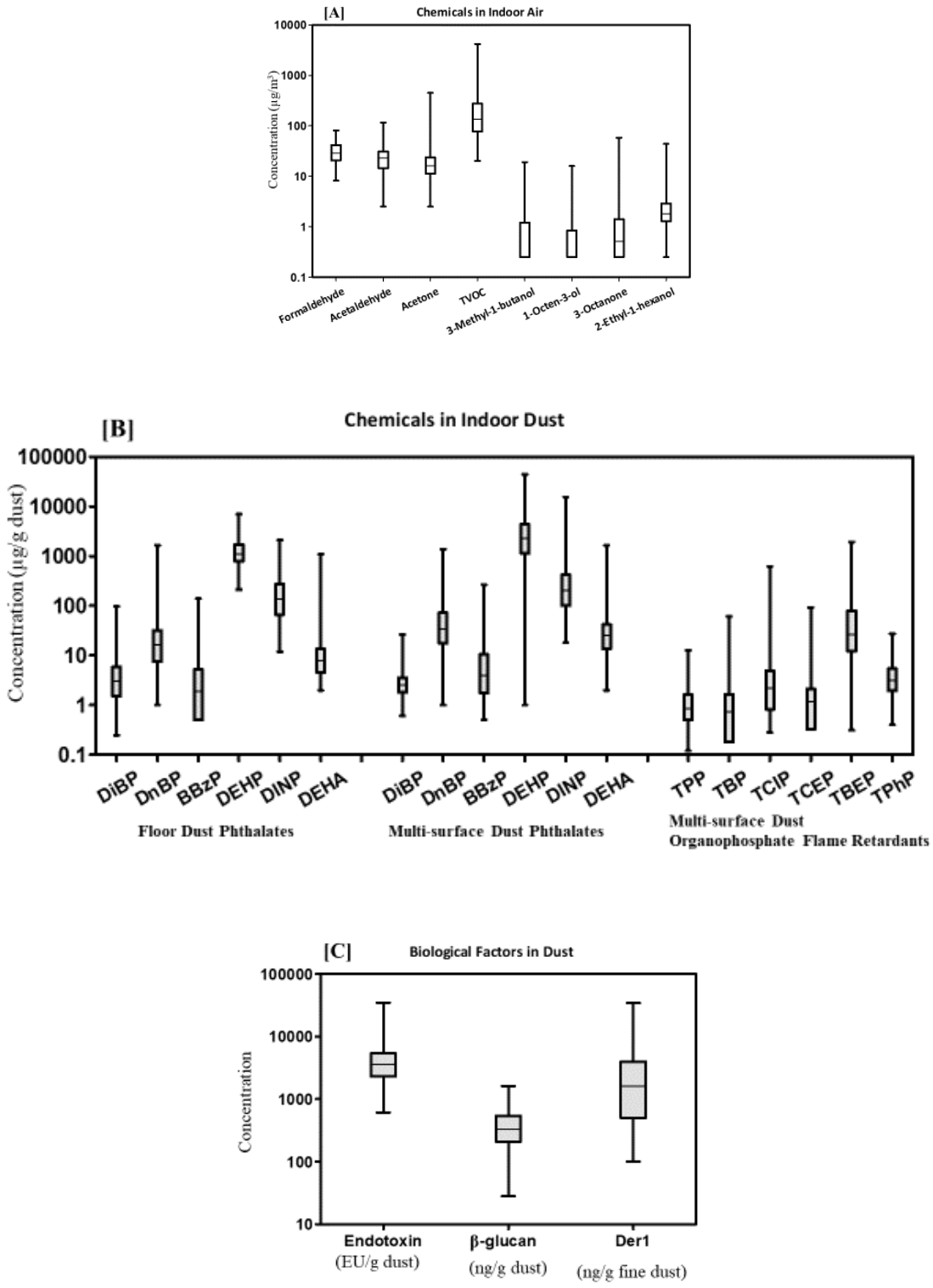


Figure 1 Concentration of indoor pollutants: [A] chemicals in air, [B] chemicals in dust and [C] biological factors in dust

Figure legend

Figure 1 Concentration of indoor pollutants [A] chemicals in Air, [B] chemicals in dust and [C] biological factors in dust

The box plot denote the 25% and 75%, with bold line indication median concentration, and error bars the concentration range of indoor pollutants.

Table 1. Personal characteristics of elementary school children and adults/adolescents

Personal Characteristics		Children (n = 184)	Adults/adolescents (n = 283)
Gender - n (%)	Male	101 (54.9)	127 (44.8)
	Female	83 (45.1)	156 (55.2)
Age (Years)	Mean (± SD)	9.2 ± 1.9	37.7 ± 11.7
Time spent at home (Hours/day)	Mean (± SD)	15.2 ± 1.5	15.0 ± 4.9
Parental history of allergies - n (%)	Yes	139 (75.5)	
Any dr. diagnosed allergies ever - n (%)	Yes	101 (54.9)	150 (53.0)
Dr. diagnosed Asthma - n (%)	Yes	51 (27.7)	51 (18.0)
Dr. diagnosed rhino- conjunctivitis - n (%)	Yes	53 (28.8)	115 (40.6)
Dr. diagnosed Atopic dermatitis - n (%)	Yes	60 (32.6)	43 (15.2)
Any SHS - n (%)	Yes	38 (20.6)	42 (15.1)
Dermal symptoms - n (%)	Yes	11 (6.0)	13 (4.6)
Mucosal symptoms - n (%)	Yes	32 (17.4)	35 (12.3)
General symptoms - n (%)	Yes	7 (3.8)	4 (1.4)

Any doctor diagnosed allergies ever (asthma, rhino-conjunctivitis or atopic dermatitis)

Table 2. Household characteristics (N = 128 Houses)

Characteristics	Variable	n (%), Median (25-75%), or Mean (± SD)
Building structure	Wood	59 (46.1)
	Reinforced concrete	69 (53.9)
Building age (years)	Continuous	10.5 (5-20)
Renovation within 5 years	Yes	31 (24.2)
Floor material	PVC	11 (8.6)
	Compressed wood	103 (80.4)
	Wall-to-wall carpet	11 (8.6)
	Others	3 (2.3)
Wall material	PVC	112 (88.2)
	Non-PVC	15 (11.7)
Dampness Index (0-5)	Continuous	2.1 ± 1.2
Condensation in the dwelling ever	Yes	92 (71.8)
Moldy odor	Yes	19 (14.8)
Visible mold	Yes	98 (76.5)
Humidity	Yes	32 (25.0)
Water leakage	Yes	28 (21.8)
Environmental Tobacco Smoke (ETS)	Yes	34 (26.5)
Mechanical ventilation in all rooms	Yes	61 (47.6)
Furry pet at home	Yes	43 (33.6)
Frequency of cleaning /week	Continuous	3.9 ± 2.1
Annual household income (yen)	<5 Million	31 (24.2)
	5-<8 Million	50 (39.1)
	≧8 Million	28 (21.9)
	Unknown	19 (14.8)

Table 3. Association between concentration of indoor air and dust pollutants with SHS

		Any SHS OR (95% CI)		Dermal symptoms OR (95% CI)		Mucosal symptoms OR (95% CI)	
		Children[a]	Adults[b]	Children[a]	Adults[b]	Children[a]	Adults[b]
Air	**Formaldehyde, VOC and MVOC (µg/m^3)**						
	Formaldehyde	1.41 (0.34-6.55)	1.41 (0.37-6.54)	14.8 (0.87-553)	0.60 (0.10-6.01)	2.85 (0.60-19.3)	1.02 (0.26-4.73)
	Acetaldehyde	0.95 (0.24-3.63)	0.80 (0.24-2.61)	1.99 (0.30-20.3)	0.50 (0.10-2.99)	1.11 (0.27-4.67)	0.56 (0.16-1.92)
	Acetone	0.70 (0.23-1.85)	0.80 (0.30-1.98)	0.98 (0.20-4.11)	0.50 (0.10-2.20)	0.66 (0.21-1.88)	0.57 (0.20-1.53)
	TVOC	1.08 (0.40-3.04)	1.03 (0.40-2.57)	3.00 (0.71-12.5)	0.90 (0.17-3.40)	1.45 (0.50-4.36)	0.93 (0.32-2.50)
	3-Methyl-1-butanol	1.02 (0.40-2.60)	0.74 (0.31-1.60)	2.50 (0.67-9.20)	0.85 (0.17-3.05)	1.20 (0.43-3.20)	0.74 (0.30-1.70)
	1-Octen-3-ol	0.87 (0.34-2.15)	1.11 (0.45-2.56)	1.56 (0.40-5.21)	0.48 (0.07-2.01)	0.85 (0.31-2.20)	1.14 (0.44-2.74)
	3-Octanone	0.96 (0.47-1.94)	0.64 (0.31-1.26)	1.14 (0.36-3.02)	0.26 (0.04-0.97)	1.22 (0.60-2.52)	0.83 (0.40-1.70)
	2-Ethyl-1-hexanol	0.34 (0.10-1.17)	4.60 (1.42-15.4) *	0.35(0.04-2.20)	1.51 (0.23-10.8)	0.51 (0.13-1.82)	4.42 (1.27-15.9) *
Dust	**Floor dust phthalates (µg/g dust)**						
	DiBP	1.00 (0.50-2.00)	0.71 (0.37-1.32)	1.24 (0.44-3.53)	0.94 (0.34-2.50)	1.12 (0.54-2.34)	0.64 (0.32-1.27)
	DnBP	1.02 (0.50-2.10)	1.05 (0.55-2.01)	0.80 (0.23-2.66)	1.07 (0.36-3.21)	1.24 (0.60-2.65)	1.00 (0.50-2.00)
	BBzP	1.00(0.16-5.86)	0.84 (0.45-1.53)	1.50 (0.55-3.87)	1.04 (0.40-2.64)	1.20 (0.60-2.36)	0.76 (0.40-1.46)
	DEHP	2.50 (0.55-11.8)	0.60 (0.17-1.92)	0.75 (0.06-7.50)	0.52 (0.06-3.61)	3.03 (0.61-16.1)	0.60 (0.16-2.10)
	DiNP	0.81 (0.30-2.21)	0.52 (0.21-1.25)	1.00 (0.20-5.22)	1.94 (0.50-8.45)	1.42 (0.50-4.16)	0.34 (0.12-0.91) *
	DEHA	1.20 (0.50-2.76)	0.71 (0.30-1.70)	1.72 (0.51-5.42)	1.05 (0.21-4.54)	1.70 (0.70-4.10)	0.82 (0.30-2.08)
	Multi surface dust phthalates (µg/g dust)						
	DiBP	0.30 (0.05-1.54)	2.40 (0.63-8.90)	0.64 (0.05-5.95)	2.41 (0.21-22.1)	0.06 (0.01-0.50) *	2.16 (0.51-8.73)

	DnBP	0.64 (0.30-1.37)	1.01 (0.51-2.01)	0.87 (0.25-2.98)	0.64 (0.21-1.98)	0.60 (0.24-1.30)	1.28 (0.62-2.70)
	BBzP	0.84 (0.40-1.74)	1.16 (0.64-2.08)	1.73 (0.60-4.83)	1.35 (0.50-3.61)	0.92 (0.40-1.98)	1.10 (0.57-2.07)
	DEHP	0.77 (0.42-1.41)	0.85 (0.47-1.65)	1.11 (0.46-3.54)	0.84 (0.34-3.06)	0.70 (0.36-1.26)	0.80 (0.42-1.65)
	DiNP	0.93 (0.43-1.90)	1.05 (0.55-1.92)	2.00 (0.70-5.47)	1.67 (0.62-4.20)	0.94 (0.42-1.98)	0.85 (0.41-1.70)
	DEHA	1.54 (0.71-3.45)	1.71 (0.85-3.51)	2.25 (0.73-7.50)	1.55 (0.50-5.31)	1.61 (0.71-3.80)	1.63 (0.77-3.56)
	Multi- surface dust PFRs (µg/g dust)						
	TPP	0.72 (0.21-2.42)	2.05 (0.77-5.46)	3.33 (0.50-24.0)	0.35 (0.05-2.06)	0.37 (0.10-1.41)	2.65 (0.95-7.51)
	TBP	1.71 (0.71-4.20)	0.62 (0.30-1.25)	0.85 (0.20-3.12)	0.99 (0.30-3.21)	1.77 (0.70-4.57)	0.51 (0.22-1.11)
	TCIPP	0.86 (0.46-1.56)	0.92 (0.50-1.70)	1.07 (0.40-2.73)	1.43 (0.50-4.13)	0.90 (0.46-1.66)	0.64 (0.32-1.23)
	TCEP	1.27 (0.57-2.80)	0.66 (0.33-1.27)	2.63 (0.80-8.50)	0.60 (0.15-1.75)	1.24 (0.53-2.85)	0.70 (0.33-1.34)
	TBEP	0.81 (0.43-1.50)	0.41 (0.23-0.70) **	0.55 (0.24-1.32)	1.31 (0.60-3.30)	0.97 (0.51-1.88)	0.33 (0.17-0.60) **
	TPHP	2.72 (0.90-8.93)	0.71 (0.30-1.88)	2.10 (0.40-11.9)	0.80 (0.14-4.06)	1.88 (0.60-6.31)	0.63 (0.21-1.81)
Dust	**Biological factors**						
	Endotoxin (EU/g dust)	0.40 (0.10-1.46)	0.30 (0.08-1.02)	0.27 (0.03-1.98)	0.03 (0.00-0.34) *	0.41 (0.08-1.71)	0.53 (0.13-2.02)
	β-glucan (ng/g dust)	2.07 (0.61-7.33)	1.11 (0.40-3.13)	1.10 (0.17-8.22)	1.06 (0.21-5.95)	1.08 (0.30-3.97)	1.23 (0.42-3.76)
	Der1 (µg/g fine dust)	0.55 (0.26-1.12)	1.20 (0.64-2.25)	1.30 (0.45-3.75)	0.34 (0.10-1.02)	0.53 (0.24-1.12)	1.63 (0.82-3.33)

[a] Adjusted gender, age, any dr. diagnosed allergies ever, parental history of allergy, dampness index and ETS

[b] Adjusted for age, gender, any dr. diagnosed allergies ever, dampness index and ETS

*p < 0.05, **p < 0.01

The odds ratios were calculated using $\log_{10}$-transformed variable

Table 4: Mean distribution of significantly associated pollutants with SHS in different building characteristics (n=128)

Building characteristics	Variables		Indoor air	Floor dust	Multi-surface dust		Floor dust
		n	2E1H µg/m3	DiNP µg/g dust	DiBP µg/g dust	TBEP µg/g dust	Endotoxin EU/g dust
Structure	Concrete	68	2.24	224	3.6	82	4110
	Wooden	59	2.29	267	3.4	106	5638
Renovation	Yes	31	2.01	202	5.2	182	4882
	No	96	2.96	257	2.9	64.9	4793
Floor material	PVC	11	6.2	211	3.1	79.6	7982
	Compressed wood	103	2.4	248	3.5	93.3	4450
	Wall-to-wall carpet	10	2.2	268	3.1	118	4807
	Others	3	2.3	113	5	53.1	5743
Wall material	PVC	112	2.8*	247	3.6*	97.6	4548
	Non-PVC	15	1.7	219	2.1	60.8	6820
ETS	Yes	34	3.3	196	3.2	99.3	4760
	No	93	2.5	261	3.6	91.2	4834
Furry pets at home	Yes	42	2	249	3.7	131	4923
	No	85	3.1	241	3.3	73.9	4760
Mechanical Ventilation in all rooms	Yes	60	2.2	257	3.5	100	4902
	No	67	3.1	232	3.5	86.6	4735
Building age $^{\rho}$	Years	128	0.05	-0.10	0.00	0.13	0.0
Dampness index $^{\rho}$	(0-5)	128	0.30*	0.10	0.10	-0.22*	-0.09
Frequency of cleaning $^{\rho}$	per week	128	0.10	-0.10	0.00	0.01	0.09

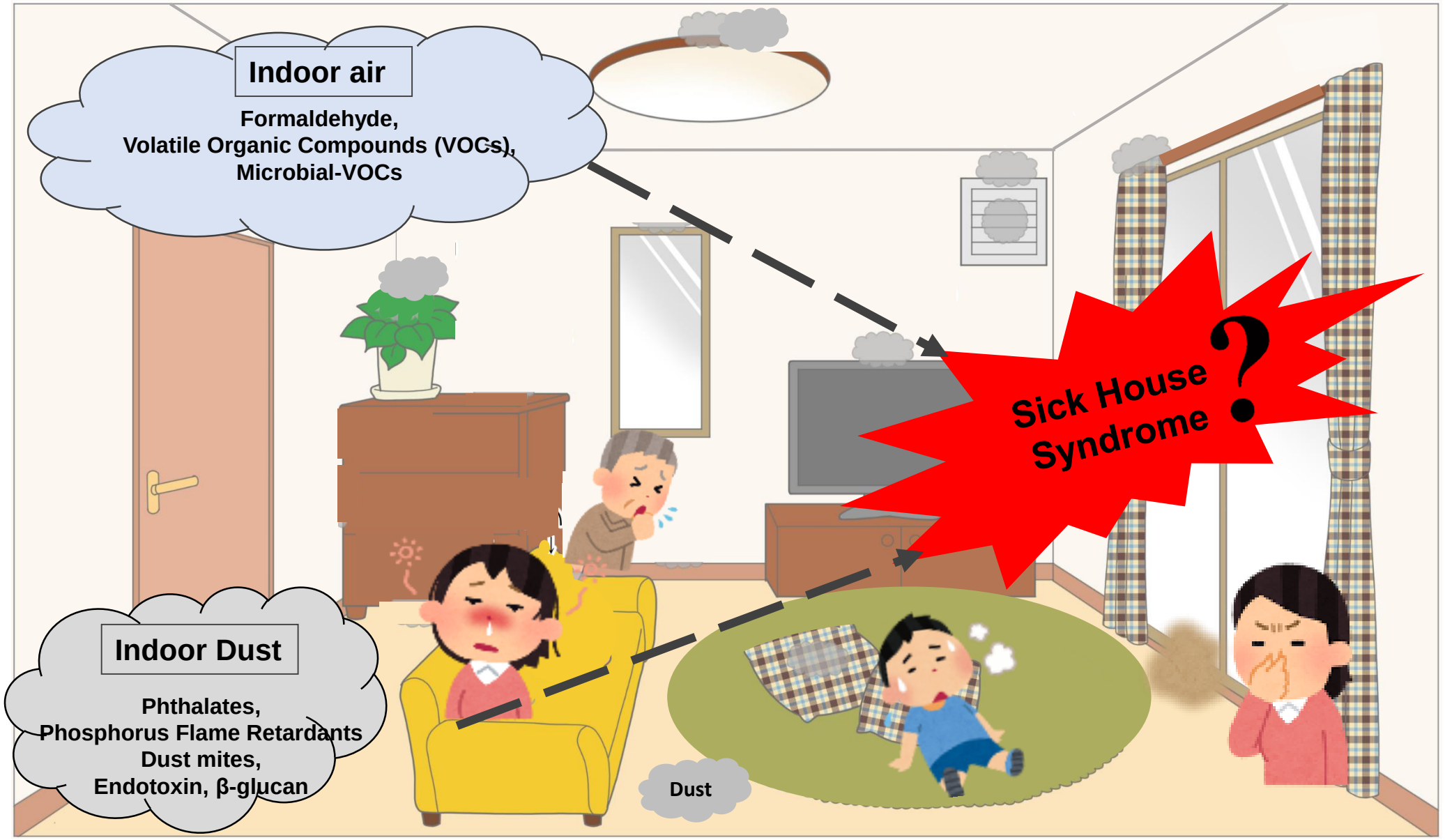
P-Values were calculated by Mann-Whitney U test

ρ: Spearman's coefficient

*$p < 0.05$

Highlights

- Association of SHS in children and adults/adolescent with indoor chemicals and biological factors was investigated.
- Building age, dampness, ventilation system, and doctor diagnosed allergies were associated with any symptoms.
- Mucosal and any symptoms were positively associated with the exposure to 2-ethyl-1-hexanol.
- Dust DiNP, DiBP, TBEP, and endotoxin showed inverse association with SHS symptoms in adults/adolescent.
- Multi-surface dust DiBP showed inverse association with mucosal symptoms in children.



Graphical Abstract