Science of the Total Environment 750 (2021) 141635

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Association between sum of volatile organic compounds and occurrence of building-related symptoms in humans: A study in real full-scale laboratory houses

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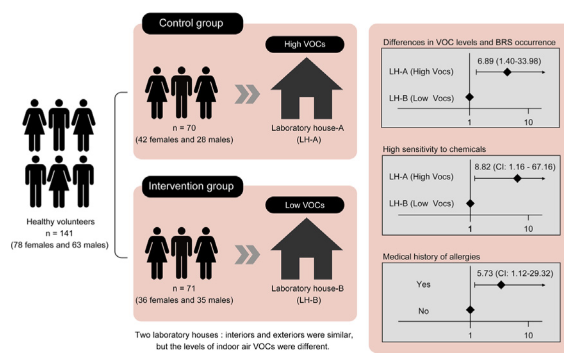
HIGHLIGHTS

- The median VOC levels of LHs A and B were 3629 μg/m^3 and 55 μg/m^3, respectively.
- BRSs occurred 6.89 times more in those staying in LH-A than those staying in LH-B.
- BRSs also more occurred in people with a history of allergy.
- BRSs were more frequent in people sensitive to chemicals.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 15 June 2020
Received in revised form 3 August 2020
Accepted 9 August 2020
Available online 15 August 2020

Editor: Henner Hollert

Keywords:
Indoor air quality
Allergy
Chemiless Town Project
Human health, laboratory houses

ABSTRACT

It is well known that the indoor environment, particularly indoor air quality (IAQ), has significant effects on building-related symptoms (BRSs) in humans, such as irritation of mucosal membranes, headaches, and allergies, such as asthma and atopic dermatitis. In 2017, Chiba University launched the “Chemiless Town Project Phase 3” to investigate the relationship between IAQ and human health. Two laboratory houses (LHs) were built on a university campus in which the interiors and exteriors were similar, but the levels of indoor air volatile organic compounds (VOCs) were different. A total of 141 participants evaluated IAQ using their sensory perception. There was a significant relationship between differences in VOC levels and BRSs occurrence (OR: 6.89, 95% CI: 1.40–33.98). It was suggested that people with a medical history of allergies (OR: 5.73, 95% CI: 1.12–29.32) and those with a high sensitivity to chemicals (OR: 8.82, 95% CI: 1.16–67.16) tended to experience BRSs. Thus, when buildings are constructed, people with a history of allergies or with a sensitivity to chemicals may be at high risk to BRSs, and it is important to pay attention to IAQ to prevent BRSs.

Abbreviations: BRSs, Building-related symptoms; EPM, Environmental preventive medicine; IAQ, Indoor air quality; ISAAC, International Study of Asthma and Allergies in Childhood; JSPS, Japan Society for the Promotion of Science; LH, Laboratory houses; MVOC, Microbial volatile organic compounds; QEESI, Quick Environmental Exposure and Sensitivity Inventory; SBS, Sick building syndrome; SD, Standard deviation; VOCs, Volatile organic compounds; WHO, World health organization.

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https://doi.org/10.1016/j.scitotenv.2020.141635

1. Introduction

It has been well recognized that the indoor environment has a significant impact on human health (Sundell, 2004; Holst et al., 2016; Mitchell et al., 2007), but the complexity of the indoor environment, which comprises of chemical, biological, physical, social and mental factors, makes dissecting the issue challenging. Several epidemiological studies have suggested that indoor airborne chemicals and molds could cause building-related symptoms (BRSs), as sick building syndrome (SBS), such as irritation of mucosal membranes, headaches and dizziness, and allergic symptoms such as asthma, atopic dermatitis, and allergic rhinitis (Sahlberg et al., 2013; Kim et al., 2007; Oh et al., 2019; Mendell, 2007). However, BRSs have been reported in indoor environments with low concentrations of chemical substances. Thus, research should focus not only on volatile organic compounds (VOCs) but also on other factors such as odor, thermal comfort, and socioeconomic and mental aspects (Lukcso et al., 2016; Rautiainen et al., 2019; Choi and Dongwoo, 2019; Vakalis et al., 2019) As there are various types of VOCs, and their compositions differ depending on the indoor air in buildings or rooms, Veenas et al. (2020) attempted to distinguish the effects of individual VOCs or patterns of VOCs on BRSs. However, few studies have investigated the actual effects of differences in the concentrations of VOCs in indoor air on BRSs under the same environmental conditions. Additionally, it was recently suggested that increased prevalence of allergic symptoms such as asthma and atopic dermatitis was due to increased exposure to environmental chemical pollutants (Choi et al., 2010; Elberling et al., 2005; Billionnet et al., 2011; Kim et al., 2016). People with allergies are more likely to develop symptoms when exposed to building-related environmental factors (Claeson et al., 2016), and Bönisch et al. reported that the allergic symptoms were associated with the exposure to VOCs using an experimental mouse model (Bönisch et al., 2012). The environmental chemical substances do not seem to have antigenic effects themselves, but they may stimulate the immune response and exert adjuvant effects (Bernstein et al., 2008). Thus, BRSs have been linked to an umbrella condition called autoimmune inflammatory syndrome induced by adjuvants (ASIA) (Shoenfeld and Agmon-Levin, 2011; Israeli and Pardo, 2011; Perricone et al., 2013). People in modern society are thought to be susceptible to allergic symptoms when exposed to chemicals in the environment (Riedl, 2008).

The Center for Preventive Medical Sciences of Chiba University (Chiba, Japan) started the “Chemiless Town Project” in 2007 to investigate the adverse health effects caused by the exposure to indoor air VOCs (Nakaoka et al., 2011). The underlying context of this project is based on environmental preventive medicine (EPM), which endeavors to prevent diseases caused by environmental pollutants by improving the environment as a whole (Mori and Todaka, 2011). “Chemiless Town” is a small model town on the university campus wherein experiments are performed to apply EPM principles in a practical setting. We developed a method to assess the effect of indoor air on human health based on the sum of VOCs (Σ VOCs) and odors.

The evaluation revealed that the building materials, construction methods, furniture, and housewares primarily contributed to the chemical concentrations in the indoor air. If the concentrations of Σ VOCs and odor were sufficiently low, there was a decreased number of individuals suffering from BRSs (Nakaoka et al., 2014; Nakaoka et al., 2018). However, there were some limitations in this project. The measurement of the indoor environment, including air sampling, and the evaluation test by the participants were not conducted at the same time. Since indoor air quality (IAQ) varies depending on ventilation, temperature, and humidity, it is important to accurately grasp IAQ when the symptoms appear. Another limitation was the different appearances of the experimental sites; the resulting psychological effects thus could not be excluded. Additionally, the relationship between allergies and BRSs was not considered because the participants were not asked about their allergic history.

The new project, “Chemiless Town Project Phase 3”, was launched in 2017. The aim of this project was to investigate the relationship between VOC levels and the occurrence of BRSs by conducting the evaluation test using human sensory perception and measurement of chemicals on the same day. The experimental sites were built with the same interior to minimize psychological effects. In addition, we investigated if people sensitive to chemicals or if people with a history of allergy were at higher risk for BRSs.

2. Material and methods

2.1. Test locations

Two laboratory houses (LHs) were built in Chemiless Town in November 2017. Their interiors and exteriors were similar (Fig. 1). The Σ VOCs of the LHs were distinct due to differences in construction structure and the building materials. LH-A is a wooden house, and LH-B was constructed of light-gage steel. Almost all the building materials of LH-B were previously measured for emission rates using a small chamber test, and lower emitted materials were carefully selected to use (Suzuki et al., 2020). There are two bedrooms and a living room in each LH, and all the bedrooms were used as the test sites.

2.2. Subjects and study design

Overall, 169 healthy volunteers were recruited to evaluate the IAQ of the LHs from May to October 2018. All participants were ordinary people such as university students, office workers, or housewives, and they were considered untrained panels. Among those, 141 participants (78 females and 63 males) completed all the questionnaires, and their data were analyzed. Before participation, the aims of the study and the test procedures were explained to the participants, and their written consents were obtained. Then, health checks were performed: the body temperature, systolic/diastolic blood pressures, and the pulse of each participant were measured before the test for two reasons. Firstly, to exclude those with fever or high blood pressure, and secondly, our study defined BRSs as symptoms claimed by participants who did not have any symptom before entering the LHs and showed some symptoms during their stay in the LHs. Thus, we needed to confirm that they were in good health before performing the sensory test. The health check revealed that all the participants were in good physical condition. The participants were randomly assigned to a bedroom in the LHs, where they remained for approximately 90 min. Almost all of the experiments were conducted with four participants simultaneously, one per bedroom. During the stay in LHs, the participants were requested to relax and sense the air in the room. Then, after about 90 min, and before leaving the LHs, they were asked sit in front of a personal computer and complete self-reported questionnaires on BRSs, odor, sensitivity to chemical substances as screened by QEESI (Quick Environmental Exposure and Sensitivity Inventory) (Miller and Prihoda, 1999a; Miller and Prihoda, 1999b), and their impressions of the test sites. All tests were conducted and tabulated according to the guideline video shown on the monitor.

In order to avoid psychological bias, the test was performed using a blind method, that is, the participants were not informed which LH had higher Σ VOCs. The furniture, such as beds, desks, and chairs in both LHs were the same, and indoor environmental factors such as room temperature, relative humidity, noise, and illumination were similarly controlled between the LHs. Both LHs were equipped with mechanical ventilation systems designed to ventilate 0.5 times per hour.

The Research Ethics Committee of the Graduate School of Medicine, Chiba University approved this study (Approval No. 2737). Approval date: September 21, 2017. Written informed consent obtained from all participants.

Fig. 1. Evaluation tests conducted in the LHs. Upper left: LH-A (typical Japanese wooden house), upper right: LH-B (light-gage steel structure), bottom left: house plan of LHs, and bottom right: an LH bedroom.

2.3. Collection of indoor air samples and analysis

We measured the VOCs in the indoor air of each LH before each evaluation test performed by the subjects. Before air sampling, the windows and the doors remained open for 30 min to allow for ventilation, after which they were shut for at least 5 h (Fig. 2). Starting at 13:00, the indoor air samples were collected for 30 min via active sampling pumps (Shibata MP-Σ30N and MP-Σ100HN, Shibata Scientific Technology Ltd. Saitama, Japan) at a height of 1.2 m in the middle of two bedrooms of each LH. Environmental factors (e.g., temperature, humidity, CO_2 levels, noise, illumination, and air pressure) were simultaneously recorded during the 90 min of the participants' stay in the LHs, and the averages were calculated. Temperature and humidity were measured and recorded with an SK-L200TH IIα datalogger (Sato Keiryoki Mfg. Co., Ltd., Tokyo, Japan), noise and illumination with an LM-8102 environmental monitor (Sato Keiryoki Mfg. Co., Ltd), air pressure with an aneroid barometer (Isuzu Seisakusho Co. Ltd., Niigata, Japan), and CO_2 concentration with a TES-1370 CO_2 densiometer (Satoshoji Digital, Kanagawa, Japan).

A total of 63 VOCs and 16 carbonyl compounds were identified and analyzed (Supplementary Material, Table S1). Mechanical ventilation systems operated during sampling. Measurements were conducted using the standard air sampling methods issued by the Ministry of Health, Labor, and Welfare of Japan (Japanese Ministry of Health, Labor and Welfare). A Tenax TA thermal desorption tube (Supelco, Sigma-Aldrich Co. LLC, MO, United States) was used for VOC capture, and a 2,4-dinitrophenylhydrazine (DNPH) active gas tube (Shibata Scientific Technology Ltd. Saitama, Japan) was used for carbonyl compound collection. Air was passed through the Tenax TA and DNPH samplers at flow rates of 100 mL/min and 1000 mL/min, respectively.

VOCs were extracted via thermal desorption and analyzed via gas chromatography–mass spectrometry. Regarding the carbonyl compounds, the gas tubes were eluted with acetonitrile, and high-performance liquid chromatography analyses were conducted. VOC and carbonyl compound analyses were performed as previously described (Suzuki et al., 2019). The quantification limit for each chemical was 1.0 μg/m^3. Target compounds in the samples were identified by comparing the retention times to reference compounds, and positive confirmation was obtained by determining the peak area ratio of the monitor ions in the samples and comparing this with known standards. Herein, Σ VOCs was calculated by summing the amounts of all identified VOCs and carbonyl compounds.

2.4. Statistical analysis

The statistical software package SPSS, version 25.0 for WIN (SPSS Inc., Chicago, IL, USA), was used for all the analyses. The Mann-Whitney *U* test was conducted to determine whether there were differences in indoor environmental factors such as temperature, relative humidity, noise, illumination, air pressure, CO_2 concentration, and VOC levels between LHs. To investigate the relationship between the differences in Σ VOCs in LH-A and LH-B and the occurrence of BRSs, a logistic regression analysis was conducted, and odds ratios and 95% confidence intervals were calculated.

The participants' gender, age, sensitivity to chemical substances, physical condition on the day of the evaluation test, medical histories of allergies, and current smoking status were covariates. Furthermore, stratifications were performed based on participants' sensitivity to chemicals, and the relationship between the differences of Σ VOCs for the two LHs and BRSs was examined by logistic regression analysis after adjusting the covariates. The BRSs occurrence questionnaire asked about the severity of symptoms on a scale of 1–5: 1, no symptoms; 2, faint symptoms; 3, weak symptoms; 4, moderate symptoms; and 5, strong symptoms. Participants who answered as 1 or 2 were defined as not having BRSs ("No"), and participants who answered as

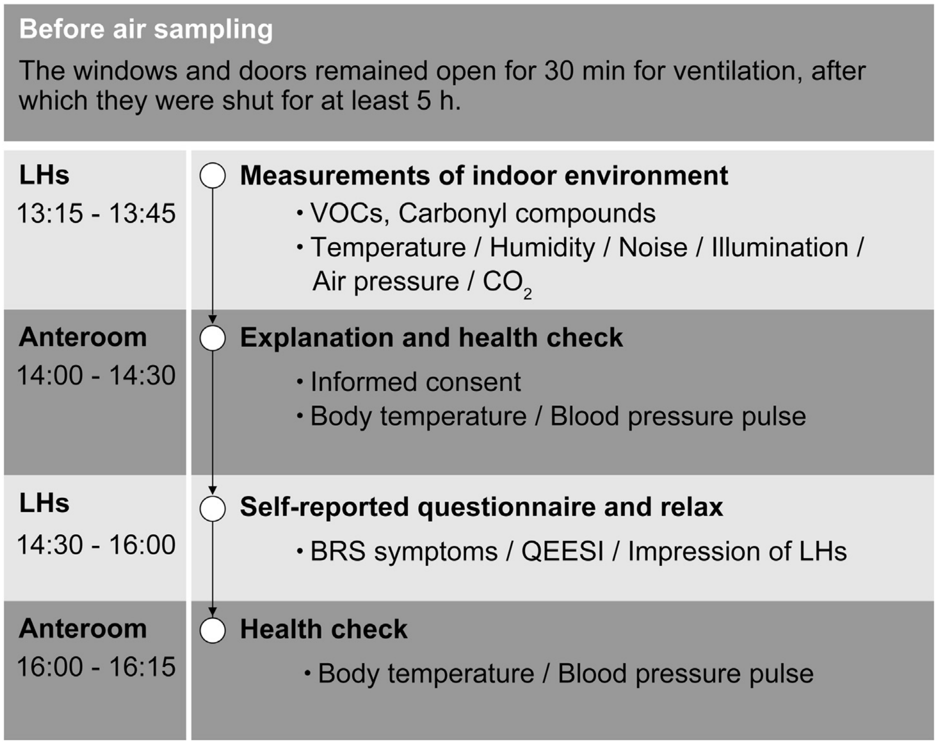

Fig. 2. The evaluation test procedure.

either 3, 4, or 5 were defined as having BRSs ("Yes"). In order to classify participants' sensitivity to chemicals, the QEESI questionnaire was used as outlined in Hojo et al. (2009). The participants were requested to score their health status on the day of the evaluation test on a scale of 1–4: 1, very good; 2, good; 3, not good; or 4, bad. We defined 1 and 2 as "good" and 3 and 4 as "bad." Participants were asked to indicate if they had been diagnosed by a physician with any of the following: asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, food allergy, or urticaria. If participants selected at least one condition, a medical history of allergies was noted. Participants were asked about their smoking status on a scale of 1–4: 1, never smoked; 2, stopped smoking more than 5 years ago; 3, stopped smoking within 4 years; 4, or still smoking. Participants who indicated 4 were designated as current smokers.

3. Results

Table 1 shows the study participants' characteristics and demographical data stratified for both LHs. A total of 70 participants (42 females and 28 males) assessed the IAQ for LH-A, and 71 participants (36 females and 35 males) assessed the IAQ of LH-B. The mean ± standard deviation of participant age for LH-A was 31.4 ± 11.6 years and 32.8 ± 12.6 years for LH-B. A total of 23 participants (32.9%) for LH-A and 39 participants (54.9%) for LH-B were more sensitive to chemicals based on the QEESI questionnaire. The difference in the number of subjects in the highly sensitive group was significant between LH-B and LH-A. However, the number of people with symptoms was more in LH-A than in LH-B (10 in LH-A, 14.3%, 3 in LH-B, 4.2%). Thus, the difference in the number subjects in the sensitive groups did not affect the results.

Thirty-four (48.6%) participants for LH-A and 34 participants (47.9%) for LH-B answered that they had been diagnosed with any allergic symptoms. Additionally, 11 and 17 people (15.7% and 23.9%) for LH-A and LH-B respectively were current smokers. No differences were found between the LHs for participant gender, age, sensitivity to chemicals, medical history of allergic symptoms, and current smoking status. The IAQ data for the LHs are shown in Table 2. The mean concentrations of Σ VOCs were 3629 μg/m^3 in LH-A and 55 μg/m^3 in LH-B, which were significantly different. The top five abundant substances

Table 1
Study participants' characteristics stratified for LHs (n = 141).

	LH-A (n = 70)		LH-B (n = 71)	
	n	%	n	T
Gender				
Male	28	40	35	49.3
Female	42	60	36	50.7
Age				
20–29	41	58.6	38	53.5
30–39	13	18.6	13	18.3
40–49	10	14.3	10	14.1
≥50	6	8.6	10	14.1
Sensitivity to chemicals (QEESI)[a]				
Low	47	67.1	32	45.1
High	23	32.9	39	54.9
Physical condition[b]				
Good	64	91.4	65	91.5
Not good	6	8.6	6	8.5
Medical history of allergy[c]				
No	36	51.4	37	52.1
Yes	34	48.6	34	47.9
Current smoking status[d]				
No	59	84.3	54	76.1
Yes	11	15.7	17	23.9
Occurrence of BRSs symptoms[e]				
No	60	85.7	68	95.8
Yes	10	14.3	3	4.2

[a] In order to classify participants' sensitivity to chemicals, the QEESI questionnaire was used in accordance with Hojo et al.
[b] Participants' physical conditions were divided into two groups: good and bad.
[c] If participants were diagnosed with at least one allergic symptom, it was defined "yes".
[d] Current smoking status was divided into two groups: "no" (never smoked, stopped smoking more than 5 years ago, and stopped smoking within 4 years) and "yes" (still smoking).
[e] The occurrence of BRSs was defined as "no" if participants did not experience any symptoms and as "yes" if they experienced any symptoms.

Table 2
Indoor environment conditions.

		LH-A		LH-B		*P* value
		Mean	SD (±)	Mean	SD (±)	
Temperature	°C	23.9	1.3	23.7	1.3	0.439
Humidity	%	54.8	13.4	56.3	12.9	0.218
Noise	dB	46.4	6.9	46.8	5.9	0.409
Illumination	Lx	172	95	202	94	0.263
Air pressure	hPa	1010	6	1009	5	0.298
CO_2	ppm	701	142	547	90	<0.001
Σ VOCs	μg/m^3	3629	1832	55	30	<0.001

detected were dichloromethane, α-pinene, texanol, 2-butoxyethanol, and 3-carene in LH-A, and pentane, acetone, ethyl acetate, 2-ethyl-1-hexanol, and undecane in LH-B. The VOC concentration in both LHs decreased over time, but the difference in the concentration of Σ VOCs between the LHs did not change. The mean CO_2 levels were 701 ppm in LH-A and 547 ppm in LH-B, which was significantly different. All the CO_2 levels in this study were less than the level of the Management Standard of Environmental Sanitation for Buildings of the Japanese Ministry of Health, Labor and Welfare (1000 ppm). However, there was a significant difference in CO_2 levels between the two LHs, so we divided the CO_2 level into two groups at the median value (625 ppm) and tried to adjust it as a covariant in the logistic regression analysis. Regarding temperature, relative humidity, noise, illumination, and air pressure, there were no significant differences between LHs.

Multiple logistic regressions were used to examine the associations between the occurrence of BRSs and differences in the two LHs as explanatory variables and personal and environmental risk factors as covariates (Table 3). The variables for each LH and the medical history of allergies were found to have associations with BRSs occurrence. BRSs occurred in participants who stayed in LH-A 6.89 times (95% CI, 1.40–33.98) higher than those who stayed in LH-B. BRSs also occurred in participants with a medical history of allergies 5.73 times (95% CI, 1.12–29.32) higher than those without a history of allergies. Furthermore, in the stratified analysis for participants either sensitive or not to chemicals as screened by the QEESI questionnaire, BRSs occurrence for sensitive participants was 8.82 times higher (95% CI, 1.16–67.16) in LH-A than in LH-B (Table 4).

Table 3
Logistic regression analysis of BRSs occurrence and personal and environmental factors.

	P value	OR	95% CI		
Gender					
Male		Ref			
Female	0.619	1.48	0.32	–	6.82
Age					
20–29	0.963	Ref			
30–39	0.836	1.19	0.23	–	6.04
40–49	0.971	1.04	0.16	–	6.90
≥50	0.600	1.66	0.25	–	11.07
Sensitivity to chemicals (QEESI)					
Low		Ref			
High	0.203	2.33	0.63	–	8.61
Physical condition					
Good		Ref			
Not good	0.942	1.09	0.10	–	11.78
Medical history of allergy					
No		Ref			
Yes	**0.036**	**5.73**	**1.12**	–	**29.32**
Current smoking status					
No		Ref			
Yes	0.475	2.39	0.22	–	25.88
CO_2 level					
≤624		Ref			
≥625	0.478	0.59	0.14	–	2.50
Laboratory house					
LH-B		Ref			
LH-A	**0.018**	**6.89**	**1.40**	–	**33.98**

Note: Boldface indicates statistical significance ($P < .05$).

Table 4
Logistic regression analysis of the association between BRSs and LHs stratified for the sensitivity to chemicals (QEESI questionnaire).

	QEESI Low					QEESI High				
	P value	OR	95% CI			P value	OR	95% CI		
Laboratory house (LH)										
LH-B		Ref					Ref			
LH-A	0.267	6.25	0.25	–	58.82	**0.035**	**8.82**	**1.16**	–	**67.16**

Note: Boldface indicates statistical significance ($P < .05$).
Adjusted for participants' gender, age, physical condition, medical history of allergy, current smoking status, and CO_2 levels in the LHs.

4. Discussion

Two LHs were used as the test sites in the present study, which were similar in appearance. The VOCs in each LH were significantly different due to distinguished construction methods and building materials between the LHs. In our previous study, designing houses with low Σ VOCs was possible even right after the completion, by carefully choosing low-emission methods and materials (Suzuki et al., 2019). In this study, we assessed differences in human health effects of two indoor air environments with high and low Σ VOCs concentration levels.

The number of the participants who claimed any BRSs during their stay at either LH was 13 (9.2%) (10 in LH-A, 14.3%, 3 in LH-B, 4.2%). According to the results of a 2017 web survey of 1500 Japanese citizens, the prevalence of having experienced BRSs was 18.8% (Nakayama et al., 2019). The prevalence in this study was lower compared to the survey. The observed low prevalence of this study is probably due to the fact that the exposure time was as short as 90 min, and the participants answered the questionnaires during their stay at test sites. Thus, any health effects that might appear after leaving the sites were not included in our analysis.

Regarding the relationship between the occurrence of BRSs and building differences, a multiple logistic regression analysis, in which participants' characteristics and environmental factors were introduced as covariates, were examined. The results showed positive and significant correlations between BRSs occurrences and a medical history of allergies and the differences of the LHs. The factors related to allergic symptoms, which have increased in recent years (Linneberg, 2011; Umetsu et al., 2002), are living, food, and sanitary environments (Benedé et al., 2016; Subbarao et al., 2009). Especially in relation to the indoor environment, dust mites and mold, which are allergens, are considered to be the main causes (WHO, 2009; Walker et al., 2003; Weinmayr et al., 2013). Allergy is also considered to be induced by chemical substances such as MVOCs (microbial volatile organic compounds) derived from microorganisms (Choi et al., 2017) and tobacco smoke (Von Mutius, 2002). Additionally, indoor VOCs may develop or exacerbate allergies through an adjuvant effect (Bernstein et al., 2008; Fraga et al., 2008), and most of these substances implicated in BRSs may be regarded as environmental adjuvants (Perricone et al., 2013). Animal studies demonstrated that VOC exposure could influence the immune responses (Fujimaki et al., 2007) and might cause airway inflammation when exposed through the respiratory tract (Ichinose et al., 2008; Steerenberg et al., 2004). The animal studies in the reference literature show that exposure to high concentrations of VOCs, from several to 100 times higher than the standard indoor air quality, causes inflammation. There were no epidemiological studies showing the adverse effects of VOC exposure in ordinary indoor environments as adjuvants in allergic inflammation. However, Kwon et al. (2018) indicated that VOC exposure in everyday life can cause airway inflammation. Further studies are necessary to determine the effects of indoor air VOC exposure on human health. On the other hand, some reports indicated that indoor VOCs are not a major determinant of risk of allergies (Venn et al., 2003) and evidence of the effects of indoor VOCs on human allergic symptoms is of poor quality and inconsistent (Nurmatov et al., 2015; Tagiyeva and Sheikh, 2014; Woong et al., 2009). The present study revealed that people with a history of allergies experienced BRSs once they were exposed to indoor VOCs. Christine and Apte (2004) also reported that the certain health conditions, such as allergy, confer increased susceptibility to BRSs.

Although there is insufficient evidence regarding the role of VOCs in the etiology or development of BRSs, people with a history of allergies may be susceptible to indoor airborne chemicals. It is better for them to avoid indoor air with high VOCs to prevent BRSs occurrence. Regarding susceptibility to chemicals, the participants were divided into two groups, high and low sensitivity, based on the QEESI questionnaire. According to the results of a previous survey by Azuma et al., the high susceptibility group in Japan was approximately 24.1% (Azuma et al., 2015), but in this study, it was 45.5%. The reason why the ratio of the high sensitivity group increased in this study could be due to participants' motivation. While recruiting participants of this study, we explained that this evaluation test was on IAQ. Lu et al. (2018) reported that individuals with chemical sensitivity and migraine were at increased risk of lower respiratory. In our previous study, the high sensitivity group was also significantly associated with symptom development when exposed to high indoor VOCs (Nakaoka et al., 2014). Despite the higher proportion of sensitive people in this study, the prevalence of BRSs occurrence was lower than in other studies, and our logistic regression analysis showed no significant association between susceptibility to chemicals and claims of BRSs. Then, we investigated the association with symptom development by stratifying the high and low susceptibility group. As a result, it was found that if the sensitivity of the participant was "low", it was not associated with BRSs occurrence during a short-time stay. It was suggested, however, that when the susceptibility was "high", entering the LH with higher Σ VOCs increased BRSs risk (OR: 8.82, 95% CI: 1.16–67.17). It is necessary to keep in mind that people who are highly sensitive to chemicals should avoid exposure to high VOCs to prevent the development of BRSs.

Since there are some reports that the complaints of BRSs were related to psychiatric components (Azuma et al., 2017; Kinman and Griffin, 2008), the participants were asked if they had a medical history of mental illness to adjust for psychiatric factors. Since no participants had a medical history of mental illness, the psychiatric components could not be added as covariates in the analysis of this study.

Regarding the difference between the results of our previous study and this one, the former revealed the baseline of Σ VOCs level that can cause BRSs, while the latter showed that actual building materials and construction methods may prevent the occurrence of BRSs.

The sensory evaluation test used in the LHs for short-time periods had several advantages. First, the two LHs were similar in appearance and indoor environments (e.g., temperature, humidity, etc.), so psychological-related biases based on these aspects were minimized. Secondly, since participants focused on IAQ during a short stay of 90 min, they could clearly recognize whether they showed the symptoms during the stay. In addition, the indoor air samples were collected just before all the evaluation tests and analyzed for VOCs and carbonyl compounds; thus, the relationship between VOCs and BRSs occurrences could be dissected in more detail.

However, there were some limitations. In this study, it was not possible to evaluate the long-term effects of IAQ. We do not know which effects occur upon long-term exposure, even at low concentrations. Additionally, the evaluation tests were carried out during the daytime on weekdays, and almost all the participants were university students and of a younger age group. Regarding the role of psychological effects, participants who may have a medical history of mental illness might have hesitated to answer as such, and our sample size and participants' demographics made it difficult to adjust for psychosocial aspects.

5. Conclusions

To the best of our knowledge, ours is the first study examining the association between the occurrence of BRSs and differences in VOCs under the same environmental conditions. The results of this study found a significant relationship between BRSs occurrence and VOC concentration after adjusting for gender, age, chemical sensitivity, current smoking status, and CO_2 concentration levels. Furthermore, the probability of developing BRSs in indoor air with low VOCs was significantly lower compared to indoor air with high VOCs. Our findings also revealed that we could create an indoor air environment that prevents the occurrence of BRSs by carefully selecting the building and structural materials. People highly sensitive to chemicals and those with a history of allergies tended to develop BRSs. Thus, these groups may be at high risk for BRSs, and it is important to pay attention to IAQ to prevent BRSs occurrence and development.

Funding

This research was funded by Sekisui House Ltd. and Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (C) Grant Number (19K12455, 18K13885). This work was supported by JST OPERA Program Grant Number JPMJOP1831, Japan. The sponsor had no control over the interpretation, writing, or publication of this work.

CRediT authorship contribution statement

Conceptualization, N.S., H.N. and Y.N.; Methodology, N.S., K.T. (Kohki Takaguchi), K.T. (Kazunari Takaya) and H.N.; investigation, N.S. and H.N. Formal analysis and interpretation of data, N.S., H.N., A.E., Y.N., K.T. (Kayo Tsumura), K.T. (Kohki Takaguchi), K.T. (Kazunari Takaya), E.T. and M.H.; Data curation, N.S., H.N., Y.N., K.T. (Kazunari Takaya), K.T. (Kayo Tsumura), K.T. (Kohki Takaguchi), M.H., E.T. and C.M.; Writing—original draft preparation, N.S.; Writing—review and editing, C.M.

All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English Language review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.141635.

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