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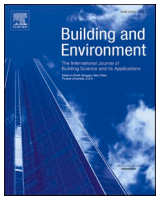

Mold, bacteria, allergens, and volatile organic compounds in homes associated with tear film break-up time, oculo-nasal symptoms, and allergic rhinitis

Juan Wang [a,*], Christer Janson [a], Thorarinn Gislason [b,c], Maria Gunnbjörnsdottir [b,c], Rain Jogi [d], Hans Orru [e,f], Dan Norbäck [g]

[a] Department of Medical Sciences, Respiratory-, Allergy- and Sleep Research, Uppsala University, Uppsala, Sweden
[b] Department of Sleep, Landspitali University Hospital, Reykjavik, Iceland
[c] Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[d] Lung Clinic, Tartu University Hospital, Tartu, Estonia
[e] Institute of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
[f] Occupational and Environmental Medicine, Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[g] Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden

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ABSTRACT

Indoor bacteria, mold, allergens, and selected volatile organic compounds (VOC) were measured at home in three Nordic cities. Data on self-reported tear film break-up time (SBUT), weekly oculo-nasal symptoms during the past three months, and allergic rhinitis of 159 adults were obtained. Among them, 58 % were females, 24.5 % were atopics, and 41 % reported home dampness. The median SBUT was 22.3 s. Oculo-nasal symptoms (15.3 %) and allergic rhinitis (32.7 %) were common. A higher level of 2-hexanone was linked to lower SBUT ($p = 0.036$). Higher levels of total mold ($p = 0.038$), allergen Fel d 1 from cat ($p = 0.045$), and allergen Der p 1 ($p = 0.012$) and Der f 1 ($p = 0.036$) from house dust mite (HDM), were related to more oculo-nasal symptoms. Higher levels of 3-methylfuran ($p = 0.003$), 2-hexanone ($p = 0.037$), 2-heptanone ($p = 0.018$), and 1-octen-3-ol ($p = 0.001$) were linked to oculo-nasal symptoms. Higher levels of viable bacteria ($p = 0.015$), 3-octanone ($p = 0.049$) and formaldehyde ($p = 0.039$) were linked to allergic rhinitis. The association between 2-heptanone and oculo-nasal symptoms (interaction $p = 0.012$), and between isobutyl acetate and allergic rhinitis (interaction $p = 0.084$) were more pronounced in women. The negative association between 2-hexanone and SBUT was stronger among atopics (interaction $p = 0.098$), and the links between viable bacteria and allergic rhinitis (interaction $p = 0.003$) and between Der f 1 and oculo-nasal symptoms (interaction $p = 0.1$) were more pronounced among non-atopics.

In conclusion, airborne mold and bacteria, and allergens in dust were associated with oculo-nasal symptoms or allergic rhinitis. 3-Methylfuran, 2-hexanone, 1-octen-3-ol, and 2-heptanone were associated with adult oculo-nasal symptoms. Increased 3-octanone and formaldehyde were related to allergic rhinitis.

1. Introduction

Allergic rhinitis can be caused by allergens from such as pollen, mold, or certain animals. An estimated 10–20 % of the population in Europe and the US is affected by allergic rhinitis [1]. Indoor dampness can cause microbial volatile organic compounds (MVOC) emissions, allergens from house dust mite (HDM), as well as indoor growth of mold and bacteria [2]. Dampness and mold exposure were demonstrated to be associated with rhinitis risk according to systematic reviews [3,4]. Apart from allergen exposures, the literature suggested that indoor chemical emissions in dwellings may influence allergies [5,6].

Some home environment studies exist on the effect of dampness/mold on rhinitis. Studies from Sweden [7,8], Finland [9] and China [10] have shown that the presence of dampness or mold in dwellings was linked to higher prevalence of nasal symptoms/rhinitis among adults. Few studies exist on microbial markers in the home environment and rhinitis. One study from the US quantified indoor molds by a DNA-based method, and showed that increased environmental relative moldiness

* Corresponding author. Department of Medical Sciences, Respiratory-, Allergy- and Sleep Research, Uppsala University, SE-751 85, Uppsala, Sweden.
E-mail address: juan.wang@medsci.uu.se (J. Wang).

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index was associated with adult rhinitis [11]. Another research conducted in the US reported that increased allergen from dog (Can f) measured in home dust was associated with allergic rhinitis [12]. Increased levels of allergens from HDM (including Der p 1 and Der f 1) in newly built dwellings in Japan were related to occupants' nose symptoms [13].

Some studies have investigated volatile organic compounds (VOC) in homes concerning rhinitis. Studies from Japan reported that nasal symptoms were more common in occupants with increased levels of formaldehyde, chlorodibromomethane, and nonanal in their homes [14,15]. Additionally, exposure to 1-octen-3-ol was linked to allergic rhinitis in occupants in another Japanese study [16]. One study from France reported higher prevalence of rhinitis among residents exposed to aromatic hydrocarbons and halogenated hydrocarbons in homes [17]. Another French home study reported associations between increased levels of ethylbenzene, trichloroethylene, m/p- and o-xylene and adult rhinitis [18]. A dose-response relation was shown between indoor level of formaldehyde and nasal symptoms among residents in a US study [19].

Some studies suggested that indoor dampness and mold in dwellings can have a negative effect on ocular symptoms. Two studies from Sweden found that dampness occurring in homes was linked to higher prevalence of adult ocular symptoms [7,8]. One Finish study [9] and one Chinese study [10] reported increased prevalence of eye symptoms among adults living dwellings with dampness and mold growth. Few studies have shown relationships between measured microbial organisms and ocular symptoms. A study from US indicated that individual exposure to higher indoor microbial concentration at home was associated with dry eye symptoms among adults [20]. Increased indoor level of *Aspergillus* was related to eye symptoms among occupants in newly built dwellings in Japan [13]. One experiment study found that higher number of microbial colonies was related to dry eye symptoms [21].

Some studies from home setting exist on indoor VOC and occupants' ocular symptoms. Two studies from Japan investigated newly built houses and reported more ocular symptoms among residents exposed to increased levels of formaldehyde, acetone, n-nonane, 2-pentanone [14], ethylbenzene, xylene and total VOC [15]. A third Japanese study indicated that 1-octen-3-ol in dwellings was connected to occupants' conjunctivitis [16]. Moreover, a study from the US reported a dose-response relationship between increased indoor concentrations of formaldehyde in homes and eye irritation among residents [19].

Ocular symptoms can be because of allergic reactions (rhinoconjunctivits related to allergic rhinitis, or because of impaired tear film (dry eye symptoms). Lacrimal tear film stability is a measure to evaluate physiological responses of the eyes to environmental exposure. Tear film break-up time (BUT) is utilized to evaluate the stability of tear film. It can be measured using fluorescein staining and ocular microscopy. Alternatively, it can be determined by the duration the subject can maintain their eyes open without pain while fixating on a point on the wall (self-reported tear film break-up time, SBUT). SBUT shows a strong correlation with the fluorescein technique [22]. A shorter BUT suggests diminished tear film stability. There are no existing studies on dampness and mold/microbial markers in home environment and tear film stability or BUT. However, some studies are available on microbial growth in other indoor environment and reduced tear film stability, mostly office environment. Reviews based on office studies suggested that indoor climates, including elevated room temperature, decreased relative air humidity and draft can be related to decreased tear film stability [23–25]. One Swedish hospital study found decreased tear film stability among hospital staff working in damp buildings [26]. One Norwegian study reported that increased level of airborne dust and and the occurrence of mold *Aspergillus fumigatus* were related to decreased tear film stability (reduced BUT) among hospital workers [27]. One Swedish intervention study among hospital staff previously working in a building with flooding history showed decreased BUT among subjects after a two-day re-exposure [28]. A Malaysian school study showed that total fungal DNA found in vacuumed dust was linked to reduce tear film stability, and DNA from *Aspergillus/Penicillium* was linked to decreased non-invasive tearscope BUT among students [29].

The relationships between airborne mold and bacteria within the household and symptoms of asthma, bronchial responsiveness and airway obstruction have been published previously [30]. The present study aimed to investigate measured home environment exposures in relation to ocular physiological reaction measured as SBUT, oculo-nasal symptoms, and allergic rhinitis among adults from three Nordic cities (including Reykjavik, Uppsala, and Tartu). Home environment exposures consisted indoor mold, bacteria, allergens, and selected indoor VOC. Previous studies have demonstrated that some of these VOC can be produced by microorganisms [2,31].

2. Materials and methods

2.1. Ethics

Approval for the study protocols was granted by the regional medical research ethics committees in Reykjavik (with reference number VSNb2011090016/03.15), Uppsala (with reference numbers 1990/257 and 1998/495), and Tartu (with reference numbers UT REC 60/3–1998 and UT REC 209 T-17). All participants provided written informed consent.

2.2. Study design

The European Community Respiratory Health Survey (ECRHS) was initially conducted at the start of the 1990s (ECRHS I), involving 22 countries [32]. The first follow-up was performed in 2000–2002 including the original participants of ECRHS I (ECRHS II). Data from three Nordic centres (Reykjavik, Uppsala, and Tartu) from ECRHS II were used in the present paper. There were in total 1238 subjects from these three centres participated in ECRHS II. In each center, 60 participants, randomly chosen and who had lived in the same place since ECRHS I, were asked to join a home investigation including measurements of the indoor environment in 2001–2002. Additionally, all participants who had previously reported dampness or mold growth inside home in the questionnaire study were asked to take part in the home investigation ($n = 228$). A sum of 159 subjects joined the study, representing a participation rate of 69.7 % (Fig. 1). Detailed study designs of the home investigation have been published previously [30,33].

2.3. Indoor measurements

Relative air humidity and temperature in homes were quantified using an Assman Psychrometer of type SK-RHG (Sato Keiryoki Mfg. Co., Tokyo, Japan). Two spot measurements of temperature and relative air humidity in the living room were done at each home visit, and the mean value was noted.

Indoor mold and bacteria in the air, including total mold, viable mold, total bacteria, and viable bacteria, were measured in homes. Microorganisms in air were collected using 25 mm nucleopore filters featuring a pore diameter of 0.4 mm, at a sampling rate of 2 l/min for a duration of 2.5 h. A refrigerator (ranged +4 to +10 °C) was used to keep the nucleopore filters after sampling. The filters were then posted to Pegasus Lab AB in Uppsala, Sweden within a week by priority mail for analysis. The quantities of total mold and total bacteria were assessed through the method of collecting airborne microorganisms on nucleopore filters [34]. Total mold and bacteria were analyzed by fluorescein microscopy and using acridine staining. Viable mold and viable bacteria were obtained through incubation using two different media. For total mold and bacteria, the detection limit was 11,000 per m^3 of air. For viable mold and bacteria, the minimum detectable limit was 30 colony forming units per m^3 (CFU/m^3).

Indoor dust from beds was gathered by an Elektrolux Mondo vacuum

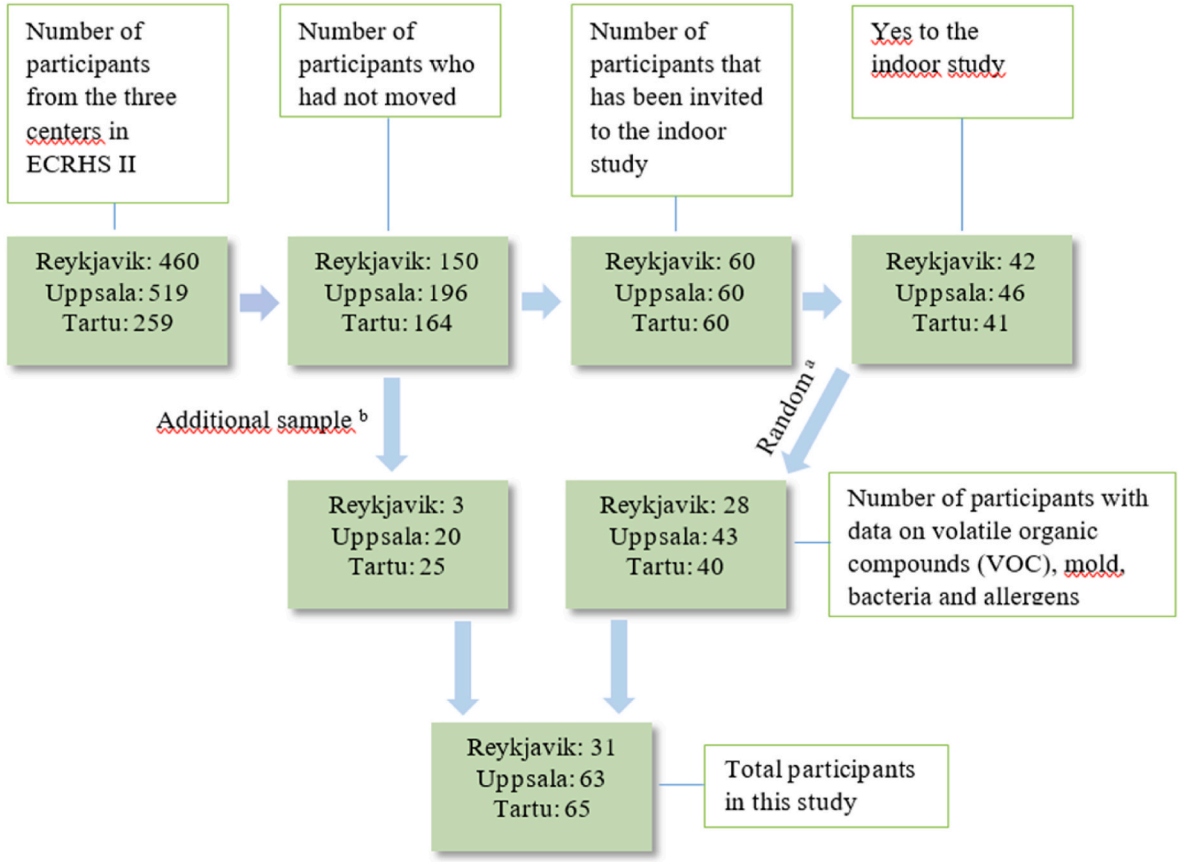

Fig. 1. Flow chart of the study. [a] A randomized sample of individuals within each center who had not relocated since the ECRHS I survey. [b] Subjects reporting dampness in the dwelling and were not included in the random sample.

cleaner (1300 W) (AB Electrolux, Stockholm, Sweden) equipped with an ALK filter (ALK-Albelló A/S, Hörsholm, Denmark). Concentrations of Fel d 1 (*Felis domesticu* 1, major cat allergen), Der p 1 (*Dermatophagoides pteronyssinus* 1, major HDM allergen) and Der f 1 (*Dermatophagoides farinae* 1, major HDM allergen), were analyzed from collected dust in dwellings utilizing standard monoclonal antibody enzyme-linked immunosorbent assays [35,36]. Concentrations of allergens were quantified as micrograms of allergen obtained from per gram of dust (μg/g). The detection limit for Fel d 1 was 0.01 μg/g, and for Der p 1 and Der f 1, it was 0.1 μg/g. A value equal to half the detection limit was allocated when the measured value was lower than the detection limit (0.005 μg/g was assigned to Fel d 1, and 0.05 μg/g was assigned to Der p 1 and Der f 1).

A total of 18 VOC (except formaldehyde) in dwellings were collected on a charcoal tube (Anasorb 747; SKC Inc., Eighty Four, PA, USA) utilizing a pump set at a sampling speed of 0.4 l/min for a duration of 3 h. The selected VOC included in the present study were chosen by Pegasus Lab AB as the lab evaluated that these VOC can have microbial origins. The charcoal tubes were desorbed by methylene chloride (2 ml) and then subjected to analysis via selective ion monitoring gas chromatography-mass spectrometry (Pegasus Lab AB, Uppsala, Sweden) [37]. For Texanol, 2-ethyl-1-hexanol, and TXIB, the detection limit was 0.1 μg/m^3. The detection limit was 0.001 μg/m^3 for other VOC (except formaldehyde). A value equal to half the detection limit was assigned when the measured value was lower than the detection limit (0.05 μg/m^3 was assigned to Texanol, 2-etyl-1-hexanol, and TXIB, and 0.0005 μg/m^3 was assigned to other VOC but not formaldehyde).

Formaldehyde levels indoors were assessed by utilizing glass fiber filters treated with 2,4-dinitrophenylhydrazine [38] to sample air with a speed of 0.4 l/min for a duration of 3 h. Analysis of the filters was performed using liquid chromatography. For formaldehyde, the detection limit was 6 μg/m^3.

2.4. Dampness in homes

The occurrence of any dampness or mold growth inside home was established by the presence of at least one affirmative "yes" response to five questions regarding indicators of dampness or mold in dwellings [39].

2.5. Demographic information and atopy

Data regarding age, gender, height, and weight were gathered from questionnaire used in the ECRHS II. Body mass index (BMI) was computed by using height and weight measurements (kg/m^2). There was one question in the questionnaire asking about smoking habit, with three alternatives (current smoker/ex-smoker/never smoker). Blood and serum were sampled during the clinical study of ECRHS II [40]. Specific serum immunoglobulin E (IgE) against the cat, timothy grass, mold (*Cladosporium*) and HDM (*Dermatophagoides pteronyssinus*), were analyzed by the CAP system used in Pharmacia Diagnostics (Uppsala, Sweden). A positive reaction was set as a specific serum IgE level >0.35 kU$_A$/L, where kU$_A$ means kilounits of specific antigen. Having at least one positive reaction to any of the mentioned allergens above was defined as atopy.

2.6. Tear film break-up time (BUT), oculo-nasal symptoms, and allergic rhinitis

Self-reported tear film break-up time (SBUT) was evaluated by measuring the duration (s) the subject could maintain open eyes without blinking while fixating on a stationary point on the wall [41]. The mean

of three trials was recorded for SBUT. SBUT has a good correlation with the non-invasive methods by ocular microscopy [22].

Three questions on eye/nose symptoms were included in the questionnaire used in ECRHS II indoor study: "Itching, burning or irritation of the eyes in the last three months", "Running nose in the last three months" and "Blocked nose/nasal congestion in the last three months". There are four alternatives in each question: yes, every day; yes, 1–4 times per week; yes, 1–3 times per month; no, never. The rate of weekly symptoms (yes/no) was evaluated: answer to "yes, every day" or "yes, 1–4 times per week" was treated as "yes"; and answer to "yes, 1–3 times per month" and "no, never" were treated as "no". These three questions with three three-month recall period have been used in previous publications [42,43]. Any oculo-nasal symptom was defined as any weekly symptom of these three questions. Additionally, one query in the ECRHS II questionnaire inquired about allergic rhinitis "presence of any nasal allergies/hay fever (yes/no)".

2.7. Statistical analysis

Indoor measurement data is presented using the geometric mean (GM) and geometric standard deviation (GSD). Two-level linear mixed regression models, which accounted for both individual and center-level effects, were conducted to examine associations between each indoor exposure, indoor air temperature, indoor air humidity, and SBUT, controlling for gender, age, BMI, and current smoking (four covariates). Associations between each indoor exposure and oculo-nasal symptoms and allergic rhinitis were examined by a logistic regression model with two levels (accounted for both individual and center-level effects) controlling for four covariates. As a next step, stratified analyses and interaction analyses were conducted for significant indoor exposures ($p < 0.1$). The stratification was performed for gender, atopy, and building dampness ($p < 0.1$ was regarded statistically significant for interaction). Correlation analysis was performed, using Spearman correlation to estimate correlations between indoor exposures. Factor analysis was conducted for indoor exposures, employing principal component analysis using varimax rotation. Log transformed exposure data (log base 10) were used in all statistic models, except for the models on indoor air temperature, and indoor air humidity associated with SBUT. Statistical analysis was conducted using SPSS 28.0 (SPSS Inc.) and STATA 15.1 (STATA Corp, Texas, USA). Associations were expressed as Beta values for linear mixed models and odds ratios (OR) for logistic regression models, accompanied by 95 % confidence intervals (CI), with significance set at 5 %.

3. Results

Totally 159 subjects participated, 42 % of them were males, and 24.5 % of them were atopics (with any positive specific IgE), 31.4 % were ex-smokers and 25.8 % were current smokers. The mean age of the participants was 44 y (Table 1). The median value of SBUT was 22.3 s. A total of 15.3 % had oculo-nasal symptoms in the last three months, and the highest prevalence was found in Tartu (20.6 %). Around one-third of the participants had allergic rhinitis (32.7 %). Uppsala had the highest prevalence of allergic rhinitis (38.1 %) (Table 2).

The mean air temperature indoor was 20.7 ± 1.11 °C (GM ± GSD), and the mean air humidity indoor was 40.7 ± 1.36 % (GM ± GSD). Levels of mold, bacteria, allergens, and chemical compounds inside homes, presented as GM and GSD, are shown in Table 3.

Table 4 shows levels of indoor mold, bacteria, allergens, and VOC in association with SBUT, oculo-nasal symptoms in the last three months, and allergic rhinitis (3-Methyl-1-butanol, 2-methyl-1-butanol, and isobutyl acetate were excluded from the analysis due to low observation rates). A higher indoor level of 2-hexanone was linked to lower SBUT. Higher levels of total mold, and allergen Fel d 1, Der p 1 and Der f 1 were associated with more oculo-nasal symptoms. Higher levels of specific VOC, including 3-methylfuran, 2-hexanone, 1-octen-3-ol, and 2-heptanone, were linked to oculo-nasal symptoms. Increased level of viable bacteria was linked to allergic rhinitis. Higher levels of 3-octanone and formaldehyde were related to more allergic rhinitis. Additional analyses investigating the connections between indoor temperature, relative air humidity, and SBUT showed that higher indoor air temperature was related to lower SBUT (Beta = −1.52, 95%CI(-2.84, −0.21), p = 0.023). No association was found between indoor air humidity and SBUT (data not shown). The negative association between 2-hexanone and SBUT remained when adjusting for indoor air temperature (Beta = −9.58, 95%CI(-17.1, −2.04), p = 0.013).

Interaction analyses on indoor exposures and SBUT, oculo-nasal symptoms, and allergic rhinitis are shown in Tables S1, S2, and S3, respectively. Women had more oculo-nasal symptoms when exposed to indoor 2-heptanone (interaction p = 0.012). Men had more allergic rhinitis when exposed to indoor formaldehyde (interaction p = 0.107). Higher indoor 2-hexanone was related to lower SBUT among atopics (interaction p = 0.098) (Fig. 2). Higher Der f 1 was related to oculo-nasal symptoms among non-atopics (interaction p = 0.106) (Fig. 3). Higher indoor viable bacteria were associated with allergic rhinitis among non-atopics (interaction p = 0.003) (Fig. 4).

Stratified analyses (stratified for gender, atopy, and any dampness) on indoor exposures in relation to SBUT, oculo-nasal symptoms, and allergic rhinitis are shown in Tables S1, S2, and S3, respectively. A total of three significant associations were discovered for males, while three were identified for females. Additionally, one significant association was

Table 1
Demographics of the participants.

		N	%	Mean (SD[a])
Gender	Men	67	42	
	Women	92	58	
Age		159		44(6.7)
BMI	kg/m^2	156		25.1(3.8)
Atopy[b]	No	117	75.5	
	Yes	38	24.5	
Smoking habit	Never smoker	68	42.8	
	Ex-smoker	50	31.4	
	Current smoker	41	25.8	

[a] SD means standard deviation.
[b] Atopy was defined as any positive specific IgE to timothy, cat, mite, or *Cladosporium*.

Table 2
Descriptive data on SBUT, oculo-nasal symptoms in the last three months, and allergic rhinitis.

			N	%	Median(IQR)
All centres	SBUT[a]	s	153		22.3 (10.3–38.0)
	Oculo-nasal symptoms in the last three months		24	15.3	
	Allergic rhinitis		52	32.7	
Reykjavik	SBUT[a]	s	31		10.3 (7.7–29.3)
	Oculo-nasal symptoms in the last three months		3	9.7	
	Allergic rhinitis		8	25.8	
Uppsala	SBUT[a]	s	61		20.0 (10.3–33.7)
	Oculo-nasal symptoms in the last three months		8	12.7	
	Allergic rhinitis		24	38.1	
Tartu	SBUT[a]	s	61		31.7 (18.3–43.7)
	Oculo-nasal symptoms in the last three months		13	20.6	
	Allergic rhinitis		20	30.8	

[a] IQR means interquartile range.
[a] SBUT means self-reported tear film break-up time.

Table 3
Descriptive data on indoor levels of mold, bacteria, allergens, and VOC.

	Exposures	Unit	Number of observations	GM[a]	GSD[b]
Mold/ bacteria	Total mold	Number/ m^3	158	12830	1.93
	Viable mold	CFU/m^3	158	216	2.60
	Total bacteria	Number/ m^3	158	16358	2.64
	Viable bacteria	CFU/m^3	158	227	3.28
Allergens in indoor dust	Fel d 1	μg/g	147	1.65	16.5
	Der p 1	μg/g	148	0.099	6.10
	Der f 1	μg/g	148	0.144	6.37
VOC	3-Methylfuran	μg/m^3	158	0.023	3.05
	Isobutanol	μg/m^3	159	1.57	2.33
	1-Butanol	μg/m^3	159	5.84	2.33
	2-Pentanol	μg/m^3	154	0.012	4.21
	3-Methyl-1-butanol	μg/m^3	74	0.274	3.50
	Dimethyl disulphide	μg/m^3	156	0.033	7.32
	2-Hexanone	μg/m^3	159	0.057	2.33
	2-Heptanone	μg/m^3	159	0.319	2.19
	1-Octen-3-ol	μg/m^3	145	0.052	2.68
	3-Octanone	μg/m^3	130	0.040	1.80
	2-Methyl-1-butanol	μg/m^3	71	0.072	2.73
	Ethyl isobutyrate	μg/m^3	158	0.001	3.74
	Isobutyl acetate	μg/m^3	71	0.056	12.1
	Ethyl 2-methylbutyrate	μg/m^3	147	0.028	7.22
	2-pentylfuran	μg/m^3	147	0.042	4.13
	2-Ethyl-1-hexanol	μg/m^3	144	2.38	2.02
	Formaldehyde	μg/m^3	158	20.0	2.08
	2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (Texanol)	μg/m^3	156	1.07	4.80
	2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB)	μg/m^3	159	1.47	2.75

[a] GM means geometric mean.
[b] GSD means geometric standard deviation.

observed for atopics, six were noted for non-atopics, four significant associations were found for the dampness group, and five for the non-dampness group. Two gender interactions were observed, indicating that women were more sensitive to indoor VOC. Three interactions were found when comparing atopics with non-atopics, suggesting that atopics were more sensitive to 2-hexanone and non-atopics were more sensitive to indoor bacteria and HDM allergen Der f 1. No significant interactions between the dampness group and the non-dampness group, suggesting no clear trends on associations between indoor exposures and SBUT, oculo-nasal symptoms, and allergic rhinitis among those exposed to building dampness and those not exposed.

Correlations between indoor exposures are shown in Tables S4 and S5. All three indoor allergens were associated with ocular-nasal symptoms, however, we found no correlations between the three allergens. Four VOC, including 3-methylfuran, 2-hexanone, 1-octen-3-ol and 2-heptanone, were positively associated with ocular-nasal symptoms. High correlations were found between 3-methylfuran and 2-heptanone (Spearman correlation = 0.68), between 2-hexanone and 2-heptanone (Spearman correlation = 0.82), between 1-octen-3-ol and 2-hexanone (Spearman correlation = 0.91) and between 1-octen-3-ol and 2-heptanone (Spearman correlation = 0.82). The high correlations between those four VOC indicated that it is impossible to separate the effect of each single compound on ocular-nasal symptoms. Extra analysis using the sum of the levels of 3-methylfuran, 2-hexanone, 1-octen-3-ol and 2-heptanone in one two-level logistic regression model showed increased risk for ocular-nasal symptoms (OR = 11.4, 95%CI(2.15,60.8), p = 0.004).

Totally seven factors were found from the factor analysis (Table S6): the first factor included total mold, viable mold, and 1-butanol; the second factor included viable bacteria, 2-methyl-1-butanol and 3-methyl-1-butanol; the third factor comprised cat allergen Fel d 1, HDM allergen Der p 1 and Texanol; the fourth factor comprised isobutanol, 2-heptanone, 2-hexanone, 3-octanone, 1-octen-3-ol, 2-ethyl-1-hexanol, and TXIB; the fifth factor involved 2-pentanol and isobutyl acetate; the sixth factor consisted ethyl isobytyrate, ethyl-2-methylbutyrate and dimethyl disulphide; and the seventh factor comprised 2-pentylfuran and 1-octen-3-ol. Total bacteria, HDM allergen Der f 1, 3-methylfuran, and formaldehyde were not included in any factor.

4. Discussion

The present study has demonstrated that microbial organisms, allergens, and VOC in the home environment may impair tear film stability, and can be associated with oculo-nasal symptoms and rhinitis among adults. An increased level of total mold was associated with oculo-nasal symptoms, and an increased level of viable bacteria was associated with allergic rhinitis. Indoor allergen exposures (Fel d 1 from cat, and Der p 1, Der f 1 from HDM) were related to oculo-nasal symptoms. A higher level of 2-hexanone was linked to lower SBUT. 3-Methylfuran, 2-hexanone, 1-octen-3-ol and 2-heptanone were associated with oculo-nasal symptoms. Moreover, 3-octanone and formaldehyde were related to allergic rhinitis. The associations between 2-heptanone and oculo-nasal symptoms, and between isobutyl acetate and allergic rhinitis were more pronounced in women. The negative association between 2-hexanone and SBUT was more pronounced among atopics. Non-atopics were more sensitive to indoor viable bacteria and Der f 1.

4.1. Indoor mold/bacteria associated with oculo-nasal symptoms and allergic rhinitis

In our study, oculo-nasal symptoms were more common among occupants in homes with increased air levels of total mold, and allergic rhinitis was more common in homes with increased air levels of viable bacteria. We found two previous studies on measured microorganisms in homes and eye symptoms. One study from Japan reported that higher *Aspergillus* level in newly built dwellings was related to increased eye symptoms among occupants [13]. One study from the US found that adults exposed to higher number of indoor microbial colonies (fungi and bacteria) at home had more often dry eye symptoms [20]. One study quantifying indoor mold at home using a DNA-based method suggested that higher environmental relative moldiness index was related to adult rhinitis [11]. Moreover, a positive association between microbial colonies and dry eye symptoms has been shown in one experiment study [21]. Our study provides new evidence on the adverse impact of indoor airborne microbial exposure in the home environment on adult oculo-nose symptoms and allergic rhinitis. Allergens from indoor mold as well as MVOC emitted by indoor microorganisms could have caused the negative health effects.

4.2. Indoor allergens associated with oculo-nasal symptoms

Subjects exposed to increased levels of allergen Fel d 1 (from cat), and allergen Der p 1 and Der f 1 (from HDM) in bed dust reported more oculo-nasal symptoms in the present study. We found no previous research on indoor allergens in dust in relation to adult ocular symptoms in homes. However, one study from Japan found that increased allergen from HDM (Der p 1 and Der f 1) measured in newly built dwellings was related to occupants' nasal symptoms [13]. Moreover, a study from Norway reported that an increased level of Der p 1 in mattress dust was linked to an increased risk of current rhinitis among girls [44]. Our results indicated that reduced indoor concentrations of allergens can potentially relieve symptoms on the eyes and nose.

Table 4
Indoor levels of mold, bacteria, allergens, and VOC associated with SBUT, oculo-nasal symptoms in the last three months, and allergic rhinitis.

Exposures		SBUT[a]	p	Oculo-nasal symptoms[b]	p	Allergic rhinitis[b]	
Mold/bacteria[c]	Total mold	−8.40 (-17.5,0.73)	0.071	4.74(1.09,20.6)	**0.038**	0.85(0.23,3.05)	0.799
	Viable mold	−4.72 (-11.2,1.77)	0.154	2.42(0.83,7.07)	0.107	0.77(0.30,1.94)	0.578
	Total bacteria	−2.32 (-8.45,3.80)	0.457	1.27(0.44,3.68)	0.662	1.15(0.50,2.63)	0.745
	Viable bacteria	−2.22 (-7.32,2.89)	0.395	1.29(0.55,3.04)	0.554	2.49(1.19,5.20)	**0.015**
Allergens in indoor dust[c]	Fel d 1	−0.75 (-2.96,1.46)	0.508	1.44(1.01,2.07)	**0.045**	0.96(0.71,1.30)	0.782
	Der p 1	−0.52 (-4.23,3.20)	0.784	1.99(1.17,3.41)	**0.012**	1.24(0.76,2.02)	0.389
	Der f 1	0.93(-2.80,4.67)	0.625	1.83(1.04,3.23)	**0.036**	1.00(0.62,1.59)	0.984
VOC[c]	3-Methylfuran	0.62(-4.82,6.05)	0.824	5.83(1.83,18.5)	**0.003**	1.00(0.48,2.07)	0.992
	Isobutanol	2.72(-4.73,10.2)	0.474	1.71(0.50,5.82)	0.391	1.58(0.60,4.13)	0.352
	1-Butanol	1.43(-5.86,8.72)	0.700	2.65(0.74,9.44)	0.133	1.79(0.66,4.82)	0.252
	2-Pentanol	−0.96 (-5.57,3.64)	0.682	1.37(0.44,4.30)	0.584	1.28(0.70,2.32)	0.419
	Dimethyldisulphide	−0.16 (-3.37,3.05)	0.921	1.11(0.65,1.90)	0.707	1.04(0.69,1.56)	0.854
	2-Hexanone	−8.54(-16.5,-0.54)	**0.036**	6.24(1.12,34.9)	**0.037**	0.84(0.29,2.41)	0.747
	2-Heptanone	0.26(-7.64,8.16)	0.948	6.02(1.36,26.6)	**0.018**	1.59(0.54,4.67)	0.400
	1-Octen-3-ol	−3.85 (-10.4,2.72)	0.251	9.51(2.45,37.0)	**0.001**	1.25(0.52,3.01)	0.621
	3-Octanone	−6.24 (-17.6,5.10)	0.281	5.29(0.62,45.2)	0.128	5.58(1.01,31.0)	**0.049**
	Ethyl isobytyrate	2.09(-2.75,6.93)	0.397	0.90(0.38,2.10)	0.800	1.15(0.63,2.12)	0.646
	Ethyl-2-methylbutyrate	0.66(-2.77,4.08)	0.707	1.23(0.69,2.20)	0.474	0.99(0.64,1.55)	0.979
	2-pentylfuran	−1.83 (-6.50,2.83)	0.441	1.80(0.75,4.31)	0.189	0.82(0.44,1.53)	0.540
	2-Ethyl-1-hexanol	−1.70 (-11.1,7.65)	0.721	1.39(0.25,7.55)	0.705	1.09(0.32,3.75)	0.889
	Formaldehyde	0.02(-8.95,9.00)	0.996	3.74(0.76,18.3)	0.105	3.63(1.07,12.4)	**0.039**
	2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (TMPD-MIB)	0.62(-3.73,4.97)	0.781	1.40(0.50,3.93)	0.517	1.33(0.79,2.26)	0.286
	2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TMPD-DIB)	3.84(-2.62,10.3)	0.244	0.78(0.26,2.30)	0.652	0.94(0.42,2.13)	0.890

Bold values indicate $p < 0.05$.
[a] Two-level linear mixed regression models (individual, center). The Beta(95%CI) was adjusted for gender, age, BMI, and current smoking.
[b] Two-level logistic regression models (individual, center). The OR(95%CI) was adjusted for gender, age, BMI, and current smoking.
[c] Log transformed exposure data (log base 10) were used in statistic models. The Beta/OR values were expressed as per 1 unit increase of a specific exposure.

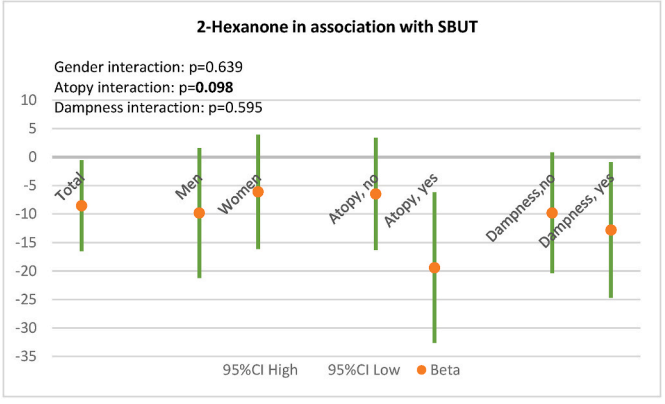

Fig. 2. 2-Hexanone associated with SBUT, stratified for gender (men/women), atopy (no/yes), and dampness (no/yes). Log-transformed data on 2-hexanone (log base 10) were used in the statistic models. The Beta values were expressed as per 1 μg/m^3 increase in indoor level of 2-hexanone. Bold value indicates p for interaction<0.1.

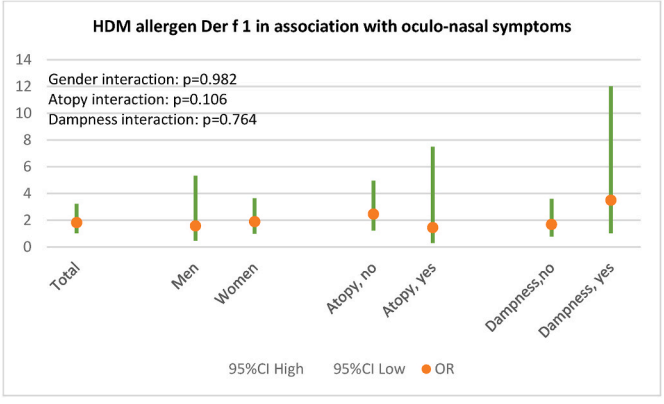

Fig. 3. HDM allergen Der f 1 associated with oculo-nasal symptoms, stratified for gender (men/women), atopy (no/yes), and dampness (no/yes). Log-transformed data on Der f 1 (log base 10) were used in the statistic models. The OR values were expressed as per 1 μg/g increase of the indoor level of Der f 1.

4.3. 3-Methylfuran associated with oculo-nasal symptoms

Exposed to 3-methylfuran was shown to be related to oculo-nasal symptoms in the present study. Subjects exposed to (1 mg/m^3) 3-methylfuran had increased blinking frequency and increased levels of myeloperoxidase and lysozyme (lavage biomarkers) according to one

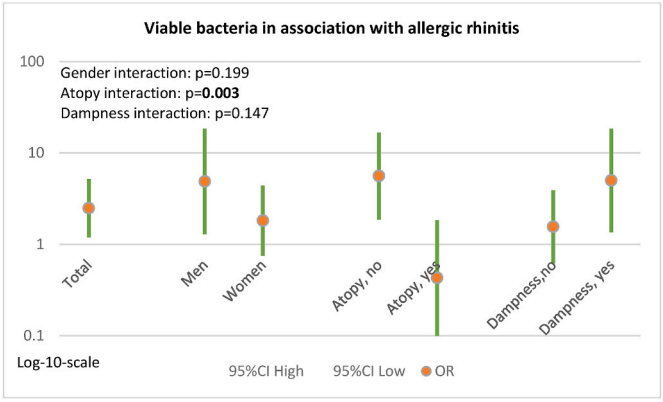

Fig. 4. Viable bacteria associated with allergic rhinitis, stratified for gender (men/women), atopy (no/yes) and dampness (no/yes). Log-transformed data on viable bacteria (log base 10) were used in the statistic models. The OR values were expressed as per 1 CFU/m^3 increase in the indoor level of viable bacteria. Bold value indicates p for interaction<0.1.

experiment chamber study [45]. We found no previous research conducted in home environment regarding this compound and ocular/nasal symptoms. The compound 3-methylfuran is a commonly reported VOC associated with microbial growth in living environments [31,46]. Our study provided new evidence of the negative health effect of 3-methylfuran from a real world setting.

4.4. 2-Heptanone associated with oculo-nasal symptoms

We found that an increased level of 2-heptanone in dwellings was related to oculo-nasal symptoms. We found no existing studies regarding this compound and ocular/nasal symptoms. Experimental studies suggested that 2-heptanone is one main metabolite produced by a combination of fungi proliferating on building materials [47,48]. One review indicated that this compound was one common volatile associated with microbial growth in indoor environments [31]. Thus, removing indoor dampness and mold in homes could reduce the exposure of this compound.

4.5. 1-Octen-3-ol associated with oculo-nasal symptoms

A higher concentration of 1-octen-3-ol in dwelling was linked to reporting of oculo-nasal symptoms in homes in our study. This aligns with findings from a Japanese study which indicated that residents exposed to elevated concentrations of 1-octen-3-ol in homes had more conjunctivitis and allergic rhinitis [16]. Several mold species found in buildings have the capability to generate1-octen-3-ol [49] and this compound is indicated in one review to be one most commonly reported MVOC in living environment [31]. The compound was reported to be related to mold status in indoor environments [50]. As previous research suggested, indoor mold exposure could be the source of 1-octen-3-ol. Our analysis adds new evidence of the negative impact of the compound on eyes and nose.

4.6. 3-Octanone associated with allergic rhinitis

Allergic rhinitis was more common among subjects with increased exposure to 3-octanone in the present study. There is no prior research regarding the impact of 3-octanone on allergic rhinitis. It is concluded in one review that 3-octanone is among the primary MVOC found in the living environment [31].

4.7. 2-Hexanone associated with reduced tear film stability and oculo-nasal symptoms

In our study, 2-hexanone was associated with shorter SBUT and more common oculo-nasal symptoms. We found no existing studies evaluating 2-hexanone in connection with ocular/nasal symptoms. The compound 2-hexanone is one commonly reported VOC related to microbial growth in living environment [31]. Moreover, it is sometimes used as a general solvent in paints [51,52].

4.8. Formaldehyde associated with allergic rhinitis

Our findings indicated an association between formaldehyde and allergic rhinitis. This is in agreement with two other studies conducted on homes. Increased levels of formaldehyde found in newly built houses in Japan were related to nose symptoms among residents [14]. A study from the US reported a positive dose-response relationship between formaldehyde in dwellings and nasal symptoms among occupants [19]. Moreover, it was shown in one toxicological chamber study that subjects exposed to 0.5 mg/m^3 formaldehyde after 2-h experienced transient rhinitis symptoms [53]. Formaldehyde can come from different indoor sources, such as pressed wood products, glues, and paints as well as combustion sources and tobacco smoke [51].

4.9. Health effects associated with gender and atopy

The associations between 2-heptanone and oculo-nasal symptoms, and between isobutyl acetate and allergic rhinitis were more pronounced in women. The negative association between 2-hexanone and SBUT was more pronounced among atopics, and the positive associations between viable bacteria and allergic rhinitis and between Der f 1 and oculo-nasal symptoms were more pronounced among non-atopics. We conclude that future studies should investigate the health effects of VOC separately among males and females and sensitized- and non-sensitized subjects.

4.10. Strengths and limitations

This is one of few multicentre studies investigating measured indoor exposures in the home environment and oculo-nasal symptoms and rhinitis. Participants were randomly recruited from three cities in Northern Europe. Objective measurements of indoor mold, bacteria, allergens, and a number of VOC were performed. Factor analysis could identify four factors (the fourth, fifth, sixth, and the seventh factor), which included most of the VOC we studied. Our study adds new evidence of the potential negative impacts of several VOC on symptoms on eyes and nose in a real world setting. Some limitations should be addressed. The number of participants was relatively small which led to limited power of the study. Increased levels of four VOC, including 3-methylfuran, 2-hexanone, 1-octen-3-ol, and 2-heptanone were all associated with oculo-nasal symptoms in our study. Moreover, formaldehyde was correlated with isobutanol, 1-butanol, 2-hexanone, 1-octen-3-ol and 2-heptanone in our study. However, mutual adjustment models could not be performed due to strong correlations between those compounds. Thus, sometimes we cannot separate the health effects of single compounds. Moreover, VOC was only sampled for 3 h, which means that the sampled VOC may not well represent the long-term exposure of VOC in those inspected homes. However, it would most likely lead to non-differential misclassification (random error causing reduced statistical power).

5. Conclusion

Indoor biological exposures, including total mold, viable bacteria, allergen Fel d 1 from cat, and allergen Der p 1 and Der f 1 from HDM in homes can be associated with oculo-nasal symptoms or allergic rhinitis.

Occupants exposed to some indoor VOC including 3-methylfuran, 2-heptanone, 2-hexanone, 1-octen-3-ol, 3-octanone, and formaldehyde may reduce tear film stability, and can be associated with oculo-nasal symptoms or allergic rhinitis. Associations between some VOC and oculo-nasal symptoms or allergic rhinitis can be stronger among females and atopics.

CRediT authorship contribution statement

Juan Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christer Janson:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Thorarinn Gislason:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Maria Gunnbjörnsdottir:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Rain Jogi:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Hans Orru:** Writing – review & editing, Validation, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Dan Norbäck:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.buildenv.2024.111923.

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