



Volatile organic compounds of possible microbial origin and their risks on childhood asthma and allergies within damp homes



Hyunok Choi^{a,*}, Norbert Schmidbauer^b, Carl-Gustaf Bornehag^{c,d}

^a Department of Environmental Health Sciences, University at Albany, School of Public Health, State University of New York, United States

^b Norwegian Institute for Air Research, PO Box 100, 2027 Kjeller, Instituttveien 18, 2007 Kjeller, Norway

^c Technical Research Institute of Sweden, Box 857, SE-501 15 Borås, Sweden

^d Department of Public Health Sciences, Karlstad University, SE-651 88 Karlstad, Sweden

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ABSTRACT

Background: Risk of indoor exposure to volatile organic compounds of purported microbial origin on childhood symptoms of wheezing, rhinitis, and/or eczema, and doctor-diagnosed asthma, rhinitis, and eczema, respectively, remain unclear.

Objective: To test hypotheses that total sum of 28 microbial volatile organic compounds ($\Sigma 28$ MVOCs): 1) poses independent risk on doctor-diagnosed asthma, rhinitis, and eczema, respectively, as well as multiple symptom presentation with a minimum of the two of the above conditions (i.e. case); 2) is associated with significant interaction with absolute humidity (AH) on additive scale.

Methods: In a case-control investigation, 198 cases and 202 controls were examined during November 2001 – March 2002 period through home indoor air sampling, air quality inspection, and health outcome ascertainment.

Results: Not only the $\Sigma 28$ MVOCs but also the global MVOC index were significantly higher within the homes of the cases with a high AH, compared to the controls with a low AH (all P s < 0.001). Only the cases, but not the controls, were associated with a dose-dependent increase in the exposure variables of interest ($\Sigma 28$ MVOCs) per quartile increase in AH (P < 0.0001 for the cases; P = 0.780 for the controls). Only among the children who live in a high AH homes, a natural log (ln)-unit of $\Sigma 28$ MVOCs was associated with 2.5-times greater odds of the case status (95% CI, 1.0–6.2; P = 0.046), compared to 0.7-times the odds (95% CI, 0.4–1.0; P = 0.074) of the same outcome among the low AH homes. Specifically, joint exposure to a high MVOCs and high AH was associated with 2.6-times greater odds of the doctor-diagnosed asthma status (95% CI, 0.7–8.91; P = 0.137).

Conclusion: Joint occurrence of high $\Sigma 28$ MVOCs and AH was associated with a significant increase in the case status and asthma risks in an additive scale.

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1. Introduction

Microbial volatile compounds (MVOCs) refer to a group of gaseous compounds, which are argued to be emitted during metabolic digestions by microbes (Korpi et al., 2009; Thrasher and Crawley, 2009; Van Lancker et al., 2008). Ever since their discovery during the 1990s,

Abbreviations: $\Sigma 28$ MVOCs, Total sum of 28 purported microbial volatile organic compounds; aOR, adjusted odds ratio; BBzP, Benzylbutyl phthalate; DBH, Dampness in Building and Health; DEHP, di-(2-ethylhexyl)phthalate; ETS, environmental tobacco smoke; MVOC, microbial volatile organic compound; NILU, Norwegian Institute for Air Research; OR, odds ratio; PFT, perfluorocarbon tracer; PVC, polyvinyl chloride; RERI, relative excess risk due to interaction; TMPD-MIB, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate; TMPD-DIB, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate; VOC, volatile organic compound; 95% CI, 95% confidence interval.

* Corresponding author at: One University Place, Rm 153, Rensselaer, NY 12144-3456, United States.

E-mail addresses: hchoi@albany.edu (H. Choi), ns@nilu.no (N. Schmidbauer), Carl-Gustaf.Bornehag@kau.se (C.-G. Bornehag).

MVOCs have been proposed as sentinel markers of microbial infestation on hidden building surfaces (Wilkins and Larsen, 1995). At the same time, MVOCs may be a misnomer because, a growing body of evidence suggest that they are produced by not only by microbes, but also by synthetic building materials (Choi et al., 2016; Kim et al., 2007; Korpi et al., 2006; Malysheva et al., 2014; Matysik et al., 2008; Sahlberg et al., 2013; Schuchardt and Strube, 2013). Synthetic sources include recently painted indoor surfaces (Järnström et al., 2008), cleaning agents, automobile emissions (Nalli et al., 2006; Singer et al., 2006). Human behavior choices within indoor space, such as cigarette smoking, cooking, closing windows, also contribute to the generation of the putative MVOCs (Korpi et al., 2009; Newsome et al., 1965; Schleibinger et al., 2008). For example, professional building painters are exposed to a high concentration of 1-octen-3-ol, well-known MVOC, in conjunction with glycol ethers and other plasticizers, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (TMPD-MIB) (Wieslander and Norback, 2010). On the other hand, laboratory experiments on microbial cultures

on common building materials under various humidity levels have failed to produce clear VOC markers of microbial growth (Korpi et al., 1998; Schleibinger et al., 2008).

Indoor human exposure to putative MVOCs represents a growing public health concern in not only developed, but also developing countries for at least two reasons. First, some purported MVOCs, such as 1-octen-3-ol and 2-pentanol are significantly associated with ocular and nasal mucosa irritation (Elke et al., 1999; Wälinder et al., 2008), asthma and respiratory symptoms, including nocturnal breathlessness in children (Kim et al., 2007), allergic rhinitis (Araki et al., 2012), and sick building syndrome (Araki et al., 2010; Takeda et al., 2009), enhanced nasal lavage-myeloperoxidase and nasal patency reduction in a group of house painters (Wieslander and Norback, 2010), respectively. Human exposure to MVOCs under controlled setting could elicit eye and respiratory irritations and discomfort (Wälinder et al., 2008). Second, MVOCs occur at a higher concentration within damp spaces or those with a history of water damage, compared to the non-damp indoor spaces (Choi et al., 2016; Wieslander et al., 2007). As an estimated 25–50% of the residences in US and in Europe are damp (Lanthier-Veilleux et al., 2016), residents within damp indoor environments are likely to be exposed to MVOC mixture for an extended period (Araki et al., 2012; Araki et al., 2010).

To date, the toxicological properties of many compounds commonly accepted as MVOCs remain unknown (Korpi et al., 2009). Only a handful of studies have examined chronic exposure to MVOC within the home environment and their effects on respiratory health status (Araki et al., 2012; Billonnet et al., 2011; Choi et al., 2010; Sahlberg et al., 2013). While preliminary evidence suggest that joint effect of a complex mixture of the putative MVOCs could be synergistic (Cometto-Muñiz et al., 1997; Korpi et al., 1999), the combined risk of the putative MVOC mixture has never been systematically investigated, particularly in children. As such, there is a critical knowledge gap regarding childhood exposure to MVOCs and their role in asthma initiation and/or exacerbation.

Within the Dampness in Building and Health (DBH) study, we have investigated the indoor sources of 28 putative MVOCs (Choi et al., 2016). Here, we examine the same group of compounds: 1) for the independent risk of the total MVOC concentration on multiple symptoms of wheezing, rhinitis, and/or eczema (i.e., case status), as well as respective doctor-diagnosed status of asthma, rhinitis, and eczema; and 2) modification of MVOC risk by a composite index of absolute humidity. We test a hypothesis that the total concentration of 28 MVOCs ($\Sigma 28$ MVOCs) is associated with a significantly larger risk within the damp homes on our health outcomes of interest, compared to the non-damp homes.

2. Material and methods

The participant enrollment and methods of an on-going Dampness in Buildings and Health (DBH) study have been described (Bornehag et al., 2004; Bornehag et al., 2005a; Bornehag et al., 2003a; Bornehag et al., 2005b; Bornehag et al., 2003b; Bornehag et al., 2005c; Choi et al., 2010; Holme et al., 2010). Present analysis focuses on Phase II case-control study ($n = 400$).

2.1. Health outcome measurements

The Phase II study incorporates both cross-sectional and nested components within its exposure assessment strategy. The nested component incorporate Phase I (March–April 2000) as well as the Phase II surveys (November 2001 – March 2002) within a case definition (Hasselgren, 2005). Specifically, four health outcomes are considered. To qualify as a ‘case’, parental reporting of a minimum of two symptoms of wheezing, rhinitis, and/or eczema without a cold within the last 12 months within two repeated surveys (Phase I and II) across 1.5-year period was required. Additional clinical examination was conducted to validate current clinical conditions of asthma ($n = 121$), rhinitis

($n = 99$), and eczema ($n = 129$), respectively. Diagnostic criteria for asthma include: a) at least three wheezing episodes prior to or since age 2; b) an observation of wheezing in addition to other atopic diseases; c) asthma medication use at any age; and d) clinical validation of asthma symptoms at any age. Diagnostic criteria for rhinitis required: a) ever having allergic rhinitis symptoms without a cold; b) mucosal tearing and/or watering symptoms following a contact with furred animals or pollen; c) present use of rhinitis medication. Eczema case definition required that the child have at least six months of remitting itching and redness in common body locations. For the control children, only those whose parent reported an absence of any allergy symptoms during both Phases I and II were invited. The controls were recruited from 1100 children, who are free of wheezing, rhinitis, and/or eczema, registered within local primary care clinics. The doctor-diagnosed cases represent subset of the questionnaire-based cases. That is, the cases children who do not meet the diagnostic criteria of given outcome were excluded ($n = 77$ for asthma; 99 for rhinitis; and 69 for eczema).

The cases and controls were further excluded if: (i) the home was renovated or remodeled due to water damage; and (ii) family relocated to a new residence between phase I and II. The medical examinations of the 400 children as well as the air, dust sample collection, and home inspection were completed concurrently during November 2001 and March 2002 period. A team of four pediatricians, allergists, and nurse practitioners examined all children following a structured anamnesis (Hederos et al., 2007). Allergy positive status was examined by screening the children's blood sample for IgE antibodies to 10 airborne allergens (Phadiatop®, Pharmacia & Upjohn Diagnostics, Uppsala, Sweden), including timothy, mugwort, birch, cat, horse, dog, house dust mites (*D. pteronyssinus* and *D. farinae*), and two mold genera (*Penicillium* and *Cladosporium*). The IgE-positive status was defined using a cut-off value at 1.2 kUA/l. Institutional ethical committee in Örebro, Sweden, approved the study.

2.2. Home exposure assessment by professional inspectors

Cross-sectional exposure assessment component include biological and air and dust samples sample collection as well as a comprehensive walk-through home inspections at the time of health outcome ascertainment (Choi et al., 2014). Average ventilation rate was measured in the room in which the index child spent most time, using validated perfluorocarbon tracer (PFT) technique (Nordtest, 1997; Stymne et al., 1994). Within the same location, temperature (°C) and relative humidity (%) were also measured instantaneously (VL2000 Temperature & Humidity Sensor, Vaisala, Helsinki, Finland) and continuously at every hour for a week (Mitec Satellite-TH, Mitec Instrument AB, Säffle, Sweden).

2.2.1. Air monitoring

The inspectors collected an air sample with SKC pocket pumps (Model 210-1002, SKC Blandford, Dorset, UK) in child's bedroom at 80 ml/min for 60 to 90 min (5 to 8 l) through Perkin Elmer adsorption tubes (glass, 300 mg Tenax TA). Sampling was conducted in a manner consistent with the family's lifestyle and habits in all children's homes. In order to monitor the extent of water damage, windows and doors were maintained shut during air sampling in the homes of cases and the controls. Samplers were placed 1 m above the floor in the room. Upon completion, the sampler was sealed with PTFE stoppers, shipped, and analyzed in Norway Institute for Air Research Norway within two weeks of collection. Use of adsorbent, preparation of adsorbent tubes, sampling equipment, sampling flow and safe sampling volumes, analytical methods, and analytical equipment follow international standards on ambient air quality DIN EN 14662-1 (DIN ISO 5725-2 and 3) with demonstrated reliability (Wu et al., 2004). Temporal reliability of Tenax TA for indoor air analysis was discussed elsewhere (Helmig, 1996; Klenø et al., 2002; Uhde, 2009).

2.3. Laboratory analysis

The VOC samples were analyzed using an automated thermo desorption unit (Perkin Elmer ATD 400, PerkinElmer Inc., Waltham, MA, USA) followed by GC–MS (Helmig, 1996; Klenø et al., 2002; Uhde, 2009). The samples were desorbed at 250 °C—refocused on a Tenax TA cold trap held at minus 30 °C and transferred to the GC–MS at 225 °C. A Hewlett Packard G 1800 A GC–MS was used as detector maintained at 250 °C. The separation column (DB-1701, 32 m length, 1 mm film, 0.32 mm id) was programmed from 40 to 250 °C. The mass range of the detector was from mass 33 to 350.

2.3.1. Detection and identification

From the Total Ion Chromatogram, the 50 peaks with the largest area were used for further identification routines (Helmig, 1996; Klenø et al., 2002; Uhde, 2009). An automated mass spectra library check (Wiley) was giving the first preliminary identification results. Each of the library suggestions for component identification were then again cross checked against Norwegian Institute for Airway Research (NILU)'s database for indoor air pollutants which contains about 1000 components. The database contains retention time indexes from compounds which were identified in indoor air samples at NILU on exact the same analytical system over the last 20 years. Most of the compounds within this database have been verified by direct injection of pure standard solutions or mixed standard solutions. The criteria for identification were over 80% confidence match from the mass spectra library and a match to the retention time database within 5 s of relative retention together with a manual check of the retrieved mass spectrogram against the library mass spectrogram. If a peak did not meet those criteria it was named as "unidentified compound". In every sample the 50 compounds with the highest concentrations were reported as Toluene-equivalents. In addition, the number of all compounds within each sample with a concentration above a baseline-threshold of 0.1 ppb (usually between 180 and

250 compounds) and the concentration-sum of all those compounds were reported (Helmig, 1996; Klenø et al., 2002; Uhde, 2009).

2.3.2. Calibration

The calibration was based on toluene equivalents (Helmig, 1996; Klenø et al., 2002; Uhde, 2009). Ten samples were run together with two standard injections before and after each series. Internal standards consisted of a solution containing 100 ng/ml of benzene, toluene, ethylbenzene and xylenes in methanol (Helmig, 1996; Klenø et al., 2002; Uhde, 2009). Standard Tenax tubes were prepared by syringe onto the adsorbent followed by 5 min of dry nitrogen (20 ml).

2.4. Statistical analysis

Demographic traits and residential characteristics of the cases and controls were described elsewhere (Bornehag et al., 2004; Bornehag et al., 2005b; Bornehag et al., 2005c). Valid value of at least one VOC measurement was observed within 377 of 390 homes (97%). Number of earlier investigations have noted that the detected VOC concentrations are influenced by the sensitivity of the analytical method as well as the prevalence of given compound (Billonnet et al., 2011; Choi et al., 2010; Edwards et al., 2005; Jurvelin et al., 2001). In the present investigation, we too observed that the prevalence and concentration distribution of 28 purported MVOCs were overall sparse and low (Table 1). As shown in Fig. S1, there was no significant association between % detected MVOC with the median concentration (Spearman's ranked agreement = −0.41; P-value = 0.10). For the compounds in which >95% samples were below the detection limit, we report 90th percentile and maximum concentrations. The non-detects were estimated as 1/2 value of respective LOD (Hornung and Reed, 1990).

Considering the sparsity of detected MVOCs, we considered Σ 28 MVOCs, rather than the individual compounds, as primary quantitative marker of exposure, consistent with dose/concentration addition (CA)

Table 1
Concentration distribution of the 28 purported MVOCs ($\mu\text{g}/\text{m}^3$).

	CAS #	Controls						Cases					
		% ND ^a	Mean	ASD ^b	Percentiles		Max	% ND ^a	Mean	ASD ^b	Percentiles		Max
					50th	90th					50th	90th	
β -myrcene	123-35-3	80	2.88	2.01	2.30	6.13	9.26	89	3.31	1.68	3.09	6.22	6.80
Verbenone	80-57-9	84	4.03	3.01	2.83	7.42	14.00	91	3.28	1.82	3.42	5.58	7.72
Cyclohexanol, 2-(1,1-dimethylethyl)-, cis-	7214-18-8	87	8.30	9.06	4.90	20.62	43.02	90	5.09	4.41	3.44	11.48	18.86
Terpinolene	586-62-9	90	4.93	2.95	4.16	9.34	13.21	93	3.62	1.69	3.43	6.50	7.30
Bornyl acetate	76-49-3	93	5.62	5.13	3.93	15.39	19.60	91	5.54	3.70	4.92	12.41	15.16
2-Pentylfuran	3777-69-3	96	3.57	2.80	3.35		9.14	92	4.12	1.27	4.04	6.01	6.61
1-Pentanol	71-41-0	96	2.48	1.14	2.31		4.91	96	4.41	2.31	4.68		7.11
2-Methyl-1-propanol	78-83-1	94	2.76	2.20	1.89	7.19	7.88	96	2.32	2.12	1.72		6.46
Camphor	464-49-3	95	3.42	1.90	2.61	7.11	7.47	96	5.08	5.65	2.35		14.93
Camphene	79-92-5	96	5.82	4.85	4.91		16.35	97	5.80	3.76	6.09		11.11
6-Methyl-5-heptene-2-one	110-93-0	98	3.23	0.83	2.95		4.48	97	4.61	1.18	4.97		5.86
Linalyl acetate	115-95-7	98	1.68	0.88	1.77		2.73	97	3.32	1.48	3.08		5.16
Sabinene	3387-41-5	98	3.60	3.00	2.39		8.80	97	4.00	2.84	3.61		9.18
2-Heptanone	110-43-0	98	2.52	1.25	1.95		4.62	98	2.49	0.43	2.24		2.98
3-Methyl-1-butanol	123-51-3	98	4.53	4.06	2.42		10.90	98	3.46	3.06	1.98		8.05
Isoterpinolene	586-63-0	98	4.15	2.06	4.21		6.08	98	3.48	1.05	3.30		4.61
β -phellandrene	555-10-2	98	2.60	1.67	1.98		5.06	100					
Butanoic acid, 3-methylbutyl ester	106-27-4	99	1.76	0.19	1.76		1.89	99			2.83		
γ -Terpinene	99-85-4	99	3.04	0.31	3.04		3.26	99			2.38		
1-Octene-3-one	4312-99-6	100						99			5.03		
2-Hexanone	591-78-6	100			4.74			100					
2-Methylfuran	534-22-5	100						99			1.45		
2-Pentanone	107-87-9	100			0.95			100					
α -Terpinene	99-86-5	100			25.21			100					
α -Phellandrene	99-83-2	100			8.48			100					
Estragole	140-67-0	100			1.96			100					
Isobornyl acetate	125-12-2	100						99			4.28		
Fenchone	1195-79-5	100			1.51			100					

– = Mean, ASD and 90th percentile are not reported if detected in <2% of samples.

^a Percentage of samples in which compound was not detected.

^b Arithmetic standard deviation.

approach taken for PGE analysis (Choi et al., 2010; Orton et al., 2014). For CA approach, total Σ 28 MVOC concentration was natural-log (ln) transformed due to their highly skewed distribution to the right (Kolmogorov-Smirnov tests < 0.05). We estimate mean, geometric mean, arithmetic standard deviation, 90th percentile, and maximum concentration. Our preliminary linear trend suggested non-linear association between Σ 28 MVOCs and the case status. As a result, we created global MVOC index. The global index was calculated by categorizing individual MVOC concentrations into binary variables using the 3rd quartile concentration as the cut-off value for high vs. low concentrations. Resulting individual compound indices were added to create a continuous variable, ranging between 0 and 28. The global VOC index indicates the number of MVOC compounds in the house with an elevated concentration. MVOC and absolute humidity were also coded as dichotomous variables, by considering the 4th quartile concentration as the cut-off value ($9.12 \mu\text{g}/\text{m}^3$ for MVOCs and $2.95 \text{ g}/\text{m}^3$ for absolute humidity). Jonckheere–Terpestra test was used to assess a linear trend in Σ 28 MVOCs with $\alpha = 0.05$.

2.4.1. Model selection

Our earlier analysis identified a large list of potential risk factors for asthma and allergy outcomes (Bornehag et al., 2004; Bornehag et al., 2005b; Bornehag et al., 2005c; Choi et al., 2014; Choi et al., 2010). In order to ensure adequate adjustment for potential confounders while precluding a chance of over-adjustment, we step-wisely reduced the largest initial model through hierarchical backward elimination strategy (Kleinbaum and Klein, 2002). The initial logistic regression model included following predictors: history of flooding/water damage at home, in conjunction with a use of PVC-based flooring material in the child's room; PVC-based wall material; (ln)-transformed concentrations of TMPD-MIB; and (ln) diethylhexyl phthalate (DEHP) and butylbenzyl phthalate (BBzP) in the dust sample. The largest initial model for respective outcome was backwardly reduced if the term under consideration was associated with a significant $-2 \log$ likelihood value under the χ^2 distributions with $\alpha = 0.05$ than that without the term. All effect modification term with variance inflation factor ≥ 30 was removed from the model. In the final models, the highest variance inflation factor was ≤ 10 , suggesting stability of the estimates. The final logistic regression models of the multiple allergy outcome account for the gender, secondhand smoke exposure at home, allergic disease in both parents (Bornehag et al., 2005c; Choi et al., 2010).

2.4.2. Test for interaction on an additive scale

We tested for combined effect of Σ MVOC and AH as departure from additivity of risk (Ahlbom and Alfredsson, 2005). The additivity of risk was considered for a total concentration as well as the global indices for MVOCs. The Relative Excess Risk due to Interaction (RERI) was calculated as shown below:

$$\text{RERI} = \text{OR}_{A+B+} - \text{OR}_{A+B-} - \text{OR}_{A-B+} + 1 \quad (1)$$

where $A + B +$, $A + B -$, $A - B +$, stand for $\text{AH} \geq 2.95 \text{ g}/\text{m}^3$ & $\Sigma 28 \text{ MVOCs} \geq 9.12 \mu\text{g}/\text{m}^3$, $\text{AH} \geq 2.95 \text{ g}/\text{m}^3$ & $\Sigma 28 \text{ MVOCs} < 9.12 \mu\text{g}/\text{m}^3$; and $\text{AH} < 2.95 \text{ g}/\text{m}^3$ & $\Sigma 28 \text{ MVOCs} \geq 9.12 \mu\text{g}/\text{m}^3$, respectively. Attributable Proportion (AP) was calculated as:

$$\text{AP} = \frac{\text{RERI}}{\text{OR}_{A+B+}} \quad (2)$$

Synergy index (S) was calculated as:

$$S = \frac{\text{OR}_{A+B+} - 1}{(\text{OR}_{A+B-} - 1) + (\text{OR}_{A-B+} - 1)} \quad (3)$$

All analyses were performed with SPSS version 20.0.1 for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Descriptive analysis

Table 1 shows concentration distribution of 28 purported MVOCs according to the case-control status. When we further stratify them according to the median absolute humidity ($\geq 2.157 \text{ g}/\text{m}^3$), the mean concentration of Σ 28 MVOCs were significantly higher for the cases from the homes with a high absolute humidity (AH), compared to the controls from low AH homes (P-value < 0.0001 , results not shown).

Table 2 shows the pattern of the central tendencies in main exposure variables of interest (i.e. $\Sigma 28 \text{ MVOCs}$ and global MVOC index), potential confounders (i.e. TMPD-MIB, BMI, age, history of repainting at least one room, atopy history in both parents, gender, and mold index), and/or effect modifiers (i.e. ventilation rate, temperature, self-reported home cleaning frequency) between the cases and the controls, stratified according to the home indoor AH. Not only the Σ 28 MVOCs but also the global MVOC index were significantly higher within the homes of the cases with a high AH (all Ps < 0.001 , Table 2). The case children who live in home with a high AH were associated with a significantly reduced ventilation rate, compared to control children who live in non-damp homes (P < 0.001 , Table 2). Even though it was not significant, the prevalence of indoor re-painting history was 20% higher among the case children with a high AH, compared to the controls from low AH homes (P > 0.05). Furthermore, a higher proportion of the case families from high AH homes reported wet-cleaning their home at least once/week, compared to the control families with low AH (50% vs. 23%; P < 0.001). Other risk factors (i.e., BMI, age, gender, temperature, and mold index) were not associated with a linear increase according to the indoor dampness and the case status (Table 2).

As shown in Table 3, only the cases were associated with a dose-dependent increase in the exposure variables of interest ($\Sigma 28 \text{ MVOCs}$) per quartile increase in absolute humidity (P < 0.0001 for the cases; P = 0.780 for the controls). Similarly, even though the magnitude of the increase was modest, global MVOC index was significantly associated with a dose-dependent increase per quartile increase in AH (P < 0.002 for the cases; P = 0.730 for the controls). All of the investigated homes demonstrated uniform indoor temperatures during the winter investigation period per increasing quartile range of AH (Ps > 0.05). However, ventilation rates were inversely correlated with an increasing AH trend (P < 0.0001 for the cases; 0.04 for the controls). In particular, the cases were associated with a larger reduction in the ventilation rate across the driest to the dampest homes (0.44 vs. 0.25 ACH), compared to the control homes (0.47 vs. 0.31 ACH).

3.2. Additive mixture effect of purported MVOCs and AH on the case status

3.2.1. Baseline risks of MVOCs

Fig. 1 and Table 4 summarize the trends in the adjusted odds ratio per increasing quartile of MVOC concentrations, stratified by absolute humidity. Only among the children who live in a high AH homes, a natural log (ln)-unit of Σ 28 MVOCs was associated with 2.5-times greater odds of the case status (95% CI, 1.0–6.2; P = 0.046), compared to 0.7-times the odds (95% CI, 0.4–1.0; P = 0.074) of the same outcome among the low AH homes (Table 4). Quartile ranges of Σ 28 MVOCs were associated with a dose-dependent increase in the odds of the case outcome (Table 4). A one ln-unit of Σ 28 MVOCs was associated with 3-times greater odds of being diagnosed with asthma (95% CI, 1.0–9.1; P = 0.052) among those in a high AH environment, compared to 0.7-times (95% CI, 0.4–1.1; P = 0.145) odds of the same outcome among the low AH homes. Similarly, quartile ranges of Σ 28 MVOC concentration were associated with a dose-responsive increase in the odds of the doctor-diagnosed asthma, only among those within a high AH environment (Table 4). A natural log (ln)-unit of Σ 28 MVOCs was

Table 2Characteristics of the case and control children stratified according to absolute humidity level (g/m³) in his/her bedroom.

	Absolute humidity	Controls					Cases				
		N	AM	ASD	GM	Median	N	AM	ASD	GM	Median
Σ 28 MVOCs (μg/m ³)	<2.95 g/m ³	76	7.66	9.03	4.95	5.09	66	4.74	3.96	3.70	3.6**
	≥2.95 g/m ³	26	7.50	6.26	5.73	5.26	28	10.46	8.10	8.23	8.4
Global MVOC INDEX	<2.95 g/m ³	129	0.3	0.6	0.0	0.0	128	0.1	0.4	0.0	0.0**
	≥2.95 g/m ³	39	0.3	0.6	0.0	0.0	47	0.5	0.8	0.0	0.0
TMPD-MIB (μg/m ³)	<2.95 g/m ³	24	8.6	12.1	3.9	2.5	29	7.0	9.4	3.6	3.2
	≥2.95 g/m ³	10	5.7	5.3	3.9	2.7	22	14.2	17.2	7.6	6.0
BMI (kg/m ²)	<2.95 g/m ³	129	16.5	2.0	16.4	16.2	128	17.1	2.4	17.0	16.8
	≥2.95 g/m ³	39	16.7	2.0	16.6	16.3	47	16.3	1.8	16.3	15.8
age (year)	<2.95 g/m ³	129	5.2	1.5	5.0	5.0	128	4.9	1.4	4.7	5.0
	≥2.95 g/m ³	39	4.5	1.5	4.3	4.0	47	5.5	1.3	5.3	5.0
Ventilation rate (ACH)	<2.95 g/m ³	124	0.41	0.27	0.35	0.3	125	0.37	0.21	0.31	0.31**
	≥2.95 g/m ³	39	0.31	0.16	0.28	0.3	45	0.25	0.14	0.22	0.22
Temperature (°C)	<2.95 g/m ³	129	20.6	1.3	20.5	20.7	128	20.8	1.4	20.7	20.8
	≥2.95 g/m ³	39	20.7	1.4	20.6	20.7	47	21.0	1.0	20.9	21.0
Repainted ≥1 room (yes)	<2.95 g/m ³	76	59%				80	63%			
	≥2.95 g/m ³	27	69%				37	79%			
Atopy in both parents (yes)	<2.95 g/m ³	5	4%				31	24%			
	≥2.95 g/m ³	4	10%				12	26%			
Gender (male)	<2.95 g/m ³	72	56%				72	56%			
	≥2.95 g/m ³	24	62%				28	60%			
Mold index (positive)	<2.95 g/m ³	22	17%				30	24%			
	≥2.95 g/m ³	12	32%				6	13%			
Wet cleaning											
Once/month or less	<2.95 g/m ³	68	53%				44	36%			
Every second week		32	25%				31	25%			
Once/week or more		29	23%				49	40%			
Once/month or less	≥2.95 g/m ³	20	51%				12	26%			
Every second week		9	23%				11	24%			
Once/week or more		10	26%				23	50%			

associated with 5.8-times greater odds of the doctor-diagnosed rhinitis (95% CI, 1.5–3.0; $P = 0.012$) among those in a high AH environment, compared to 0.6-times the odds (95% CI, 0.4–1.1; $P = 0.101$) of the same outcome among the low AH homes (Table 4). Due to the sparseness of the individual cell counts, the quartile range-based model for rhinitis was associated with unstable risk estimates (Table 4). Even though it was not significant, a ln-unit of Σ 28 MVOCs was associated with 1.9-times greater odds of the doctor-diagnosed eczema (95% CI, 0.7–5.2; $P = 0.189$) among those in a high AH environment, compared to 0.6-times the odds (95% CI, 0.4–1.0; $P = 0.052$) of the same outcome among the low AH homes.

3.2.2. Test of interaction in additive scale

Table 5 and Fig. 2 summarize the test for an interaction in an additive scale on four health outcomes of interest. In particular, a highest quartile of Σ 28 MVOCs ($\geq 9.12 \mu\text{g}/\text{m}^3$) was associated with 0.3-times the odds of the doctor-diagnosed asthma status (95% CI, 0.1–0.9; $P = 0.036$) within those with low AH (Model A). Within the same model, a high AH ($\geq 2.95 \text{ g}/\text{m}^3$) was associated with 0.7-times the odds (95% CI, 0.3–1.3; $P = 0.251$) greater odds of the same outcome. The joint exposure to a high MVOCs and an absolute humidity was associated with 2.6-times greater odds of the doctor-diagnosed asthma status (95% CI, 0.7–8.91; $P = 0.137$).

Table 3

Association between exposure, potential confounders, and case-control status within absolute humidity strata in DBH Phase II study.

Exposures of interest	Interaction variable	Controls				P	Cases				P
		N	AM	ASD	Max		N	AM	ASD	Max	
Σ28 MVOCs (μg/m ³)	<1.54	22	6.49	7.46	28.20	0.780	24	3.43	1.82	7.53	<0.0001
	1.54–2.15	20	7.10	5.63	18.97		25	5.37	4.85	21.63	
	2.16–2.95	34	8.75	11.37	56.10		17	5.68	4.42	18.14	
	≥2.96	26	7.50	6.26	25.67		28	10.46	8.10	39.07	
	Overall	102	7.62	8.38	56.10		94	6.45	6.08	39.07	
Global MVOC index	<1.54	38	0.24	0.63	3.00	0.730	47	0.02	0.15	1.00	0.002
	1.54–2.15	37	0.16	0.37	1.00		49	0.18	0.49	2.00	
	2.16–2.95	54	0.30	0.69	4.00		32	0.13	0.42	2.00	
	≥2.96	39	0.28	0.56	2.00		47	0.45	0.83	4.00	
	Overall	168	0.25	0.59	4.00		175	0.20	0.56	4.00	
Temperature (°C)	<1.54	38	20.69	1.41	23.39	0.87	47	20.65	1.64	24.59	0.669
	1.54–2.15	37	20.61	1.40	22.70		49	20.76	1.18	23.79	
	2.16–2.95	54	20.49	1.15	23.26		32	20.89	1.26	23.24	
	≥2.96	39	20.68	1.38	24.93		47	20.97	1.01	24.17	
	Overall	168	20.60	1.31	24.93		175	20.81	1.29	24.59	
Ventilation rate (ACH)	<1.54	36	0.47	0.31	1.74	0.04	47	0.44	0.27	1.05	<0.0001
	1.54–2.15	37	0.40	0.29	1.79		48	0.35	0.17	0.80	
	2.16–2.94	51	0.36	0.20	1.45		30	0.28	0.13	0.60	
	≥2.95	39	0.31	0.16	1.02		45	0.25	0.14	0.69	
	Overall	163	0.38	0.25	1.79		170	0.34	0.20	1.05	

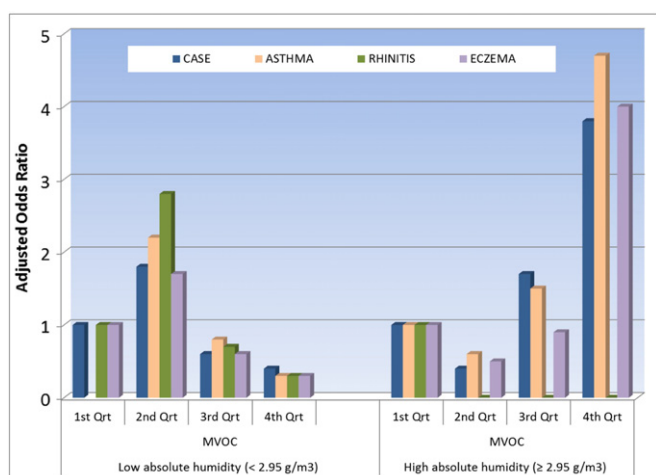


Fig. 1. Adjusted odds ratio for four outcomes of interest per quartile increase in Σ 28 MVOCs stratified according to absolute humidity.

Global MVOC index-based models (model B) were associated with a 0.4-times the odds of the asthma diagnosis (95% CI, 0.2–1.1; $P = 0.072$) within those with low AH (Model B). Within the same model, a high AH (≥ 2.95 g/m³) was associated with 0.8-times the odds (95% CI, 0.4–1.6; $P = 0.522$) greater odds of the same outcome. However, joint exposure to a high MVOC index as well as absolute humidity ≥ 2.95 g/m³ was associated with 1.2-times greater odds of the asthma diagnosis (95% CI, 0.4–4.0; $P = 0.733$).

Furthermore, when we stratified the cases according to allergic sensitization status, the sensitized cases were associated with the highest median concentration of Σ 28 purported MVOCs, compared to the non-sensitized controls only within a high absolute humidity environment (Jonckheere-Terpstra $P < 0.05$). Within restricted analysis of the cases only, one (ln)-unit increase in Σ 28 purported MVOCs was associated with similarly elevated odds of sensitization for both high and low absolute humidity environment (Table 6). The highest quartile of the purported MVOCs as well as high global MVOC index was not associated a significant increase in the odds of the allergic sensitization among the cases (Table 6).

4. Discussion

To date, the respiratory health risks from the exposure to gases from the building materials facilitated by humidity and microbial infestation remain unknown. In this regard, the present investigation offers two novel insights. First, not only the Σ 28 MVOCs but also the global MVOC index increased in significantly linear fashion per increasing levels of absolute humidity only within the homes of the cases, but not in controls (all P s < 0.01 , Tables 2 and 3). While an increase in absolute humidity was associated with a significant reduction in the ventilation rate in both case and control homes, the magnitude of the reduction was larger within the homes of the case children, compared to those of the controls ($P < 0.0001$ vs. 0.04 in case vs. control homes). This suggests that poor ventilation might have contributed to not only an elevated absolute humidity, but also an increase concentration of Σ 28 MVOCs. Second, the purported Σ 28 MVOCs was associated with significantly elevated odds of the case status as well as the doctor-diagnosed rhinitis, only within the homes with high absolute humidity (Table 4). A same unit of exposure to the purported MVOCs was associated with a marginally significant, yet dose-responsive, increase in the odds of doctor-diagnosed asthma only within a damp home environment (Table 4). In fact, joint occurrence of Σ 28 MVOCs and absolute humidity was associated with an indication of a significant interaction in an additive scale. Specifically, a joint exposure to a high Σ 26 MVOCs (≥ 9.12 μ g/m³) and AH (≥ 2.95 g/m³) was associated with a significant interaction in an additive scale for the case status as well as the doctor-diagnosed asthma and rhinitis outcomes, respectively (Table 5).

4.1. health associations for the so-called MVOC

Our findings add to a growing body of evidence for heightened respiratory symptoms among those who were exposed not only to building dampness, but also to VOC exposures (Kim et al., 2007; Wieslander et al., 2007). Robust body of evidence has shown that qualitative markers of damp/moldy air quality and self-reported use of commercial products, respectively, represent robust and dose-responsive risk factor of respiratory symptoms and/or diagnoses (Mendell et al., 2011; Zock et al., 2007). However, MVOCs, to date, are considered sentinel markers of other microbial toxins (Claeson et al., 2002; Claeson et al., 2009). They are suspected to occur at too low a concentration range to pose a

Table 4
Indoor Σ 28 MVOC concentration and adjusted odds ratios (95% C.I.) of allergy and asthma diagnoses in children. All adjusted ORs were adjusted for gender, ETS, and self-reported atopy in both parents.

	Absolute humidity	Main exposure variable coding scheme									
		One ln-unit		1st QRT MVOC		2nd QRT MVOC		3rd QRT MVOC		4th QRT MVOC	
		aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
		P	P	P	P	P	P	P	P	P	P
Case	<2.95 g/m ³	0.7	(0.4–1.0) 0.074	1.0		1.8	(0.8–4.5) 0.182	0.6	(0.2–1.7) 0.348	0.4	(0.1–1.1) 0.081
	≥ 2.95 g/m ³	2.5	(1.0–6.2) 0.046	1.0		0.4	(0.0–4.7) 0.502	1.7	(0.2–13.6) 0.626	3.8	(0.5–30.6) 0.212
Asthma	<2.95 g/m ³	0.7	(0.4–1.1) 0.145	1.0		2.2	(0.8–6.0) 0.121	0.8	(0.3–2.4) 0.741	0.3	(0.1–1.3) 0.121
	≥ 2.95 g/m ³	3.0	(1.0–9.1) 0.052	1.0		0.6	(0.0–10.1) 0.694	1.5	(0.1–22.2) 0.764	4.7	(0.4–59.6) 0.234
Rhinitis	<2.95 g/m ³	0.6	(0.4–1.1) 0.101	1.0		2.8	(0.9–8.4) 0.07	0.7	(0.2–2.4) 0.574	0.3	(0.1–1.7) 0.18
	≥ 2.95 g/m ³	5.8	(1.5–3.0) 0.012	1.0		n.a.		n.a.		n.a.	
Eczema	<2.95 g/m ³	0.6	(0.4–1.0) 0.052	1.0		1.7	(0.7–4.6) 0.257	0.6	(0.2–1.8) 0.409	0.3	(0.1–1.1) 0.064
	≥ 2.95 g/m ³	1.9	(0.7–5.2) 0.189	1.0		0.5	(0.0–6.3) 0.614	0.9	(0.1–8.5) 0.935	4.0	(0.4–44.4) 0.257

Table 5

Interaction models in additive scale of Σ 28 MVOC (model A) or global MVOC index (model B) with absolute humidity. All ORs were adjusted for gender, ETS, and self-reported atopy in both parents.

	Case			Asthma			Rhinitis			Eczema		
	aOR	(95% CI)	P	aOR	(95% CI)	P	aOR	(95% CI)	P	aOR	(95% CI)	P
(A) Concentration-based model												
Odds ratios representing joint effects												
AH < 2.95 g/m ³ & Σ 28 MVOCs < 9.12 μ g/m ³	1	(Reference)		1	(Reference)		1	(Reference)		1	(Reference)	
AH < 2.95 g/m ³ & Σ 28 MVOCs $\geq$ 9.12 μ g/m ³	0.3	(0.1–1.0)	0.027	0.3	(0.1–0.9)	0.036	0.2	(0.1–1.2)	0.251	0.2	(0.1–0.9)	0.035
AH $\geq$ 2.95 g/m ³ & Σ 28 MVOCs < 9.12 μ g/m ³	0.8	(0.5–1.5)	0.509	0.7	(0.3–1.3)	0.251	1.0	(0.5–2.1)	0.952	0.7	(0.4–1.4)	0.689
AH $\geq$ 2.95 g/m ³ & Σ 28 MVOCs $\geq$ 9.12 μ g/m ³	2.3	(0.8–7.1)	0.137	2.6	(0.7–8.9)	0.137	2.9	(0.9–9.9)	0.086	2.2	(0.6–7.7)	0.235
Measures of interaction on additive scale												
RERI	1.9			1.9			2.6			1.6		
AP	1.0			1.0			0.9			1.0		
S	–0.7			–0.7			–2.6			–0.5		
(B) Index-based model												
Odds ratios representing joint effects												
AH < 2.95 g/m ³ & global MVOC index = 0	1	(Reference)		1	(Reference)		1.0	(Reference)		1	(Reference)	
AH < 2.95 g/m ³ & global MVOC index $\geq$ 1	0.4	(0.2–0.9)	0.020	0.4	(0.2–1.1)	0.072	0.3	(0.1–0.9)	0.035	0.4	(0.2–1.0)	0.060
AH $\geq$ 2.95 g/m ³ & global MVOC index = 0	0.8	(0.4–1.5)	0.478	0.8	(0.4–1.6)	0.522	1.0	(0.5–2.2)	0.899	0.7	(0.3–1.4)	0.268
AH $\geq$ 2.95 g/m ³ & global MVOC index $\geq$ 1	1.7	(0.6–4.8)	0.275	1.2	(0.4–4.0)	0.733	2.0	(0.6–6.2)	0.240	1.8	(0.6–5.8)	0.304
Measures of interaction on additive scale												
RERI	1.3			0.8			1.8			1.2		
AP	0.9			0.8			0.9			0.9		
S	–0.6			–0			–1.5			–0.3		

significant risk (Korpi et al., 2009). In contrast, our analysis demonstrates for the first time that the purported MVOC risks on the case status, asthma, and rhinitis, respectively, are significant within the indoor environment with high absolute humidity and/or poor ventilation. In particular, significantly elevated concentration of MVOCs in the atopic cases suggests that allergic sensitization might underlie the case status (Fig. 3). Other observational investigations also noted that the purported MVOCs might induce respiratory risks, including acute mucosal layer irritation (Araki et al., 2012; Araki et al., 2010), and respiratory function impairments in children (Kim et al., 2007). Even in buildings without clear signs of water damage, total concentration of MVOCs was associated with nocturnal breathlessness as well as asthma diagnosis in children (Kim et al., 2007). In another study, one MVOC compound, 1-octen-3-ol, within residential buildings was significantly associated with a history of allergic rhinitis and conjunctivitis, respectively (Araki et al., 2012).

At the same time, the homes within the present investigation demonstrated moderate to high mutual correlations among a number of VOCs, absolute humidity and ventilation rate, consistent with a number of earlier investigations (Choi et al., 2016; Kim et al., 2007; Wieslander and Norback, 2010). Specifically, MVOC concentrations in indoor or personal air samples are often positively correlated with glycol ethers and

other plasticizers (Kim et al., 2007; Wieslander and Norback, 2010). Thus, absolute humidity might exacerbate MVOC risk by promoting joint emission and/or retention of other unmeasured pollutants, for example, formaldehyde (Andersen et al., 1975) and 2-ethyl-1-hexanol (Norback et al., 2000). Therefore, experimental validation of biological plausibility of the MVOC risk is warranted in the future.

4.2. Strength and limitations

The strengths of the present study include representativeness of the initial respondent pool ($n = 10,852$ children), based on 79% response rate of the entire population within Värmland county, Sweden (Bornehag et al., 2005c). The case and control children were carefully selected from the initial pool to enroll a representative subset. The participants of the present investigation and the non-participants did not differ significantly in terms of home dampness or other building characteristics (Bornehag et al., 2006), thereby precluding bias as a threat to the validity of our conclusions. In addition, we validated repeated symptom-based case identification with an in-depth clinical assessment.

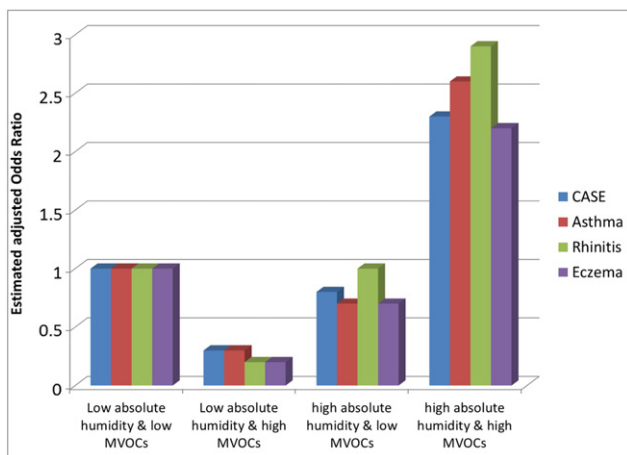


Fig. 2. Interaction models in additive scale of Σ 28 MVOC concentration (model B) with absolute humidity.

Table 6

Indoor Σ 28 MVOCs and adjusted odds ratios (95% CI) of allergic sensitization among cases, stratified according to absolute humidity. All adjusted ORs were adjusted for gender, ETS, and self-reported atopy in both parents.

Σ 28 MVOC coding	Absolute humidity < 2.95 g/m ³				≥2.95 g/m ³			
	Count				Count			
	IgE –	IgE +	aOR	(95% CI)	IgE –	IgE +	aOR	(95% CI)
			P				P	
One In-unit (continuous)			1.2 (0.6–2.6)				1.3 (0.3–5.5)	
			0.586				0.693	
MVOC categories								
1st QRT	62	56	1.0		18	15	1.0	
4th QRT	3	3	1.1 (0.2–6.2)		7	6	0.8 (0.2–3.3)	
			0.894				0.777	
MVOC index								
Low	59	54	1.0		17	15	1.0	
High	6	5	0.8 (0.2–2.8)		8	6	0.8 (0.2–3.1)	
			0.678				0.692	

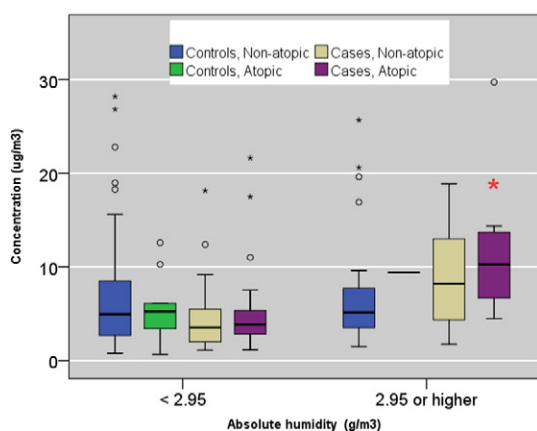


Fig. 3. Concentration distribution of Σ 28 purported MVOCs among atopic cases and controls, stratified by high vs. low absolute humidity (g/m^3). The symbol, *, denotes $P < 0.05$, using Jonckheere-Terpestra test for linear trend.

Primary limitation includes a uniform VOC and MVOC exposure assessment approach with Tenax tube, followed by thermal desorption and GC–MS analysis. Tenax has a limited capacity to quantify compound with less than six carbon atoms. In addition, we used scan mode during the GC–MS analysis, and quantified VOCs as toluene equivalents without an internal standard for each compound. Such quantification approach might have contributed to relatively high detection limit and an associated exposure misclassification in our samples.

5. Conclusions

Total concentration and global index of Σ 28 MVOC were significantly associated with an enhanced risk of multiple allergy symptoms, doctor-diagnosed asthma, and rhinitis, only within severely damp homes. A focused remediation strategy to reduce absolute humidity and to elevate ventilation rate is warranted for the protection of children against asthma, rhinitis, and multiple allergy symptoms during their critical developmental stages.

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Conflict of interest

All authors declare that they have no competing financial interest.

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Figure S1: The relationship between % Non-detects and Median concentration of the MVOCs.

