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# Volatile organic compounds (VOC) in homes associated with asthma and lung function among adults in Northern Europe☆

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

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

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ABSTRACT

Associations between measured specific VOC reported to be associated with dampness and microbial growth in dwellings and asthma, lung function were investigated in 159 adults (one adult/home) from three North European cities (Reykjavik, Uppsala and Tartu). Spirometry was performed and forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$) and $FEV_1$/FVC were measured. Among 159 participants, 58% were females, 24.5% atopics, 25.8% current smokers and 41% reported dampness or mold at home. Dimethyl disulphide ($p = 0.004$), ethyl isobutyrate ($p = 0.021$) and ethyl 2-methylbutyrate ($p = 0.035$) were associated with asthma. Isobutanol ($p = 0.043$), 3-methyl-1-butanol ($p = 0.020$), 2-hexanone ($p = 0.033$), 1-octen-3-ol ($p = 0.027$), 2-methyl-1-butanol ($p = 0.022$) and 2-ethyl-1-hexanol ($p = 0.045$) were associated with lower $FEV_1$. Isobutanol ($p = 0.004$), 3-methyl-1-butanol ($p = 0.001$), 2-heptanone ($p = 0.047$) and 2-methyl-1-butanol ($p = 0.002$) were associated with lower $FEV_1$/FVC. The association between dimethyl disulphide and asthma was more pronounced in females (p for interaction 0.099). The association between 1-butanol and lower $FEV_1$ was more pronounced in males (p for interaction 0.046). The associations between 3-octanone (p for interaction 0.064), 2-ethyl-1-hexanol (p for interaction 0.049) and lower $FEV_1$, and between 2-heptanone (p for interaction 0.021), 3-octanone (p for interaction 0.008) and lower $FEV_1$/FVC were stronger in homes with dampness/mold. Factor analysis identified one VOC factor related to asthma and two VOC factors related to lower lung function. Increased air concentrations of 2-heptanone, ethyl 2-methylbutyrate and ethyl isobutyrate were related to prescence of certain mold species (*Aspergillus* sp., *Cladosporum* sp. and *Penicillium* sp.) or building dampness. Some VOC were associated with type of dwelling, building age and pet keeping. In conclusion, some VOC reported to be associated with dampness and microbial growth can be associated with asthma and lower lung function in adults. Associations between these VOC and respiratory illness can be stronger in homes with dampness/mold. There can be gender differences in respiratory health effects when exposed to indoor VOC.

## 1. Introduction

The prevalence of asthma is estimated to be between 1 and 18% in different regions of the world (GINA, 2022). Asthma is increasing globally, especially in developed western countries (Lundback et al., 2016). Indoor environment exposure can be associated with asthma risk (Quansah et al., 2012; Heinrich, 2011; Fisk, Lei-Gomez, and Mendell, 2007; Mendell, 2007; WHO, 2009) and can impair lung function (Mendell et al., 2011). The indoor environment is complex, and contains different types of exposure such as environmental tobacco smoke (ETS), allergens, mold, bacteria and volatile organic compounds (VOC) which can influence respiratory health (Norbäck and Cai, 2020; Mendell, 2007;

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* Corresponding author. Department of Medical Sciences, Occupational and Environmental Medicine, Uppsala University, 751 85, Uppsala, Sweden.
*E-mail address:* juan.wang@medsci.uu.se (J. Wang).

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Janson, 2004; Pomes, Chapman, and Wunschmann, 2016; Mendell et al., 2011; Jie et al., 2011).

Two recent reviews have demonstrated that the most studied volatile organic compounds (VOC) in home environment are benzene, toluene, xylenes and formaldehyde (Vardoulakis et al., 2020; Ye et al., 2017). Another review concluded that the most widely investigated VOC classes in homes were total VOC, aromatic, aliphatic, microbial VOC and aldehydes (Tagiyeva and Sheikh, 2014). VOC in homes can come from different indoor sources, including tobacco smoking, use of organic solvents, renovations, new building materials and household products (Vardoulakis et al., 2020). Moreover, outdoor air pollution e.g. traffic exhausts can affect indoor VOC concentrations (Chikara, Iwamoto, and Yoshimura, 2009; Han and Naeher, 2006). In addition, some indoor VOC can be produced by mold and bacteria (Korpi, Jarnberg, and Pasanen, 2009; Norbäck and Cai, 2020).

A recent review concluded that VOC in dwellings can influence adult asthma and allergies (Tagiyeva and Sheikh, 2014). Another review demonstrated a medium-sized effect of indoor VOC on asthma onset and wheeze (Alford and Kumar 2021). Both reviews concluded that formaldehyde is the compound most clearly associated with asthma (Tagiyeva and Sheikh, 2014; Alford and Kumar 2021). Benzene is another common VOC associated with adult asthma (Tagiyeva and Sheikh, 2014; Alford and Kumar 2021).

Some studies exist on associations between indoor VOC in homes and asthma, bronchial hyperresponsiveness or fraction of exhaled nitric oxide (FeNO). The compounds n-undecane and 1,2,4-trimethylbenzene were related to occupants' asthma according to one French study (Billionnet et al., 2011). Moreover, this study found that a total VOC score and specific scores for aromatic hydrocarbons and aliphatic hydrocarbons were associated with asthma (Billionnet et al., 2011). A Finish study demonstrated that 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB) in homes was associated with asthma incidence (Villberg et al., 2008). One study from USA found an association between benzene in households and severe asthma symptoms (Gordian, Stewart, and Morris, 2010). In a study from Swedish homes, ethylbenzene, toluene, xylenes and terpenes were associated with nocturnal breathlessness, and limonene was related to bronchial hyperresponsiveness among young adults (Norback et al., 1995). Limonene was associated with wheeze and increased FeNO in Canadian homes (Dales and Cakmak, 2019). We found no previous studies on indoor 2-ethyl-1-hexanol in homes and respiratory health. However, 2-ethyl-1-hexanol in workplace buildings was related to asthma among office workers (Tuomainen, Seuri, and Sieppi, 2004) and hospital staff (Norback et al., 2000).

Few studies exist on domestic VOC exposure and lung function. One large population study from Canada reported that 10 specific VOC in household air were associated with lower lung function (Cakmak et al., 2014). These VOC included octanal, nonanal, hexanal, 2-furancarboxaldehyde, decanal, styrene, benzene, a-pinene, naphthalene and 2-methyl-1,2-butadiene (Cakmak et al., 2014). One population study from Sweden found that concentrations of two terpenes (alpha-pinen and delta-karen) in dwellings increased the variability of peak expiratory flow (PEF) among adults (Norback et al., 1995). Moreover, a study in a Swedish office building found that 2-ethyl-1-hexanol was related to incresed airway obstruction in office workers (Wieslander, Kumlin, and Norback, 2010).

Some later reviews have concluded that residential dampness and mold can increase respiratory symptoms and asthma (WHO, 2009) and incidence of asthma (Quansah et al., 2012). Dampness and mold in dwellings can increase the risk of adult asthma (Wang, Pindus, et al., 2019; Wang, Zhao, et al., 2019; Norbäck et al., 2013). Moreover, the prospective study European Community Respiratory Health Survey (ECRHS) found that dampness and indoor mold in dwellings can increase lung function decline in adults (Norback et al., 2011; Tischer et al., 2015). The most common VOC found in damp buildings are 3-methyl-1-butanol, 2-methyl-1-propanol, 3-methyl-2-butanol, 3-octanol, 2-pentanol, 1-octen-3-ol, 3-methylfuran, 2-octen-1-ol, 3-octanone, 2-heptanone, 2-hexanone, dimethyl disulphide and 2-etyl-1-hexanol (Korpi, Jarnberg, and Pasanen, 2009; Wakayama et al., 2019). Two French studies reported that a combined fungal VOC index (calculated from VOC measurements in homes) increased the risk of asthma in children and adults (Flamant-Hulin, Annesi-Maesano, and Caillaud, 2013; Hulin et al. increased the risk of 2013). However, we found no previous studies on associations between specific VOC produced by microorganisms and asthma or lung function.

The main aim of this article is to study associations between selected VOC in dwellings, reported in the literature to be produced by microorganisms, and adult asthma symptoms and lung function in this three Nordic city study. The second aim is to investigate associations between these VOC and selected home environment factors e.g. indoor microorganisms, dampness and mold, type of building, building age and furry pet keeping.

## 2. Methods

### 2.1. Ethics statement

The study protocols were approved by the regional committees of medical research ethics in Reykjavik (reference no. VSNb2011090016/03.15), Uppsala (reference no. 1990/257 and 1998/495) and Tartu (reference no. UT REC 60/3–1998 and UT REC 209 T-17). All participants gave written informed consent.

### 2.2. Study design

We used data from three Northern European cities (Reykjavik, Uppsala and Tartu), included in the prospective study European Community Respiratory Health Survey (ECRHS) (Janson et al., 2001). Initially, the study population in the ECRHS study was obtained by random selection of young adults (20–44 y) in municipalities (cities) with a lung medicine specialist clinic. This population is then followed as a cohort, with medical investigation every 10 year. The study population is mainly an urban and well-educated population since smaller cities without a university usually have no lung medicine specialist clinic. Participation rates and potential selection bias in the ECRHS study has been reported in a previous publication (Johannessen et al., 2014). The second follow up of the original subjects participated in ECRHS I was performed in 2000–2002 (ECRHS II). There were totally 1238 participants from ECRHS II in the three centres (Reykjavik, Uppsala and Tartu). A total of 60 randomly selected participants, who had not moved since ECRHS I, were invited from each centre. In addition, all participants reporting indoor dampness or mold at home in the earlier questionnaire study were invited to participate in the home investigation including indoor measurements (N = 48). The steps in the recruitment process are described in Fig. 1. In total, 159 out of 228 invited subjects participated (69.7%). The home investigations were performed in 2001–2002. More details of the study design of the three city home study can be found in our previous publications (Sahlberg et al., 2013; Gunnbjornsdottir et al., 2009).

### 2.3. Indoor measurements in homes

Data on indoor temperature, indoor relative air humidity, 16 airborne VOC and airborne microorganisms were collected for all participants. These measurements were performed in the middle of the living room, at a fixed site about 1 m above the floor level. An Assman Psychrometer SK-RHG was used to record temperature and relative air humidity. The laboratory for VOC analysis (Pegasus Lab AB, Uppsala, Sweden) offered a package with quantification of 16 VOC which can be emitted from microbial agents, dampness related degradation of floor materials or plastic materials used in indoor environment (Norbäck and Cai, 2020; Korpi, Jarnberg, and Pasanen, 2009). VOC were sampled by pumping air to a charcoal tube (Anasorb 747) for 3 h (air flow rate 0.4

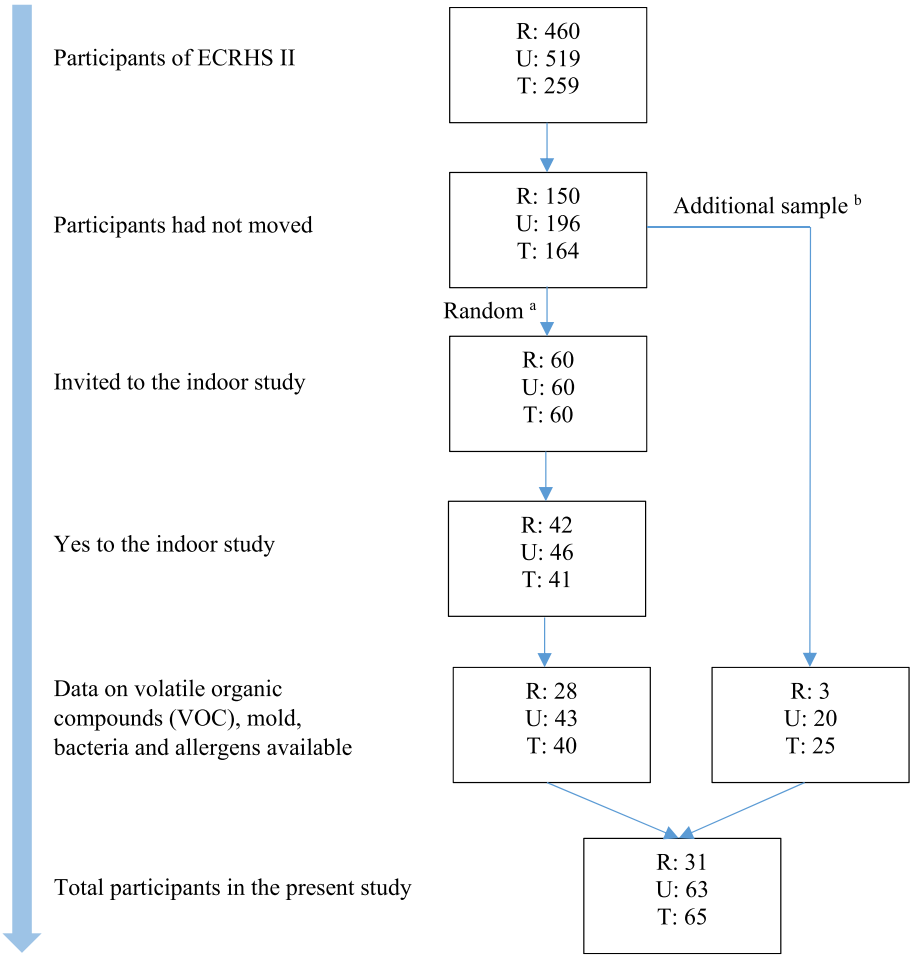


**Fig. 1.** Flow chart on the selection of participants. R, T and U stand for Reykjavik, Uppsala and Tartu, respectively. [a] A random selection of participants in each centre among those who had not moved since ECRHS I. [b] Subjects with home dampness and were not included in the random sample.

l/min). The charcoal tubes were analysed at Pegasus Lab AB, Uppsala, Sweden (Wessén and Schoeps, 1996). The detection limit was 0.1 μg/m$^3$ for the compound 2-ethyl-1-hexanol and 0.001 μg/m$^3$ for all the other VOC. Half of the detection limit was addressed as concentration if the measured value was below detection limit. Airborne microorganisms were sampled by pumped sampling on Nucleopore filters with a pore size of 0.4 μm and a sampling rate of 2 l/min for 2.5 h. Mold and bacteria were analysed by the CAMNEA method by cultivation on two media (Palmgren et al., 1986). The detection limit for total mold and bacteria were 11,000 per m$^3$ of air and 30 colony forming units per m$^3$ (CFU/m$^3$) for viable organisms. Microbial species were reported by the laboratory as presence or absence of the particular species, only (no quantification of air concentrations of specific species).

Allergens were measured in vacuumed bed dust from the homes. Dust was collected from the beds using an Elektrolux Mondo (AB Electrolux, Stockholm, Sweden) vacuum cleaner (1300 W) with an ALK dust collection device (ALK Albelló A/S, Hörsholm, Denmark). The vacuumed dust was analysed for major allergens as previously reported (Gunnbjornsdottir et al., 2009). A limited number of indoor allergens, including major cat allergen *Felis domesticu* 1 (Fel d 1) and major house dust mite (HDM) allergens, including *Dermatophagoides pteronyssinus* 1 (Der p 1) and *Dermatophagoides farinae 1* (Der f 1) were analysed. Allergen levels were expressed as microgram allergen per gram of dust (μg/g). For Fel d 1, the detection limit was 0.01 μg/g. For Der p 1 and Der f 1, the detection limit were 0.1 μg/g. Half of the detection limit was addressed as concentration if the measured value was below detection limit.

### 2.4. Other exposures in home environment

Information on type of dwelling (detached/semi-detached/apartment/other), construction year of the building (exact year), environment tobacco smoke (ETS) at home (yes/no), building dampness or mold (yes/no), painting in the last four years (during 1998–2001) (yes/no), painting during the past eight years, wall-to-wall carpet in at least one room (yes/no), wall-to-wall carpet in at least one room during the past eight years (yes/no), keeping cat/dog (yes/no), total number of persons at home (number) and occupational status (active/not active) were obtained from the ECRHS II questionnaire. Since many changes of building technology occurred in Northern Europe (especially in Sweden) after 1975 (Wang et al., 2014), construction year was categorized into two equal groups using 1975 as cut-off point. Any building dampness or mold was defined as at least one "yes" answer to five questions on signs of dampness or mold at home (Wang, Pindus, et al., 2019).

### 2.5. Assessment of personal factors and atopy

Data on gender, age, weight and height were collected from the ECRHS II questionnaire. Body mass index (BMI, kg/m$^2$) was calculated. Smoking habit (current smoker/ex-smoker/never smoker), age of finishing full education and occupational status (active/not active) were collected from the questionnaire. Education level was assessed by the age when the full education was finished. Age when finishing full education was divided into four groups (21–45 y; 17–20 y; 15–16 y and missing) as in a previous study (Norback et al., 2017)). Samples of blood and serum were obtained in the frame of ECRHS II clinical study (Zock

et al., 2006). Specific serum immunoglobulin E (IgE) against timothy grass, house dust mite (*Dermatophagoides pteronyssinus*), mold (*Cladosporium*) and cat were analysed using Pharmacia CAP system. A positive reaction was defined as a specific serum IgE level above 0.35 kU/L. Atopy means at least one positive reaction to any of the allergens mentioned above.

### 2.6. Assessment of asthma and lung function

We used eight yes/no questions included in the ECRHS II questionnaire to calculate an asthma score. Five questions were about specific symptom occurred at any time in the past 12 months: (1) wheezing or whistling in the chest; (2) been woken up with a feeling of tightness in the chest; (3) attack of shortness of breath that came on during the day when at rest; (4) attack of shortness of breath that came on following strenuous activity and (5) been woken by an attack of shortness of breath. Questions (6) to (8) were: (6) ever had physician diagnosed asthma; (7) had an attack of asthma in the past 12 months and (8) currently taking asthma medication including tablets, aerosols or inhalers. For each question, "yes" was coded as "1" and "no" was coded as "0". A validated asthma score (0–8) was calculated by summing up all "yes" answers from all the sub-questions (Pekkanen et al., 2005). Since few subjects had a score higher than 2, a 0, 1, 2 classification of the score (categorized asthma score (0–2)) was created for statistical reasons. The categorized asthma score (0–2) was coded as 0, 1 and 2 when the continuous asthma score (0–8) equals 0, 1 and $\geq$ 2, respectively. Moreover, detailed data on types of current asthma medication (short acting beta-2-agonist inhalers and inhaled steroids) was obtained through the ECRHS II questionnaire.

Spirometry was performed in the clinical part of the ECRHS II study following the ERS/ATS guidelines. Spirometry was performed before the indoor measurements. Forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) were measured by dynamic spirometry. The predicted value of $FEV_1$ and FVC for each participant were calculated (Anonymous, 1983). Moreover, the $FEV_1$/FVC ratio was calculated.

### 2.7. Statistical analysis

The program STATA 15.1 was used in the statistical analysis. Mann-Whitney *U* test was used to compare differences in concentrations of chemical compounds between exposed and non-exposed group, in relation to specific home environment factors. Correlation analysis (Spearman correlation) was applied to calculate correlations between indoor concentrations of VOC, mold, bacteria, allergens and total number of persons at home, and to calculate correlations between indoor temperature, indoor relative air humidity and indoor mold, bacteria and allergens. If the median of a specific compound were similar in exposed and non-exposed group, Chi-squared test was applied to compare presence of the specific compound in exposed and non-exposed group. Factor analysis was applied using principal component analysis with varimax rotation. Associations between each chemical compound and the categorized asthma score were calculated by two-level ordinal logistic regression model (individual, centre) with adjustment of gender, age, BMI, smoking habit, education level and occupational status (six covariates). Two-level linear mixed regression models (individual, centre) were applied for the associations between each chemical compound and FVC, $FEV_1$ (expressed as % of predicted) and $FEV_1$/FVC, adjusting for same covariates. Extra analyses by controlling home environment factors were performed, adjusting for same covariates. Moreover, stratified analyses and interaction analyses were performed, stratifying for gender, atopy and any reported dampness for significant or almost significant associations ($p < 0.1$). In interaction analysis, an interaction $p < 0.1$ was considered significant. Log transformed VOC and microbial exposure data were applied in all statistic models. Associations were reported as odds ratios (OR) with a 95% confidence interval (CI) for ordinal regression models and Beta with 95%CI for linear mixed models, with $p < 0.05$ as significance level.

## 3. Results

Among participants, 67 (42%) were men and 92 (58%) were women, 38(24.5%) had any positive specific IgE (atopy), 91(57.2%) were current smokers or ex-smokers, 15(9.4%) were taking short acting beta-2-agnonist inhalers and 9(5.7%) were taking inhaled steroids. The mean age was 44 (range 28–54 y). Most of the participants finished their full education at an age above 20 years and most of them (92%) were occupationally active when the study was done. Totally 54 (34%) reported any asthmatic symptom, and many had more than one asthma symptom. The mean values of FVC, $FEV_1$ (% of predicted) and $FEV_1$/FVC were 110%, 105% and 79.9%, respectively (Table 1).

The geometric mean (GM) of indoor air temperature was 20.7 °C (geometric standard deviation (GSD) = 1.11) and the GM of indoor air humidity was 40.7% (GSD = 1.36). Data on indoor concentrations of VOC is shown in Table 2. There were no differences in concentrations of any VOC between those with and without ETS at home. Ethyl isobutyrate was the only compound associated with reported dampness at home, with higher levels in damp homes (0.002 $\mu g/m^3$) as compared to non-damp homes (0.001 $\mu g/m^3$) ($p = 0.004$).

Table S1 shows indoor levels of mold, bacteria and allergens. Data on types of indoor mold and other home environment exposures is reported in Table 3. The main types of viable mold were *Aspergillus* sp., *Cladosporium* sp., *Penicillium* sp., and *Streptomyces* sp., all detected in at least 10 homes. These mold families were further analysed for associations with specific VOC. Other mold species were detected in a few homes, only. There were in average 3.5 persons living at home (ranged from 1 to 7 persons) (data shown in text only).

Totally nine factors were identified from factor analysis of indoor exposure variables: the first factor included isobutanol, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone and 2-ethyl-1-hexanol; the second factor included dimethyl disulphide, ethyl isobutyrate and ethyl 2-methylbutyrate; the third factor included 3-methyl-1-butanol, 2-methyl-1-butanol and viable bacteria; the fourth factor included 2-pentanol and

**Table 1**
Demographic data and data on categorized asthma score, FVC, $FEV_1$ and $FEV_1$/FVC.

| | | n | % or 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 |
| Age of finishing full education | 21-45 (high education) | 88 | 55.3 |
| | 17 -20 (medium education) | 58 | 36.5 |
| | 15-16 (low education) | 11 | 6.9 |
| | Missing | 2 | 1.3 |
| Occupationally active | Yes | 146 | 92 |
| Use of asthma medicine | Short acting beta-2-agonist inhalers | 15 | 9.4 |
| | Inhaled steroids | 9 | 5.7 |
| Categorized asthma score [c] | 0 | 105 | 66.0 |
| | 1 | 27 | 17.0 |
| | 2 | 27 | 17.0 |
| FVC | % | 155 | 110(15) |
| $FEV_1$ | % | 155 | 105(17) |
| $FEV_1$/FVC | % | 155 | 79.9(7.9) |

[a] SD: standard deviation.
[b] Atopy means any positive specific IgE.
[c] Categorized asthma score was coded as 0, 1 and 2 when the continuous asthma score (0–8) equals 0, 1 and $\geq$ 2, respectively.

**Table 2**
Data on indoor concentrations of VOC in homes.

| VOC (μg/m$^3$) | Cas number | Detection rate % [a] | Number of obervations | GM(GSD) [b] | Median(IQR) [c] | Max |
|---|---|---|---|---|---|---|
| 3-Methylfuran | 930-27-8 | 99 | 158 | 0.023(3.05) | 0.024(0.013–0.044) | 0.69 |
| Isobutanol | 78-83-1 | 100 | 159 | 1.57(2.33) | 1.52(0.93–2.37) | 18 |
| 1-Butanol | 71-36-3 | 100 | 159 | 5.84(2.33) | 5.83(3.37–10.0) | 78 |
| 2-Pentanol | 6032-29-7 | 99 | 154 | 0.012(4.21) | 0.014(0.004–0.033) | 0.22 |
| 3-Methyl-1-butanol | 123-51-3 | 99 | 74 | 0.274(3.50) | 0.300(0.190–0.540) | 5.32 |
| Dimethyl disulphide | 624-92-0 | 99 | 156 | 0.033(7.32) | 0.022(0.009–0.053) | 5.87 |
| 2-Hexanone | 591-78-6 | 100 | 159 | 0.057(2.33) | 0.060(0.030–0.110) | 0.32 |
| 2-Heptanone | 110-43-0 | 100 | 159 | 0.319(2.19) | 0.300(0.200–0.500) | 3.17 |
| 1-Octen-3-ol | 3391-86-4 | 100 | 145 | 0.052(2.68) | 0.050(0.030–0.100) | 2.33 |
| 3-Octanone | 106-68-3 | 100 | 130 | 0.040(1.80) | 0.037(0.027–0.062) | 0.35 |
| 2-Methyl-1-butanol | 137-32-6 | 99 | 71 | 0.072(2.73) | 0.081(0.044–0.120) | 0.94 |
| Ethyl isobutyrate | 97-62-1 | 68 | 158 | 0.002(3.74) | 0.001(0.0005–0.003) | 0.072 |
| Isobutyl acetate | 110-19-0 | 85 | 71 | 0.056(12.1) | 0.098(0.024–0.260) | 17.25 |
| Ethyl 2-methylbutyrate | 7452-79-1 | 93 | 147 | 0.028(7.22) | 0.027(0.008–0.150) | 2.39 |
| 2-Pentylfuran | 3777-69-3 | 100 | 147 | 0.042(4.13) | 0.039(0.014–0.120) | 46 |
| 2-Ethyl-1-hexanol | 104-76-7 | 100 | 144 | 2.38(2.02) | 2.30(1.65–3.40) | 14.2 |
| Sum VOC group 1 [d] | – | 100 | 159 | 4.47(2.03) | 4.67(2.86–6.67) | 25.9 |
| Sum VOC group 2 [e] | – | 100 | 159 | 0.078(6.42) | 0.053(0.019–0.26) | 7.06 |
| Sum VOC group 3 [f] | – | 48 | 77 | 0.318(3.50) | 0(0–0.339) | 6.26 |

[a] Detection rate: total number of sample with value above detection limit/total number of sample with one value in the data file.
[b] GM means geometric mean. GSD means geometric standard deviation.
[c] IQR means interquartile range.
[d] Compounds included in VOC group 1 are isobutanol, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone and 2-ethyl-1-hexanol.
[e] Compounds included in VOC group 2 are dimethyl disulphide, ethyl isobutyrate and ethyl 2-methylbutyrate.
[f] Compounds included in VOC group 3 are 3-methyl-1-butanol and 2-methyl-1-butanol.

**Table 3**
Data on four viable mold and other exposures in home environment.

| Other exposures in home environment | | n | % |
|---|---|---|---|
| *Aspergillus* sp. in air samples | | 23 | 15 |
| *Cladosporium* sp. in air samples | | 64 | 40 |
| *Penicillium* sp. in air samples | | 24 | 15 |
| *Streptomyces* sp. in air samples | | 11 | 7 |
| Type of dwelling | Detached houses | 69 | 45 |
| | Semi-detached houses | 22 | 14 |
| | Apartment | 62 | 41 |
| | Other | 0 | 0 |
| Construction year | Pre-1975 | 86 | 54 |
| | After 1975 | 73 | 46 |
| ETS | | 49 | 31 |
| Dampness or mold | | 64 | 41 |
| Painting in the last four years | | 33 | 21 |
| Wall-to-wall carpet in at least one room | | 23 | 14 |
| Keeping cat/dog | | 55 | 35 |

total bacteria (opposite correlated); the fifth factor included painting in the last four years and total mold; the sixth factor included *Cladosporium* sp., *Penicillium* sp. and viable mold; the seventh factor included ETS and wall-to-wall carpet; the eighth factor included Fel d 1 and Der p 1; and the ninth factor included Der f 1 and total number of persons at home. The compounds 3-methylfuran, 1-butanol, isobutyl acetate and 2-pentylfuran, and type of dwelling, construction year, dampness or mold and keeping cat/dog were not included in any factor. Three VOC concentration subgroups (VOC group 1, VOC group 2 and VOC group 3), were created by adding up the concentrations of all VOC included in the first factor, the second factor and the third factor, respectively.

Associations between concentrations of chemical compounds and the categorized asthma score, FVC, $FEV_1$ and $FEV_1$/FVC are shown in Table 4. Higher levels of dimethyl disulphide, ethyl isobutyrate, ethyl 2-methylbutyrate and VOC group 2 were associated with categorized asthma score. Higher levels of isobutanol, 3-methyl-1-butanol, 1-octen-3-ol, 2-methyl-1-butanol, VOC group 1 and VOC group 3 were associated with lower $FEV_1$. There was a tendency that 1-butanol, 2-hexanone, 3-octanone and 2-ethyl-1-hexanol were related to lower $FEV_1$ ($p = 0.079$, 0.085, 0.096 and 0.068, respectively). Higher concentrations of isobutanol, 3-methyl-1-butanol, 2-heptanone, 2-methyl-1-butanol, VOC group 1 and VOC group 3 were associated with lower $FEV_1$/FVC. There was a tendency that 1-butanol, 3-octanone and 2-ethyl-1-hexanol were associated with lower $FEV_1$/FVC ($p = 0.099$, 0.094 and 0.067, respectively). For the VOC group 3, further adjustments for viable bacteria in the models gave the same associations ($p = 0.005$ for $FEV_1$ and $p = 0.001$ for $FEV_1$/FVC). No significant associations were found between concentrations of any chemical compounds and FVC.

As a next step, interaction by gender, atopy and dampness at home on associations between specific VOC and the respiratory illness variables were investigated (Tables S2-S4 and Table 6). For asthma score, only one significant interaction was found in the interaction analyses: females had more asthma symptoms than men when exposed to dimethyl disulphide (p for interaction 0.099) (Fig. S1); no interactions were found for atopy or dampness. For $FEV_1$, males had more reduced level of $FEV_1$ than women when exposed to 1-butanol (p for interaction 0.046) (Fig. S2); participants in dampness group were more likely to have a reduced level of $FEV_1$ when exposed to 3-octanone (p for interaction 0.064) and 2-ethyl-1-hexanol (p for interaction 0.049) (Table 6); no interactions were found for atopy. For $FEV_1$/FVC, subjects with atopy had lower level of $FEV_1$/FVC when exposed to 1-butanol (p for interaction 0.083); participants in the dampness group were more likely to have lower $FEV_1$/FVC when exposed to 2-heptanone (p for interaction 0.021) and 3-octanone (p for interaction 0.008); no interactions were found for gender.

In all sensitivity analysis, totally nine significant associations were found for men and seven were found for women, and nine significant associations were found for non-atopics and seven for atopics (Table S2-S4). Two gender interactions were found, suggesting males and females can be more sensitive to different VOC compounds. Only one interaction between non-atopics and atopics was found. Four significant interactions were found when stratifying for dampness (Table 5), showing that participants in the dampness group had lower lung function as compared to the non-dampness group when exposed to 2-heptanone, 3-octanone and 2-ethyl-1-hexanol and 2-heptanone.

Correlations between individual VOC and other home environment exposures are shown in Table S5 and Table S6 (all Spearman correlation<0.3). The associations between air temperature, relative humidity and indoor mold, bacteria and allergens are shown in Table S7 (all Spearman correlation<0.4). The median and interquartile range

**Table 4**
Associations between indoor levels of VOC and categorized asthma score, FVC, $FEV_1$ and $FEV_1$/FVC.

| VOC [a] | Categorized asthma score [b] | p | FVC [c] | p | $FEV_1$ [c] | p | $FEV_1$/FVC [c] | p |
|---|---|---|---|---|---|---|---|---|
| 3-Methylfuran | 1.41(0.71,2.81) | 0.329 | −3.01(-7.65,1.62) | 0.202 | −4.36(-9.76,1.03) | 0.113 | −0.76(-3.23,1.71) | 0.545 |
| Isobutanol | 0.72(0.28,1.81) | 0.481 | −1.94(-8.16,4.29) | 0.542 | −7.40(-14.6,-0.24) | **0.043** | −4.89(-8.22,-1.56) | **0.004** |
| 1-Butanol | 1.22(0.50,2.95) | 0.663 | −3.16(-9.32,3.00) | 0.315 | −6.39(-13.5,0.74) | 0.079 | −2.83(-6.19,0.53) | 0.099 |
| 2-Pentanol | 1.23(0.60,2.52) | 0.565 | −2.75(-6.70,1.19) | 0.171 | −3.07(-7.67,1.53) | 0.191 | −0.67(-2.83,1.49) | 0.541 |
| 3-Methyl-1-butanol | 0.58(0.23,1.48) | 0.253 | −3.61(-9.74,2.52) | 0.249 | −7.80(-14.4,-1.22) | **0.020** | −4.69(-7.57,-1.80) | **0.001** |
| Dimethyl disulphide | 1.77(1.20,2.59) | **0.004** | −0.26(-2.95,2.44) | 0.851 | 0.005(-3.12,3.13) | 0.998 | −0.01(-1.47,1.44) | 0.985 |
| 2-Hexanone | 0.81(0.30,2.19) | 0.673 | −3.92(-11.0,3.11) | 0.274 | −7.13(-15.3,0.99) | 0.085 | −2.49(-6.20,1.21) | 0.187 |
| 2-Heptanone | 1.46(0.54,3.96) | 0.461 | −0.15(-7.15,6.84) | 0.966 | −5.05(-13.1,3.05) | 0.222 | −3.83(-7.61,0.06) | **0.047** |
| 1-Octen-3-ol | 1.16(0.50,2.71) | 0.731 | −3.80(-9.33,1.72) | 0.177 | −7.08(-13.3,-0.83) | **0.027** | −1.87(-4.77,1.02) | 0.204 |
| 3-Octanone | 1.77(0.39,8.00) | 0.461 | −3.89(-14.4,6.68) | 0.471 | −9.97(-21.7,1.77) | 0.096 | −4.58(-9.93,0.78) | 0.094 |
| 2-Methyl-1-butanol | 0.85(0.28,2.61) | 0.778 | −6.27(-14.4,1.84) | 0.130 | −10.4(-19.4,-1.48) | **0.022** | −5.80(-9.42,-2.17) | **0.002** |
| Ethyl isobutyrate | 1.97(1.11,3.50) | **0.021** | −1.18(-5.26,2.90) | 0.571 | −0.82(-5.58,3.93) | 0.735 | 0.22(-1.97,2.41) | 0.845 |
| Isobutyl acetate | 0.80(0.49,1.30) | 0.363 | 2.41(-1.15,5.98) | 0.185 | 2.21(-1.72,6.15) | 0.269 | −0.43(-2.19,1.33) | 0.630 |
| Ethyl 2-methylbutyrate | 1.60(1.03,2.48) | **0.035** | −0.92(-3.89,2.06) | 0.545 | −2.01(-5.49,1.46) | 0.256 | −1.04(-2.59,0.52) | 0.190 |
| 2-pentylfuran | 0.77(0.41,1.42) | 0.397 | 0.17(-3.64,3.98) | 0.930 | −0.43(-4.88,4.02) | 0.850 | −0.68(-2.67,1.32) | 0.508 |
| 2-Ethyl-1-hexanol | 0.91(0.28,2.89) | 0.868 | −3.13(-10.8,4.55) | 0.424 | −8.07(-16.7,0.58) | 0.068 | −3.75(-7.77,0.27) | 0.067 |
| Sum VOC group 1 | 0.81(0.26,2.45) | 0.704 | −5.68(-13.1,1.72) | 0.133 | −10.7(-19.2,-2.19) | **0.014** | −4.54(-8.56,-0.51) | **0.027** |
| Sum VOC group 2 | 1.59(1.05,2.39) | **0.028** | 0.02(-2.79,2.84) | 0.987 | −0.29(-3.57,2.99) | 0.862 | −0.39(-1.90,1.12) | 0.612 |
| Sum VOC group 3 | 0.70(0.28,1.74) | 0.441 | −4.62(-10.6,1.37) | 0.130 | −9.21(-15.7,-2.74) | **0.005** | −4.83(-7.65,-2.01) | **0.001** |

Bold values: $p < 0.05$.
[a]Log transformed values.
[b]Two-level ordinal logistic regression models (individual, centre), adjusting for gender, age, BMI, smoking habit, education level and occupational status.
[c]Two-level linear mixed regression models (individual, centre), adjusting for gender age, BMI, smoking habit, education level and occupational status.
[d]Compounds included in VOC group 1 are isobutanol, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone and 2-ethyl-1-hexanol.
[e]Compounds included in VOC group 2 are dimethyl disulphide, ethyl isobutyrate and ethyl 2-methylbutyrate.
[f]Compounds included in VOC group 3 are 3-methyl-1-butanol and 2-methyl-1-butanol.

**Table 5**
Associations between indoor levels of VOC, $FEV_1$ and $FEV_1$/FVC, stratified for dampness (no/yes).

| | VOC [a] | | Beta(95%CI) | p | p interaction |
|---|---|---|---|---|---|
| $FEV_1$ [b] | 3-Octanone | Dampness, no | −2.70 (-18.4,13.0) | 0.737 | **0.064** |
| | | Dampness, yes | −24.8 (-43.9,-5.62) | **0.011** | |
| | 2-Ethyl-1-hexanol | Dampness, no | 0.94 (-12.4,14.3) | 0.890 | **0.049** |
| | | Dampness, yes | −13.3 (-24.2,-2.40) | **0.017** | |
| $FEV_1$/FVC [b] | 2-Heptanone | Dampness, no | −1.56 (-6.47,3.36) | 0.535 | **0.021** |
| | | Dampness, yes | −10.4 (-15.7,-5.01) | **<0.001** | |
| | 3-Octanone | Dampness, no | −0.17 (-7.42,-7.09) | 0.964 | **0.008** |
| | | Dampness, yes | −15.5 (-23.5,-7.54) | **<0.001** | |

Bold values: $p < 0.05$.
[a] Log transformed values.
[b] Two-level linear mixed regression models (individual, centre), adjusting for gender, age, BMI, smoking habit, education level and occupational status.

(IQR) of each individual VOC are presented, comparing exposed and non-exposed groups in relation to a specific home factor, respectively (Table 6). Three fungal families were associated with measured specific VOC: *Aspergillus* sp., was associated with increased levels of 2-heptanone and ethyl 2-methylbutyrate; *Cladosporium* sp. was associated with higher levels of 2-heptanone and 2-ethyl-1-hexanol; and *Penicillium* sp. was related to higher level of ethyl isobutyrate but lower level of 2-hexanone. Homes with cat/dog had higher level of ethyl 2-methylbutyrate. Homes with dampness had higher level of ethyl isobutyrate. Homes with indoor painting in the last four years had lower level of 2-hexanone. As compared to detached/semi-detached houses, apartments had lower levels of 2-hexanone, 2-heptanone and 1-octen-3-ol. Older buildings (constructed before 1975) had higher levels of ethyl isobutyrate and ethyl 2-methylbutyrate but lower level of isobutanol, as compared to newer buildings. No correlations were found between any VOC and measured mold, bacteria, Fel d 1, Der p 1, Der f 1 or total number of persons living in the home. Chi-square analysis showed that presence of ethyl isobutyrate was more common in homes with *Penicillium* sp. ($p = 0.006$), with dampness ($p = 0.003$) and in older buildings ($p = 0.025$): 81% of homes with *Penicillium* sp. had detected levels of ethyl isobutyrate but in homes without *Penicillium* sp., only 60% had detected levels ethyl isobutyrate.; 81% of homes with dampness had detected levels ethyl isobutyrate while only 59% of the homes without dampness and had detected levels ethyl isobutyrate; and 76% homes of older buildings had detected levels of ethyl isobutyrate while only 59% of newer buildings had detected levels of ethyl isobutyrate.

Health associations in models with additional adjustments for possible effects of home environment factors on the associations between each chemical compound and the health variables are presented in Table 7. Most of the health associations remained significant in the models with additional adjustment and the magnitude of the associations were similar even if there were small changes of the p-values. Significant associations were found between isobutanol, lower $FEV_1$ and $FEV_1$/FVC when adjusting for construction year in the model, between 2-hexanone and lower $FEV_1$ when adjusting for painting in the last four years in the model, between 1-octen-3-ol and lower $FEV_1$ when adjusting for type of dwelling in the model, between ethyl isobutyrate and categorized asthma score when adjusting *Penicillium* sp., dampness or mold or construction year in the model, between ethyl 2-methylbutyrate and categorized asthma score when adjusting *Aspergillus* sp., keeping cat/dog or construction year in the model, and between 2-ethyl-1-hexanol and lower $FEV_1$ when adjusting *Cladosporium* sp. in the model, respectively. The association between 2-heptanone and lower $FEV_1$/FVC disappeared when adding *Aspergillus* sp. and *Cladosporium* sp. or type of dwelling in the model. Moreover, the associations between ethyl 2-methylbutyrate and categorized asthma score disappeared when controlling for construction year in the model ($p = 0.065$).

## 4. Discussion

Indoor concentrations of nine VOC compounds were associated with

**Table 6**
The median and IQR of VOC, stratified for exposed (coded as 1) and non-exposed (coded as 0) for each specific home environment factor.

| Specific home environment factor | VOC | The specific home environment factor was coded as 1, exposed | | The specific home environment factor was coded as 0, non-exposed | | p |
|---|---|---|---|---|---|---|
| | | n | Median (IQR) | n | Median (IQR) | |
| *Aspergillus* sp. (0/1) [a] | 2-Heptanone | 23 | 0.620(0.240,1.080) | 135 | 0.280(0.190,0.460) | **0.018** |
| | Ethyl 2-methylbutyrate | 22 | 0.080(0.020,0.200) | 124 | 0.021(0.007,0.140) | **0.039** |
| *Cladosporium* sp. (0/1) [a] | 2-Heptanone | 24 | 0.485(0.220,0.785) | 134 | 0.280(0.190,0.450) | **0.024** |
| | 2-Ethyl-1-hexanol | 23 | 3.200(2.500,4.900) | 120 | 2.200(1.450,3.345) | **0.005** |
| *Penicillium* sp. (0/1) [a] | 2-Hexanone | 63 | 0.042(0.024,0.088) | 95 | 0.084(0.031,0.130) | **0.015** |
| | Ethyl isobutyrate | 62 | 0.001(0.001,0.005) | 95 | 0.001(<0.001,0.003) | **0.044** |
| Keeping cat/dog (0/1) [a] | Ethyl 2-methylbutyrate | 50 | 0.031(0.013,0.190) | 97 | 0.019(0.007,0.098) | **0.043** |
| Dampness or mold (0/1) [a] | Ethyl isobutyrate | 64 | 0.001(<0.001,0.009) | 91 | 0.001(<0.001,0.002) | **0.004** |
| Painting in the last four years (0/1) [a] | 2-Hexanone | 33 | 0.031(0.022,0.055) | 126 | 0.072(0.032,0.120) | **0.001** |
| Type of dwelling (0/1) [b] | 2-Hexanone | 62 | 0.035(0.021,0.087) | 91 | 0.085(0.042,0.130) | **<0.001** |
| | 2-Heptanone | 62 | 0.260(0.160,0.360) | 91 | 0.310(0.220,0.660) | **0.004** |
| | 1-Octen-3-ol | 59 | 0.037(0.022,0.070) | 80 | 0.067(0.032,0.120) | **0.005** |
| Construction year (0/1) [c] | Isobutanol | 86 | 1.365(0.900,2.040) | 73 | 2.060(0.980,3.100) | **0.009** |
| | Ethyl isobutyrate | 85 | 0.001(<0.001,0.005) | 73 | 0.001(<0.001,0.002) | **0.041** |
| | Ethyl 2-methylbutyrate | 77 | 0.052(0.015,0.170) | 70 | 0.018(0.007,0.088) | **0.024** |

Bold values: $p < 0.05$.

[a] For each specific home environment factor, exposed means presence of *Aspergillus* sp. at home, presence of *Cladosporium* sp. at home, presence of *Penicillium* sp. at home, keeping cat/dog at home, presence of building dampness or mold at home and indoor painting in the last four years, respectively; non-exposed means absence of *Aspergillus* sp. at home, absence of *Cladosporium* sp. at home, absence of *Penicillium* sp. at home, not keeping cat/dog at home, absence of building dampness or mold and no indoor painting in the last four years, respectively.

[b] Type of dwelling: apartment was coded as 1 (exposed) and detached/semi-detached house was coded as 0 (non-exposed).

[c] Construction year: coded as 1 if the building was built before 1975 (exposed), and coded as 0 if it was built after 1975 (non-exposed).

adult asthma symptoms or airway obstruction ($FEV_1$, $FEV_1$/FVC). Asthma symptoms were more common at higher air concentrations of dimethyl disulphide, ethyl isobutyrate, ethyl 2-methylbutyrate and VOC group 2. $FEV_1$ was lower at higher concentrations of isobutanol, 3-methyl-1-butanol, 2-hexanone, 1-octen-3-ol, 2-methyl-1-butanol, 2-ethyl-1-hexanol, VOC group 1 and VOC group 3. Lower $FEV_1$/FVC was related to higher concentrations of isobutanol, 3-methyl-1-butanol, 2-heptanone, 2-methyl-1-butanol, VOC group 1 and VOC group 3. Females could be more sensitive to effects of dimethyl disulphide on asthma. Males could be more sensitive to effects of 1-butanol on $FEV_1$. Participants in homes with dampness could be more sensitive to airway obstruction related to indoor concentrations of 2-heptanone, 3-octanone and 2-ethyl-1-hexanol.

### 4.1. VOC associated with asthma

We found that dimethyl disulphide was positively associated with asthma score. One Swedish school study found that dimethyl disulphide concentration in classrooms was associated with nocturnal breathlessness among pupils (Kim et al., 2007). This compound can be produced by bacteria (Tomita et al., 1987) and fungi (Kalalian et al., 2020; Gao et al., 2002). One study investigating chemical emissions from moldy building materials concluded that dimethyl disulphide was from fungal metabolism (Moularat et al., 2008). Thus, there can be microbial sources of dimethyl disulphide in dwellings.

Ethyl isobutyrate was positively associated with asthma score in our study. We found no previous studies on associations between this compound and asthma. One previous study found that ethyl butyrate was one of the main esters produced by ascomycetous yeast strains (Buzzini et al., 2003). In our study, higher level of ethyl isobutyrate was found in homes with *Penicillium* sp. and signs of dampness. Moreover, the concentration of ethyl isobutyrate was significantly higher among dampness group than non-dampness group, suggesting that indoor microbial growth could have contributed to the indoor level of this compound.

Ethyl 2-methylbutyrate was positively associated with asthma score in our study. One school study from Sweden investigated associations between ethyl 2-methylbutyrate exposure in classrooms and respiratory health among pupils, but found no health associations for this compound (Kim et al., 2007). We found no previous studies on emission of ethyl 2-methylbutyrate from microbial growth in buildings. However, we found that ethyl 2-methylbutyrate concentration was related to presence of *Aspergillus* sp. spores in the air, suggesting potential indoor microbial sources of this compound.

### 4.2. VOC associated with impaired lung function

Increased exposure to 3-methyl-1-butanol at home was associated with lower $FEV_1$ and $FEV_1$/FVC. We found no previous studies on indoor 3-methyl-1-butanol and lung function. However, one Swedish school study found that 3-methyl-1-butanol concentration in classroom air was associated with nocturnal breathlessness (Kim et al., 2007). Some other studies have reported that 3-methyl-1-butanol can be emitted from many mold species found in damp buildings (Fiedler, Schütz, and Geh, 2001), from yeast fermentation (Hazelwood et al., 2008) and can be related to mold status of the building (Schleibinger et al., 2008). Thus, one indoor source of 3-methyl-1-butanol could be microbial growth.

2-Methyl-1-butanol was related to lower $FEV_1$ and $FEV_1$/FVC in our study. To our knowledge, no previous studies have investigated indoor 2-methyl-1-butanol and lung function. However, one Swedish school study showed that 2-methyl-1-butanol in classroom air was associated with nocturnal breathlessness and physician diagnosed asthma (Kim et al., 2007). Previous exposure studies indicated that 2-methyl-1-butanol was associated with mold status (Schleibinger et al., 2008) and can be released from many mold species growing in moisture damaged buildings (Fiedler, Schütz, and Geh, 2001). Yeast fermentation can also generate this compound (Hazelwood et al., 2008). Thus, one indoor source of 2-methyl-1-butanol in our study could be microbial growth.

Isobutanol was associated lower $FEV_1$ and $FEV_1$/FVC in our study. No previous studies on indoor isobutanol and lung function have been found. This compound is used in many consumer products. We found no previous studies on emission of isobutanol from microbial growth in buildings. Our study found higher level of isobutanol in newer buildings (vs. older buildings) suggesting that the main source of indoor concentrations in our homes could be material emissions from newer building materials.

1-Octen-3-ol was associated with lower $FEV_1$ according to our results. We found no previous studies on indoor 1-octen-3-ol and lung function. Indoor 1-octen-3-ol was reported to be associated with nocturnal breathlessness in pupils in one school environment study (Kim

**Table 7**
Associations between indoor levels of VOC and categorized asthma score, FVC, $FEV_1$ and $FEV_1$/FVC, with extra adjustment of home environment factors.

| | VOC [a] | Categorized asthma score [b] | p | FVC [c] | p | $FEV_1$ [c] | p | $FEV_1$/FVC [c] | p |
|---|---|---|---|---|---|---|---|---|---|
| Original model in Table 4 | Isobutanol | 0.72(0.28,1.81) | 0.481 | −1.94 (-8.16,4.29) | 0.542 | −7.40(-14.6,-0.24) | **0.043** | −4.89(-8.22,-1.56) | **0.004** |
| Extra adjustment for construction year (0/1) | Isobutanol | 0.99(0.37,2.62) | 0.982 | −2.02 (-8.39,4.34) | 0.533 | −7.84(-15.2,-0.53) | **0.036** | −5.12(-8.53,-1.72) | **0.003** |
| Original model in Table 4 | 2-Hexanone | 0.81(0.30,2.19) | 0.673 | −3.92 (-11.0,3.11) | 0.274 | −7.13 (-15.3,0.99) | 0.085 | −2.49 (-6.20,1.21) | 0.187 |
| Extra adjustment for *Penicillium* sp. (0/1) | 2-Hexanone | 0.87(0.31,2.42) | 0.783 | −4.03 (-11.1,3–07) | 0.266 | −7.38 (-15.5,0.77) | 0.076 | −1.84 (-5.51,1.83) | 0.325 |
| Extra adjustment for painting in the last four years (0/1) | 2-Hexanone | 1.16(0.34,3.89) | 0.812 | −5.65 (-12.3,1.03) | 0.098 | −8.39(-16.1,-0.69) | **0.033** | −2.13 (-5.76,1.51) | 0.252 |
| Extra adjustment for type of dwelling (0/1) | 2-Hexanone | 0.68(0.23,1.97) | 0.477 | −3.05 (-10.4,4.29) | 0.415 | −6.28 (-14.8,2.26) | 0.149 | −2.26 (-6.11,1.58) | 0.249 |
| Original model in Table 4 | 2-Heptanone | 1.46(0.54,3.96) | 0.461 | −0.15 (-7.15,6.84) | 0.966 | −5.05 (-13.1,3.05) | 0.222 | −3.83 (-7.61,0.06) | **0.047** |
| Extra adjustment for *Aspergillus* sp. (0/1) and *Cladosporium* sp. (0/1) | 2-Heptanone | 1.32(0.47,3.72) | 0.605 | 0.27 (-6.99,7.53) | 0.942 | −4.17 (-12.5,4.19) | 0.328 | −3.69 (-7.64,0.26) | 0.067 |
| Extra adjustment for type of dwelling (0/1) | 2-Heptanone | 1.26(0.44,3.65) | 0.668 | −0.07 (-7.39,7.25) | 0.985 | −4.69 (-13.2,3.85) | 0.282 | −3.29 (-7.20,0.61) | 0.099 |
| Original model in Table 4 | 1-Octen-3-ol | 1.16(0.50,2.71) | 0.731 | −3.80 (-9.33,1.72) | 0.177 | −7.08(-13.3,-0.83) | **0.027** | −1.87 (-4.77,1.02) | 0.204 |
| Extra adjustment for type of dwelling (0/1) | 1-Octen-3-ol | 1.02(0.42,2.47) | 0.971 | −3.34 (-9.04,2.37) | 0.251 | −7.09(-13.6,-0.62) | **0.032** | −2.23 (-5.15,0.69) | 0.135 |
| Original model in Table 4 | Ethyl isobutyrate | 1.97(1.11,3.50) | **0.021** | −1.18 (-5.26,2.90) | 0.571 | −0.82 (-5.58,3.93) | 0.735 | 0.22 (-1.97,2.41) | 0.845 |
| Extra adjustment for *Penicillium* sp. (0/1) | Ethyl isobutyrate | 1.93(1.08,3.44) | **0.026** | −1.07 (-5.16,3.02) | 0.607 | −0.51 (-5.28,4.27) | 0.836 | 0.06 (-2.08,2.20) | 0.956 |
| Extra adjustment for dampness or mold (0/1) | Ethyl isobutyrate | 2.26(1.23,4.15) | **0.008** | −1.96 (-6.14,2.22) | 0.358 | −1.59 (-6.42,3.24) | 0.518 | −0.28 (-2.48,1.92) | 0.804 |
| Extra adjustment for construction year (0/1) | Ethyl isobutyrate | 1.94(1.08,3.48) | **0.026** | −1.18 (-5.27,2.91) | 0.572 | −0.80 (-5.57,3.96) | 0.742 | 0.22 (-1.98,2.42) | 0.843 |
| Original model in Table 4 | Ethyl 2-methylbutyrate | 1.60(1.03,2.48) | **0.035** | −0.92 (-3.89,2.06) | 0.545 | −2.01 (-5.49,1.46) | 0.256 | −1.04 (-2.59,0.52) | 0.190 |
| Extra adjustment for *Aspergillus* sp. (0/1) | Ethyl 2-methylbutyrate | 1.58(1.01,2.45) | **0.044** | −0.73 (-3.74,2.28) | 0.637 | −1.65 (-5.15,1.85) | 0.355 | −0.95 (-2.54,0.64) | 0.242 |
| Extra adjustment for keeping cat/dog (0/1) | Ethyl 2-methylbutyrate | 1.58(1.01,2.46) | **0.045** | −0.81 (-3.80,2.18) | 0.597 | −1.86 (-5.35,1.63) | 0.297 | −1.01 (-2.58,0.57) | 0.212 |
| Extra adjustment for construction year (0/1) | Ethyl 2-methylbutyrate | 1.52(0.97,2.36) | 0.065 | −0.93 (-3.91,2.06) | 0.543 | −2.02 (-5.51,1.47) | 0.257 | −1.07 (-2.62,0.49) | 0.180 |
| Original model in Table 4 | 2-Ethyl-1-hexanol | 0.91(0.28,2.89) | 0.868 | −3.13 (-10.8,4.55) | 0.424 | −8.07 (-16.7,0.58) | 0.068 | −3.75 (-7.77,0.27) | 0.067 |
| Extra adjustment for *Cladosporium* sp. (0/1) | 2-Ethyl-1-hexanol | 0.90(0.28,2.90) | 0.858 | −3.93 (-11.7,3.86) | 0.323 | −8.95(-17.7,-0.19) | **0.045** | −3.73 (-7.82,0.36) | 0.074 |

Bold values: $p < 0.05$.
[a] Log transformed values.
[b] Two-level ordinal logistic regression models (individual, centre), adjusting for gender, age, BMI, smoking habit, education level, occupational status and home environment factor (factors) described in the first column.
[c] Two-level linear mixed regression models (individual, centre), adjusting for gender age, BMI, smoking habit, education level, occupational status and home environment factor (factors) described in the first column.

et al., 2007) and was associated with allergic rhinitis in one home environment study (Araki et al., 2012). The compound 1-octen-3-ol can be related to indoor mold status (Schleibinger et al., 2008) and many mold species can emit 1-octen-3-ol (Fiedler, Schütz, and Geh, 2001). Oxidation of linoleic acid is one source of 1-octen-3-ol (Lee et al., 2020). Thus, indoor 1-octen-3-ol found in the homes in our study can be from microbial sources.

2-Hexanone was associated with lower $FEV_1$ when controlling for indoor painting in the last four years. We found no previous studies on 2-hexanone and lung function. The compound 2-hexanone can be emitted from microbial growth in buildings (Korpi, Jarnberg, and Pasanen, 2009). However, this compound can sometimes be used in paints (Tagiyeva and Sheikh, 2014; Spencer and Schaumburg, 1985). Since we found health associations for this compound when adjusting for indoor painting, the source can be microbial growth.

2-Heptanone was related to lower $FEV_1$/FVC in our study. We found no previous studies on 2-heptanone and lung function but one Swedish school study found that 2-heptanone concentration in classrooms was associated with pupils' nocturnal breathlessness and doctor diagnosed asthma (Kim et al., 2007). Two experimental studies found that 2-heptanone can be emitted from a mixture of fungi growing on building materials (Claeson et al., 2002; Sunesson et al., 1996). We found that 2-heptanone was higher in homes with *Aspergillus* sp. and *Cladosporium* sp. spores in the air. Thus, the source of 2-heptanone in our study can be indoor microbial growth.

### 4.3. 2-Ethyl-1-hexanol, 3-octanone and 2-heptanone associated with impaired lung function among those in damp homes

Our study indicated that there can be synergistic effect between VOC and other types of microbial components in damp buildings on human airway since subjects in homes with dampness were more likely to have reduced lung function (lower $FEV_1$ and/or lower $FEV_1$/FVC) when exposed to 2-ethyl-1-hexanol, 3-octanone and 2-heptanone, as compared to subjects in homes without reported dampness.

2-Ethyl-1-hexanol was related to lower $FEV_1$ when controlling for *Cladosporium* sp. spores in the air. To our knowledge, our study is the first to show that 2-ethyl-1-hexanol in air in dwellings can be associated with impaired respiratory health among adults. Two previous studies have reported respiratory effects of this compound in occupational

settings. Working in Swedish hospital buildings with 2-ethyl-1-hexanol emission due to the degradation of the plastic floor coverings was related to increased prevalence of asthma (Norback et al., 2000) and onset of asthma among office workers in Finland (Tuomainen, Seuri, and Sieppi, 2004). It has been suggested that microorganisms can decompose plasticizers and emit 2-etyl-1-hexanol to air in indoor environment (Wakayama et al., 2019). However, chemical degradation of water-based glues or plasticizers in floor materials is believed to be the main sources of 2-ethyl-1-hexanol (Wakayama et al., 2019; Tuomainen, Seuri, and Sieppi, 2004). Increased concentrations of 2-ethyl-1-hexanol was found in homes with *Cladosporium* sp. in the present study. Thus, this compound can be associated with microbial exposure in our study.

Participants living in homes with signs of dampness were more likely to have lower $FEV_1$ and $FEV_1$/FVC when exposed to 3-octanone in our study. We found no previous studies on the effect of 3-octanone on lung function. Indoor 3-octanone concentrations in classrooms was shown to be related to nocturnal breathlessness in pupils (Kim et al., 2007). One review suggested that 3-octanone is one main microbial VOC found in homes (Korpi, Jarnberg, and Pasanen, 2009), suggesting that 3-octanone in our study can be from microbial sources.

### 4.4. VOC groups associated with asthma and impaired lung function

Three groups of VOC were identified according to the factor analysis. We found that VOC group 2 was associated with asthma, and VOC group 1 and VOC group 3 were associated with lower $FEV_1$ and lower $FEV_1$/FVC. Our results indicated that factor analysis can be a good way to study health effects of VOC compounds produced by microbial growth.

### 4.5. Interaction between dimethyl disulphide, 1-butanol and gender

We found that females had more asthma symptoms than men when exposed to dimethyl disulphide. The reason for this gender difference is unclear. However, women can have lower odor threshold than men (Doty and Cameron, 2009). Dimethyl disulphide has an unpleasant, garlic-like odor and thus female participants in our study could more easily detect this compound. In contrast, males in our study had lower $FEV_1$ than women when exposed to 1-butanol. The reason of this gender difference is not clear.

### 4.6. VOC associated with other exposures in home environment

We found that some VOC were related to other factors in homes than dampness and mold. This agrees with other studies reporting that some VOC known to be produced by microorganisms can also be emitted from dry building materials, including plastic materials (Choi, Schmidbauer, and Bornehag, 2017; Korpi, Jarnberg, and Pasanen, 2009; Schuchardt and Strube, 2013). Dampness and mold can be more common in older buildings (Norback et al., 2017). Thus, higher levels of ethyl isobutyrate and ethyl 2-methylbutyrate in older houses in our study could be related to higher prevalence of mold and dampness in older buildings. The reason that higher level of ethyl 2-methylbutyrate was found in homes with cat/dog in our study is unclear but one study reported that homes with furry pets (especially dogs) had increased concentrations of microbial components in mattress dust (Tischer et al., 2015). Thus, living in homes with furry pets can increase the exposure to microbial compounds. The reasons for increased levels of 2-heptanone, 2-hexanone and 1-octen-3-ol in detached/semi-detached houses, and lower level of 2-hexanone level in recently painted homes remains unclear.

### 4.7. Biological plausibility of the findings

It is difficult to conclude on biological plausibility of our findings, since there is a lack of experimental human data on these VOC in relation to respiratory effects. However, it is well known that dampness and mold in indoor environments can impair respiratory health, even if the causative agents have not been identified. Our finding of an interaction between some VOC and signs of dampness and mold growth in homes, suggests that dampness can cause a complex exposure, including emission of VOC and microbial exposure, which can influence respiratory health. However, the sources of the VOC associated with respiratory health can also be of non-microbial origin.

### 4.8. Strengths and limitations

Our study is the first to investigate associations between individual VOC reported to be associated with dampness and microbial growth in dwellings and adult respiratory health. All participants had lived in the same dwelling since the previous medical study in ECRHS (eight years or more) which increased the long term validity of our exposure assessment. We used objective health data and objective exposure data in our study which reduce the risk of reporting bias. We randomly recruited the study population from three Nordic cities which would reduce selection bias. Moreover, the sample was enriched by including additional participants living in damp homes, which increase the power of the study. For health associations, we have adjusted home environment factors related to relevant VOC compounds.

Some limitations should be noted. It is a cross-sectional study in a limited geographic area in Northern Europe, with a relatively small number of subjects. We have only data on visible dampness or mold in the dwellings. Potential hidden dampness can exist in dwellings which cannot be observed. One more limitation is that COPD and asthma can give similar symptoms. However, COPD can be expected to be uncommon in such a young population. Lack of data on ethnicity of the participants and information on use of home cleaning chemicals is another limitation. We did not adjust p values for multiple testing, instead we looked on patterns of associations in different statistical models. Therefore, we cannot exclude that some statistically significant associations were random findings. However, many associations were on $p < 0.01$ level.

## 5. Conclusions

Indoor exposure to some individual VOC, including dimethyl disulphide, ethyl isobutyrate and ethyl 2-methylbutyrate, can be related to adult asthma. Some VOC, including isobutanol, 3-methyl-1-butanol, 2-methyl-1-butanol, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone and 2-ethyl-1-hexanol can be associated with reduced lung function. Associations between these VOC and respiratory illness can be stronger in homes with dampness and indoor mold growth. There can be gender difference in respiratory health effects when exposed to indoor VOC. Factor analysis can be a method way to study health effects of VOC in respiratory health epidemiology on VOC which can be produced by microorganisms.

## Author statement

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

review & editing.Dan Norbäck: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Software; Supervision; Resources; Validation; Writing – review & editing.

## 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

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