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**Indoor air pollution, physical and comfort parameters related to schoolchildren's health:
data from the European SINPHONIE study**

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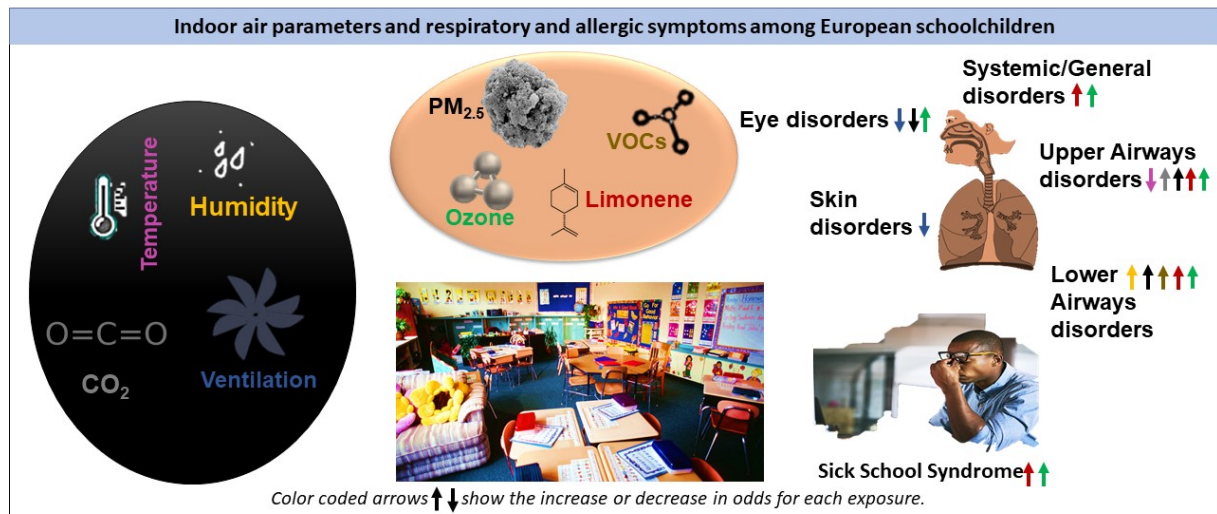
130 None

131 **Abbreviations**

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133	ACH	Air change rate per hour
134	aOR	Adjusted odds ratio
135	ALRI	Acute lower respiratory infection
136	C°	Temperature in Centigrade
137	CO	Carbon monoxide
138	CO ₂	Carbon dioxide
139	EC	European Commission
140	ETS	Environmental tobacco smoke
141	IAQ	Indoor air quality
142	IAP	Indoor air pollution
143	PM _{2.5}	Particulate matter with a diameter of
144		2.5 µm or less
145	SBS	Sick building syndrome
146	SD	Standard deviation
147	SINPHONIE	School indoor pollution and health:
148		Observatory network in Europe
149	VOCs	Volatile organic compounds
150	WHO	World Health Organization

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Highlights

- Indoor air physical and comfort parameters in 114 schools across 23 European countries were measured.
- $\text{PM}_{2.5}$, radon and carbon dioxide concentrations were higher compared to air quality guidelines.
- VOCs, particulate matter and physical parameters were positively and negatively associated with different disorders.

Abstract

Substantial knowledge is available on the association of the indoor school environment and its effect among schoolchildren. In the same context, the SINPHONIE (School indoor pollution and health: Observatory network in Europe) conducted a study to collect data and determine the distribution of several indoor air pollutants (IAPs), physical and thermal parameters and their association with eye, skin, upper-, lower respiratory and systemic disorder symptoms during the previous three months. Finally, data from 115 schools in 54 European cities from 23 countries was collected and included 5,175 schoolchildren using a harmonized and standardized protocol. The association between exposures and the health outcomes were examined using logistic regression models on individual indoor air pollutants (IAPs); a VOC (volatile organic compound) score defined as the sum of the number of pollutants to which the children were highly exposed (concentration > median of the distribution) in classroom was also introduced to evaluate the multiexposure – outcome association, while adjusting for several confounding factors. Median concentration levels of PM_{2.5}, benzene, limonene, ozone and radon in classrooms were associated with increased odds among schoolchildren to suffer from upper, lower airways, eye and systemic disorders. Increased odds were also observed for any symptom (sick school syndrome) among schoolchildren exposed to concentrations of limonene and ozone above median values. Furthermore, the risks for upper and lower airways and systemic disorders significantly increased with the VOCs score. Results also showed that increased ventilation rate was significantly associated with decreased odds of suffering from eye, skin disorders whereas similar association was observed between temperature and upper airways symptoms. The present study provides evidence that exposure to IAPs in schools is associated with allergic and respiratory symptoms in children. Further investigations are needed to confirm our findings.

185 Keywords: indoor air pollution, allergy, VOC, sick building syndrome, multi-pollution, thermal
186 parameters
187

1. Introduction

Children are more vulnerable than adults to environmental risks because of a number of factors: children are constantly growing, they breathe more air, consume more food, and drink more water than adults do, in proportion to their weight (*WHO / Environmental Risks*, n.d.). Their developing respiratory and immune systems and different responses to environmental exposure puts children at increased risk of developing various diseases including respiratory and allergic symptoms compared to adults (Scientific Committee on Health and Environmental Risks (SCHER), 2007). Many studies have reported that the overall indoor environment in schools can cause or contribute to acute and chronic health problems such as rhino conjunctivitis, and other allergic and general symptoms (Annesi-Maesano et al., 2012; Daisey et al., 2003; Hulin et al., 2012; Ramachandran et al., 2005; Siskos et al., 2001). In industrialized countries, people spend around 90% of their time indoors, where both the number and the concentrations of air pollutants can be higher than those outdoors (Klepeis et al., 2001; C.-Y. Lu et al., 2018). Additionally, surrounding outdoor air pollution is also a matter of concern indoors as it can contribute to the indoor environment by entering through windows, doors and other openings (Jantunen et al., 2011), thus compromising the indoor air quality (IAQ) further.

In school environments, and in particular primary schools, children are likely to be exposed to poor IAQ (Annesi-Maesano et al., 2012). A review published on the impact of indoor air pollution and its sources in the school's environment showed that higher concentrations of indoor air pollutants in schools can be related to various adverse health outcomes, namely allergic and respiratory symptoms and diseases (Annesi-Maesano et al., 2013). Furthermore, decreases in learning performance and academic execution were seen in schoolchildren as a result of exposure to various socio-demographic factors and indoor air pollutants in classroom (Grineski et al., 2016). While evidence exists, there is still a lack of comprehensive and accurate information as based on a standardized protocol about indoor air environments in schools and

their effects on health, existing data are heterogeneous and there have been few studies with similar case definitions. Previously, no study used a large comprehensive and multi-perspective standardized protocol (Bentayeb et al., 2013).

In order to overcome those shortcomings, the European Schools Indoor Pollution and Health: Observatory Network in Europe (SINPHONIE) study aimed to broaden the knowledge on the health status of schoolchildren in relation to the school environment in a large sample of European schools by applying the same standardized and comprehensive protocol. The primary aims of the study were using a standardized protocol: i) to measure levels of particulate matter (PM), volatile organic compounds (VOCs), ozone, carbon monoxide (CO) and radon and physical and comfort parameters; ii) to investigate the associations between the assessed air pollutants and comfort parameters in schools and the recorded health outcomes in children taking as reference the last 3 months.

2. Material and Methods

2.1. Overview and study design

SINPHONIE was a two-year multidisciplinary cross-sectional study conducted in European schools, in which data on schoolchildren, parents/guardians, teachers, surrounding outdoor environments and indoor air quality of schools were collected using standardized and harmonized procedures and protocols. More detailed information about the SINPHONIE study and its methodology is provided elsewhere (www.sinphonie.rec.org, Csobod et al., 2014).

2.2. Study Population

The SINPHONIE study targeted 115 schools in 54 cities of 23 European countries. The field survey collected data from November 2011 to March 2012 after the start of usual the academic session. A total of 7,089 children, aged 7-14 years, and their parents/guardians, were given questionnaires on the children's health and household characteristics, as well as perceived

notions on their classroom environments, while teachers in 319 classrooms were given questionnaires to ascertain both physical and perceived characteristics of both the classrooms and school environment in general.

Parents/guardians of 5175 eligible schoolchildren responded to the health questionnaire. In order to account for heterogeneity, countries were grouped into four geographical regions on the basis of climatic conditions, such as mean temperature during colder months (the heating season). Each country was represented by three to six schools. Schoolchildren were included in the study based on availability of data for the outcomes of interest.

2.3. Sampling

Levels of key air pollutants and comfort parameters and other environmental factors, recognized by World Health Organization (WHO) and European Commission (EC) as of interest (Csobod et al., 2014; European Commission, 2008; WHO Regional Office for Europe, 2010) were measured both indoors and outdoors in each participating school by teams of centrally trained researchers. For the present analysis, the concentrations of VOCs ($\mu\text{g}/\text{m}^3$), $\text{PM}_{2.5}$, CO (ppm), ozone, and radon (Bq/m^3) were taken into consideration. VOC samples were collected using Radiello diffusive samplers (Fondazione Salvatore Maugeri, FSM). Passive air sampling was conducted for five days (from Monday morning to Friday afternoon during school hours with the exception of measurements for radon which spanned 4 weeks. All reported levels of VOC concentrations are time-averaged values on the week of assessment. Radon samples were assessed using passive track counts on film exposed using Gammadata RAPIDOS (www.gammadata.se). All passive samplers were installed at 1.5 meters above the floor level. For the determination of the $\text{PM}_{2.5}$ mass fraction ($\mu\text{g}/\text{m}^3$), a MS&T area sampler with quasi noiseless pump (Air Diagnostics and Engineering Inc: Indoor Air Quality) was used, whereas CO was assessed using the Neotronics Impulse XP through a short-term assessment (30 minutes in each room). Simultaneously, physical and comfort parameters such as temperature

(°C), relative humidity (%) and CO₂ (ppm) were continuously tracked by a low-cost logger (CaTec Klimabox) during the period of data collection. Finally, ventilation rates (air change rate per hour (ACH)) were calculated for 290 out of 319 classrooms based on CO₂ measurements in each classroom.

2.4. Sample analysis, quality assessment and quality control

VOCs were collected using stainless-steel sampling tubes containing Tenax® TA (60/80 mesh). After sampling, the Tenax tubes were thermally desorbed (Dani STD 33.50) and quantified using a non-polar column by gas chromatography (Agilent Technologies 6890N) coupled to a mass spectrometry detector (Agilent Technologies 5973). To control contamination during transport and sampling, a field blank was employed in every school. All samples were taken in duplicate to test the reproducibility of measurements.

Formaldehyde was sampled by Radiello (RAD 165, Sigma Aldrich) passive devices consisting of a cartridge filled with 2,4-dinitrophenylhydrazine (2,4-DNPH), which was desorbed in 2 ml of acetonitrile (Sigma-Aldrich) and manually stirred for 30 minutes. Then, the solution was passed through a polyvinyl difluoride 0.45 mm-syringe filter (13 mm Syringe Filter, Specanalítica) and determined using isocratic reverse phase High Performance Liquid Chromatography (HPLC) (Agilent Technologies, 1220 Infinity LC) with a UV detector operated at 360 nm. Each cartridge was sealed after sampling and refrigerated at <4 °C. As an internal quality control, duplicate samplings were collected in 1 school per set of 3 schools. Field blanks were collected and analyzed to assess possible contamination through the sample collection and analysis process.

Carbon monoxide (CO) concentrations were measured continuously using an IAQ-CALC monitor (model 7545, TSI, Inc.). PM_{2.5} concentrations were continuously monitored using two TSI DustTrak DRX photometers (model 8533; TSI Inc.). The measurements were conducted for 24 hours indoors at 1-minute intervals.

Carbon dioxide (CO₂) concentrations, temperature and relative humidity were measured continuously using an IAQ-CALC monitor (model 7545, TSI, Inc.). The ventilation rate (ACH) was estimated based on decay of the indoor CO₂ concentration when classrooms were occupied. The ventilation rate values were estimated using the average outdoor CO₂ concentration over the 5-day measurement period. The estimated final ventilation rate in the classroom is the time-weighted average of the ventilation rates obtained during the school week. The ACH was calculated based on the ASTM E 741-00 (2006) and ASTM D 6245-98 (2002) standards. All instruments were calibrated each year at the factory.

2.5. Health outcomes at the period of the survey

To determine whether or not a health outcome was significantly associated with air pollutants and comfort parameters in schools and classrooms, parents/guardians were asked to complete a standardized questionnaire including questions on the past 3 months.

The questionnaire was based on previous studies conducted in Europe among schoolchildren that investigated children's health. These studies include the ISAAC (International Study of Asthma and Allergies in Childhood) (M Innes Asher et al., 2006), HESE (Health Effects of School Environment) (*Health Effects of School Environment (HESE) - Final Scientific Report*, 2006) and the SEARCH (School Environment and Respiratory Health of Children) study (Csobod et al., 2010).

Symptoms and diseases were assessed through the question "*During the past three months, has your child had any of the symptoms/disease?*", with four possible answers i.e. never, 1-3 times per month, 1-4 times per week and daily. These were categorized into five dichotomous outcomes according to the type of affected organ: eye symptoms, skin related symptoms, upper airways-, lower airways symptoms, and systemic symptoms (Table A.1). A variable indicating "At least one disorder" occurring was also introduced if schoolchildren reported any disorder during the mentioned period. To further support the fact that symptoms and diseases in the past

3 months were related to the school environment, the parents/guardians were queried on whether children' symptoms improved during the weekend (Table A.3.).

2.6. Confounders

Information on other risk factors that were considered potential confounders of the relationships between school environment and health, such as age, gender, race, maternal education and employment, exposure to environmental tobacco smoke at home (ETS), pets, country and family history of allergy, were also collected through the structured questionnaire.

2.7. Statistical analysis

A descriptive analysis was performed using percentages for categorical variables and means, medians, standard deviations (SD) for continuous variables, such as concentrations of indoor air pollutants, physical and comfort parameters and ventilation rates. A dichotomous variable was introduced to classify exposure of the schoolchildren, namely "low" (variable=0) versus "elevated" (variable=1), with respect to the median value of the distribution of each of the pollutants for all classrooms. To take into account exposure to multiple pollutants, a total VOC (TVOC) score was computed as the sum of the number of elevated exposure (>median) to the 5 VOCs, namely formaldehyde, benzene, naphthalene, limonene and tetrachloroethylene (Billionnet et al., 2011). The score ranged from 0 to 5; TVOC is important to consider as it can provide additional data from indoor construction products and other indoor activities such as cleaning activities, furniture, etc. (Virji et al., 2019).

At first, we described the characteristics of the population of schoolchildren, their exposure to air pollutants and comfort parameters and their frequency of past 3-month disorders. Population characteristics between groups were compared using the Pearson χ^2 test for categorical variables. We then investigated the association between each indoor air pollutant and each health outcome or any symptom using adjusted logistic regression models taking into account heterogeneity among countries. Three logistic models (1, 2 and 3) were performed and their

respective adjusted odds ratios (aOR) and their 95% confidence interval (95% CI) were calculated. Model 1 was adjusted on confounders which included age, gender, ethnic group, maternal education and employment, ETS, pets, country and family history of allergy; Model 2 was further adjusted on ventilation rate and Model 3 was adjusted on confounders from Model 1 with addition of CO₂. In the case of VOCs, aORs were calculated for each of 5 strata (from not being exposed to (stratum 0) to being exposed to all the 5 (stratum 5)) while adjusting for confounders. The same logistic regression models were applied to investigate the association between any of the symptoms and physical and comfort parameters. The significance level was set at an alpha value of <0.05. All analyses were carried out using STATA 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

3. Results

3.1. *Description of population, health outcomes and air pollutants, physical and comfort parameters*

Overall, 5,175 schoolchildren in 319 classrooms from 115 schools across 23 European countries were ultimately included after obtaining consent from their parents/guardians, corresponding to a participation rate of 73%. The schoolchildren had a mean age of 8.91 years (SD=1.53) for females and 8.98 years (SD=1.51) for males. Population characteristics are shown in Table 1.

The Caucasian ethnic group was the most frequent. Most parents/guardians were highly educated and fully employed. Of the total, 11.62% of the schoolchildren were exposed to maternal smoking during pregnancy and 26.45% were exposed to ETS at home. Few schoolchildren (8.33%) were exposed to molds or dampness in bedrooms. Approximately ¼ of the children (26.19%) lived in zones close to heavy traffic. Almost 50% of the participants had a family history of allergy. Ethnicity was significantly associated with gender whereas all other socio-demographic variables and risk factors showed no significant association.

During the past three months, systemic disorders (11.77%) and upper airways symptoms (10.82%) were the most frequently reported health outcomes among schoolchildren followed by lower airways symptoms, skin and eye symptoms respectively (Table 2). The reporting of skin disorders and upper airways symptoms differed significantly across gender.

Table 3 shows distributions of the concentrations of air pollutants. A quarter of schoolchildren were exposed to elevated indoor PM_{2.5}, benzene, radon and CO₂ levels according to the EU Commission and WHO standards (European Environment Agency, 2019; WHO Regional Office for Europe, 2010; European Commission, 2008). Summary statistics of indoor air pollutants according to geographic clusters are reported. Indoor air concentrations of benzene, naphthalene, PM_{2.5}, ozone and radon were significantly higher in Southern and Central Eastern Europe. No significant difference in concentrations of CO was observed between clusters and values were below WHO guidelines. CO₂ concentrations were also below the WHO indoor air quality and/or EU guidelines in the Western Europe region (WHO Regional Office for Europe, 2010). The lowest median temperature and ventilation rates were observed in Western Europe (Table A.2). A comparison between different guidelines and sources and SINPHONIE is described in Table A.3.

In terms of VOC scores, 29%, 19% and 11% of schoolchildren were exposed to two, three and four VOCs respectively, whereas around 11 % were relatively free of VOC exposure, with values the below median concentration for all 5 VOCs included in this study (Figure 1). A Pearson correlation heatmap between indoor air pollutants, physical and comfort parameters is shown in Table 4. The highest correlation was observed between naphthalene and limonene, followed by relative humidity and ozone and CO₂, whereas, a negative correlation was observed between temperature and both relative humidity and CO₂. The median indoor temperature, relative humidity and CO₂ concentration inside the classrooms was 22°C, 39% and 1369 ppm respectively. The median ventilation rate was in the classrooms was 0.40 ach.

3.2. Relationship of indoor air pollutants to past 3-month health disorders

Independently of the type of model (Table 5), upper airways disorders were related to elevated levels of exposure to benzene, limonene, radon and ozone. A similar association was found with PM_{2.5}, but the effect diminishes when controlling for CO₂. Lower airways disorders were related to benzene, PM_{2.5}, ozone and limonene. Systemic disorders were associated with tetrachloroethylene (when controlling for ventilation rate), benzene (when controlling for model 1 and ventilation rate), limonene, ozone and radon. An inverse relationship was observed in cases of eyes-related symptoms and PM_{2.5}. Ozone exposure increased the odds of all the considered outcomes except for skin related disorders in all three logistic regression models. Elevated levels of limonene and ozone were significantly related to any symptom in all three models (Table 6) whereas temperature showed protective effect on symptoms. Increased odds were observed between occurrence of any disorder and relative humidity when controlling for ventilation rate. An inverse relationship was found between higher levels of PM_{2.5} and any symptom that become significant when controlling for CO₂ (aOR = 0.81, 95% CI: 0.68 – 0.98). Multi-pollutant exposure to VOCs showed an even more pronounced effect in the case of upper airways, lower airways and systemic symptoms, with the odds increasing with the number of VOCs in the mixture (Table 7). A significant negative association was found between exposure to one VOC and lower airways disorders (aOR = 0.55, 95% CI: 0.31 – 0.96).

3.3. Relationship of physical and comfort parameters to past 3 month health disorders

Children exposed to higher levels of CO₂ in school were at a significantly higher risk of experiencing upper, lower airways and systemic outcomes (Table 8). Relative humidity was also significantly associated with increased odds of suffering from lower airways and systemic disorders among schoolchildren. Furthermore, schoolchildren in classrooms with higher temperatures in classrooms seemed to be significantly protected against upper airways disorders. Similarly, ventilation rate also had an apparent protective effect over eye and skin

related disorders. When parents were asked if the children feel better when away from school, we observed significant relationships between the improvement when children were far from schools during the week-end of all symptoms except for skin disorders across both genders (Table A.3).

4. Discussion

4.1. Key Findings

The main objective of our study was to investigate the relationship between indoor air quality and comfort conditions in classrooms and health among European schoolchildren. In our sample, schoolchildren were excessively exposed to elevated concentrations of several air pollutants. Of note, the mean concentrations of benzene, limonene, PM_{2.5} and CO₂ exceeded the WHO and/or EU air quality guidelines (World Health Organization, 2010; World Health Organization. Occupational and Environmental Health Team, 2006). Furthermore, 28.87%, 19.43%, 11.68% of children were co-exposed to 2, 3 and 4 VOCs known to be dangerous for health, respectively. Additionally, in our study, we found the median temperature to be over the 90% acceptability limit according to ASHRAE guidelines on thermal environmental conditions for human occupancy (American Society of Heating et al., 2004).

Our study findings indicate that after adjustment for confounders and either ventilation or CO₂, elevated levels in classrooms of PM_{2.5}, benzene, limonene, CO, ozone and radon were associated with increased risks of upper and lower airways, eye and systemic disorders in schoolchildren. Suffering from any symptom was also significantly associated with limonene and ozone. Additionally, the risks for upper and lower airways and systemic disorders significantly increased with the VOCs score.

4.2. Comparison of findings with other published work

Several studies have suggested a potential relationship between multi-pollutant exposures and adverse health outcomes including respiratory and/or allergic symptoms, headaches, skin symptoms, and nausea in children (Annesi-Maesano et al., 2012; *Health Effects of School Environment (HESE) - Final Scientific Report*, 2006; Rumchev et al., 2002; G. Smedje et al., 1997; G Smedje & Norbäck, 2001; Zhao et al., 2008). Further, both indoor and outdoor air pollution along with indoor environmental factors, including temperature and relative humidity have been shown to be associated with occurrence of any symptom or sick building syndrome (sick school syndrome in schools) (Deng et al., 2016; Jiang et al., 2018; C. Lu et al., 2016). Although PM_{2.5} has been associated with several health outcomes, impacts from PM_{2.5} levels specifically in classrooms has only been described in (Annesi-Maesano et al., 2007, 2012). In the current study, elevated levels of benzene in classrooms were significantly associated with upper airways, lower airways and systemic symptoms in schoolchildren. These findings are in agreement with earlier studies (Annesi-Maesano et al., 2012; *Health Effects of School Environment (HESE) - Final Scientific Report*, 2006; Rumchev et al., 2002; G. Smedje et al., 1997; G Smedje & Norbäck, 2001; Zhao et al., 2008). Our study also found no significant association between formaldehyde and allergic symptoms as observed by Ezratty et al., 2007. The difference in outcomes among the studies might be due to different exposure levels, which could blur the real association with benzene (Peder Wolkoff & Nielsen, 2010). For the first time, we observed an adverse effect of limonene in schoolchildren. Limonene measured in classrooms can be introduced through the use of cleaning products, air fresheners and perfumes (Peder Wolkoff & Nielsen, 2017; Steinemann et al., 2011; Nazaroff & Weschler, 2004). Limonene is generally considered a harmless substance and the most significant health effects associated with limonene are irritation of eyes, nose, throat and skin (Kotzias et al., 2005). However, a recent Canadian study provides evidence that household exposure to limonene may increase the prevalence of asthma at the general population level overall in children (Dales & Cakmak, 2019). Our study also found a significant relationship between upper

airways symptoms and the concentration of CO, contrary to those found in previous literature (Castro et al., 2009; Chen et al., 1999).

Formaldehyde was seen to have no effect in our study, which is contrary to previous work (Mendell, 2007). A recent meta-analysis on formaldehyde exposure in children calculated a pooled odds ratio (OR) of 1.03 (95% CI: 1.02 -1.04) for an increase of 10 µg/m³ (McGwin et al., 2010). Two other studies focusing on respiratory symptoms in relation to formaldehyde also found increased risk of sensory irritation with higher indoor concentrations (Rumchev et al., 2002; G Smedje & Norbäck, 2001). Although, it is not excluded that such studies were flawed by yet to be unidentified confounding variables, a formaldehyde indoor air limit of 0.1 ppm should protect even particularly susceptible individuals from both irritation effects and any potential cancer hazard (Golden 2011).

It is well established that outdoor ozone is associated with school absenteeism among schoolchildren with asthma-related symptoms due to respiratory illnesses (Gilliland et al., 2001; Ramachandran et al., 2005). In our study, we found that indoor ozone was highly significantly associated with eye, upper and lower airways and systemic disorders. Whether ozone resulted from transfer from outdoors or from school activities and characteristics could not be established. Ozone reacts chemically with components of buildings and building furnishings as well as with some indoor air pollutants. These reactions usually reduce indoor ozone levels to below outdoor air levels, unless strong indoor sources of ozone are present, however these chemical reactions can produce new air pollutants that may possibly cause adverse health effects (P. Wolkoff et al., 2000).

Our analysis showed statistically significant associations between elevated concentrations of radon and upper airways and systemic disorders on which extreme caution is needed. It is well known that elevated radon concentrations increase the risk of lung cancer (Baysson et al., 2004; Darby et al., 1998; Field et al., 2000; Krewski et al., 2006), however, other adverse effects of radon have been observed, namely in the case of chronic obstructive pulmonary disease

(Turner et al., 2012) However, the rationale for a possible relationship of radon with non-malignant diseases is weak since radon mainly affects the human body by releasing alpha particles. The dose and response and other confounding factors should also be considered (Keith et al., 2012).

Due to the multi-pollution phenomenon, we considered a VOCs score summarizing simultaneous exposures to high levels of more than 1 VOC. A recent systematic review of 30 studies investigating the relation between domestic (day care, school, home) VOCs and asthma/allergic disease found approximately equal number of studies reporting either adverse associations of numerous VOCs or supporting no association (Nurmatov et al., 2015). The same review determined the majority of the studies to be of low quality, but also suggested that VOC exposure may not be a major risk factor for the onset of asthma/allergy in the general population based on the modest effect sizes and heterogeneous findings. In addition, short-term exposure to VOCs is found to cause irritation of eyes, nose, throat, and mucosal membranes, while long duration exposure include toxic reactions (*Indoor Air Quality May Be Hazardous to Your Health - MSU Extension*, n.d.). Predictable assessment of the toxic effects of complex VOC mixtures is difficult to estimate, as these pollutants can have synergic, antagonistic, or indifferent effects (Ebersviller et al., 2012; Mølhave et al., 1997). In a previous study, authors showed that the risk of respiratory symptoms in adults increased with the number of VOCs existing in the environmental mix (Billionnet et al., 2011). This was confirmed by our current study that demonstrated a stronger linear positive association between the VOCs score and systemic symptoms, as well as upper and lower airways symptoms. We found increasing odds with all respiratory symptoms and systemic disorders, whereas no association was seen for eye or skin symptoms. An inverse association was found between exposure to only one VOC and lower airways disorders, which could be explained due to small number of cases. Our relationships could be due to low ventilation and/or high CO₂, and/or indoor contaminants, e.g.

microbiological, and or odor annoyance. However, our models took into account both ventilation and CO₂ level, which suggests the importance of indoor contaminants.

Our study also found that schoolchildren exposed to higher levels of CO₂ had a higher association of reporting systemic, upper and lower airway symptoms. In terms of comfort parameters, earlier studies have found an association between asthma symptoms and CO₂ concentrations in schools (Norbäck et al., 1995). A cross-sectional study on asthma related symptoms and sick building syndrome (SBS) conducted in Swedish schools among school staff and students found that installing new ventilation systems in schools increased the air exchange rate from -0.1 to 4.0 and decreased the concentration of CO₂ in classrooms (Greta Smedje & Norbäck, 2000). When we look at ventilation rates, we found a protective effect on eye and skin related disorders.

Our results suggest a strong protective effect of temperature on upper airway symptoms, and of ventilation on eye and skin symptoms. In line with these findings, a study conducted in China found that classroom temperature and CO₂ had also positive association with daytime breathlessness, asthma attacks, current asthma, whereas no association was observed between relative humidity and symptoms (Mi et al., 2006). The same study also found a significant protective effect of indoor ozone in daytime breathlessness which is contrary to our findings where the ozone had a negative impact on all addressed symptoms except for skin disorders. Further studies are needed to investigate the role of the interaction between temperature and CO₂.

Examining a parameter denoting the occurrence of any symptom to take into account the fact that the school environment itself may have several health adverse effects yielded a relationship to limonene, ozone and PM_{2.5}. In a survey of 500 schools in New York city, it was observed that having at least one or more health symptoms was positively associated with IAQ-related classroom characteristics such as mold, carpeting, floor condition etc. even after controlling for relevant confounders (Kielb et al., 2015). A longitudinal study of a sample of junior high school

students followed for two years found higher concentrations of environmental pollutants such as PM₁₀, sulphur dioxide and nitrogen dioxide to be detrimental in increasing the prevalence and incidence of SBS and in decreasing the remission of the same symptoms (Zhang et al., 2014). In our study, we found a clear association between higher levels of exposure to limonene and ozone and the occurrence of any symptom, even when all confounders were considered. No associations were found between other pollutants and occurrence of any symptom. Because we also found that children feel better when they are away from school, the hypothesis of a potential impact of the school environment can be raised; although another possible explanation could be the decrease in the psychosocial and psychological load that children face during school hours. The design of our study, however, does not permit to infer the causality of the impact of the school environment.

4.3. *Possible mechanisms*

Several possible biologic mechanisms have been proposed supporting the association between exposure to indoor air pollution and adverse health symptoms. Previous studies have reported associations between VOCs and respiratory and allergic symptoms through different pathways such as oxidative stress and coagulation factors and genomics (Holloway et al., 2012). Inflammation may be another mechanism behind a number of self-reported health population among schoolchildren, such as upper- lower airways symptoms and systemic disorders.

4.4. *Strength and limitations*

Our study has several strengths. Study participants were included from 23 countries across Europe and considered 3 to 6 schools per country with multiple environmental settings (rural to urban, near and far from potential pollutant sources). Further, the included schools and classrooms had intentional variability in terms of flooring, surface area, and orientation of building to achieve a comprehensive sample of school environments, thus, minimizing the

likelihood of selection bias (Csobod et al., 2014). Multiple pollutants and ventilation rates were assessed to obtain a comprehensive observation of IAQ. We also adjusted for a large range of potential confounders such as socioeconomic factors, family history of asthma or allergies, passive smoking, and country to better assess the relation between IAQ among school children. In terms of limitations, although the questionnaire used in our study has been validated and used in previous international studies (M. I. Asher et al., 1995), we cannot completely rule out potential misclassification of disease arising from self-reporting of health symptoms unconfirmed by a physician. Measurements of IAPs and physical and comfort parameters exposure were conducted for one week only, which may not be representative of long-lasting exposure. Outdoor air pollution was not considered in this study; however, it may have an impact on IAQ and on health outcomes. Further, it is difficult to tease out the multiple environmental contributions to a particular health outcome, as children do not spend all of their time in the school setting. Finally, the cross-sectional nature of our study did not warrant a causal relationship between the school environmental exposures and the development of health symptoms.

4.5. Public health policy implications

The main strategy for the management of IAQ consists of developing a comprehensive, scientifically sound and detailed action plan. Such a plan should be targeted to new construction, as well as existing buildings, and should entail actions at both national and local levels. Action plans as such need to consider specific local conditions such as building design, type of building material and behavior and knowledge of occupants concerning the indoor environment. They have to involve both air quality and comfort parameters? Since such initiatives are strongly influenced by political and economic actors, harmonization of policies is inevitable.

5. Conclusion

587 Overall, the SINPHONIE data suggest that in Europe i) children are exposed to a variety of air
588 pollutants with levels above the recommended standards at school; ii) exposures to elevated
589 concentrations of several indoor air pollutants, including VOCs, and comfort parameters in the
590 classroom, are adversely associated with various adverse health outcomes among
591 schoolchildren and iii) there is a significant potential protective effect of some physical and
592 comfort parameters (temperature and ventilation) on respiratory and allergic symptoms.
593

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804

805 Table 1. Characteristics and risk factors of schoolchildren of the SINPHONIE study according to
806 gender (N = 5175)

	Gender			p-value
	Female	Male	Total	
	(n = 2588)	(n = 2557)	(N=5175)	
	n (%)	n (%)	N (%)	
Age				0.34
<7	180 (6.97)	164 (6.43)	344 (6.70)	
7 - 10	2160 (83.66)	2120 (83.10)	4280 (83.38)	
11 - 14	242 (9.37)	267 (10.47)	509 (9.92)	
Ethnic group				0.01
Asian	56 (2.57)	28 (1.28)	84 (1.92)	
Black	38 (1.74)	38 (1.74)	76 (1.74)	
Caucasian	1764 (80.88)	1839 (84.20)	3603 (82.54)	
Middle-Oriental	43 (1.97)	32 (1.47)	75 (1.72)	
Other	280 (12.84)	247 (11.31)	527 (12.07)	
Mother's education				0.47
College University	1054 (41.83)	1096 (44.02)	2150 (42.91)	
Secondary School	894 (35.48)	866 (34.78)	1760 (35.13)	
Completed Primary School	209 (8.29)	189 (7.59)	398 (7.94)	
Less Than Primary School	48 (1.90)	52 (2.09)	100 (2.00)	
Vocational School	315 (12.50)	287 (11.53)	602 (12.02)	
Father's education				0.12
College University	861 (35.85)	930 (38.98)	1791 (37.41)	
Secondary School	802 (33.39)	788 (33.03)	1590 (33.21)	

Completed Primary School	229 (9.53)	204 (8.55)	433 (9.04)
Less Than Primary School	36 (1.50)	26 (1.09)	62 (1.29)
Vocational School	474 (19.73)	438 (18.36)	912 (19.05)
Maternal employment	0.60		
Fully Employed	1459 (59.84)	1479 (61.29)	2938 (60.56)
Part time Employed	413 (16.94)	374 (15.50)	787 (16.22)
Pensioner	12 (0.49)	8 (0.33)	20 (0.41)
Unemployed	537 (22.03)	534 (22.13)	1071 (22.08)
Disabled	17 (0.70)	18 (0.75)	35 (0.72)
Paternal employment	0.82		
Fully Employed	1973 (84.57)	1996 (85.23)	3969 (84.90)
Part time Employed	140 (6.00)	139 (5.94)	279 (5.97)
Pensioner	28 (1.20)	20 (0.85)	48 (1.03)
Unemployed	178 (7.63)	173 (7.39)	351 (7.51)
Disabled	14 (0.60)	14 (0.60)	28 (0.60)
Maternal smoking during pregnancy	0.95		
No	2257 (88.41)	2230 (88.35)	4487 (88.38)
Yes	296 (11.59)	294 (11.65)	590 (11.62)
Family history of allergy	0.58		
No	1447 (59.50)	1443 (60.28)	2890 (59.88)
Yes	985 (40.50)	951 (39.72)	1936 (40.12)
ETS in the home	0.99		
No Never	1881 (73.62)	1856 (73.48)	3737 (73.55)
Yes Sometimes	302 (11.82)	298 (11.80)	600 (11.81)
Yes Often	372 (14.56)	372 (14.73)	744 (14.64)

Dampness or mold in bedroom				0.66
No	2342 (91.84)	2304 (91.50)	4646 (91.67)	
Yes	208 (8.16)	214 (8.50)	422 (8.33)	
Location of the home				0.09
Away from busy traffic	493 (19.59)	543 (21.75)	1036 (20.67)	
Little traffic	1372 (54.51)	1292 (51.76)	2664 (53.14)	
Busy traffic	652 (25.90)	661 (26.48)	1313 (26.19)	
Type of ventilation				0.76
Mechanical	92 (3.68)	96 (3.88)	188 (3.78)	
Natural	2255 (90.24)	2216 (89.61)	4471 (89.92)	
Naturally assisted exhaustion	152 (6.08)	161 (6.51)	313 (6.30)	
Pets				0.35
No	1601 (62.74)	1615 (64.01)	3216 (63.37)	
Yes	951 (37.26)	908 (35.99)	1859 (36.63)	

Table 2. Distribution of health outcomes by organs during the past three months among schoolchildren in the SINPHONIE study according to gender (N = 5175)

Symptoms	Gender			p-value
	Female	Male	Total	
	n (%)	n (%)	N (%)	
Eye				0.80
No	2380 (96.95)	2341 (96.82)	4721 (96.88)	
Yes	75 (3.05)	77 (3.18)	152 (3.12)	
Skin				<0.01

No	2337 (93.82)	2347 (96.03)	4684 (94.91)
Yes	154 (6.18)	97 (3.97)	251 (5.09)
Upper airways			0.03
No	2246 (90.13)	2165 (88.22)	4411 (89.18)
Yes	246 (9.87)	289 (11.78)	535 (10.82)
Lower airways			0.96
No	2295 (92.13)	2249 (92.10)	4544 (92.11)
Yes	196 (7.87)	193 (7.90)	389 (7.89)
Systemic			0.38
No	2193 (87.83)	2176 (88.64)	4369 (88.23)
Yes	304 (12.17)	279 (11.36)	583 (11.77)

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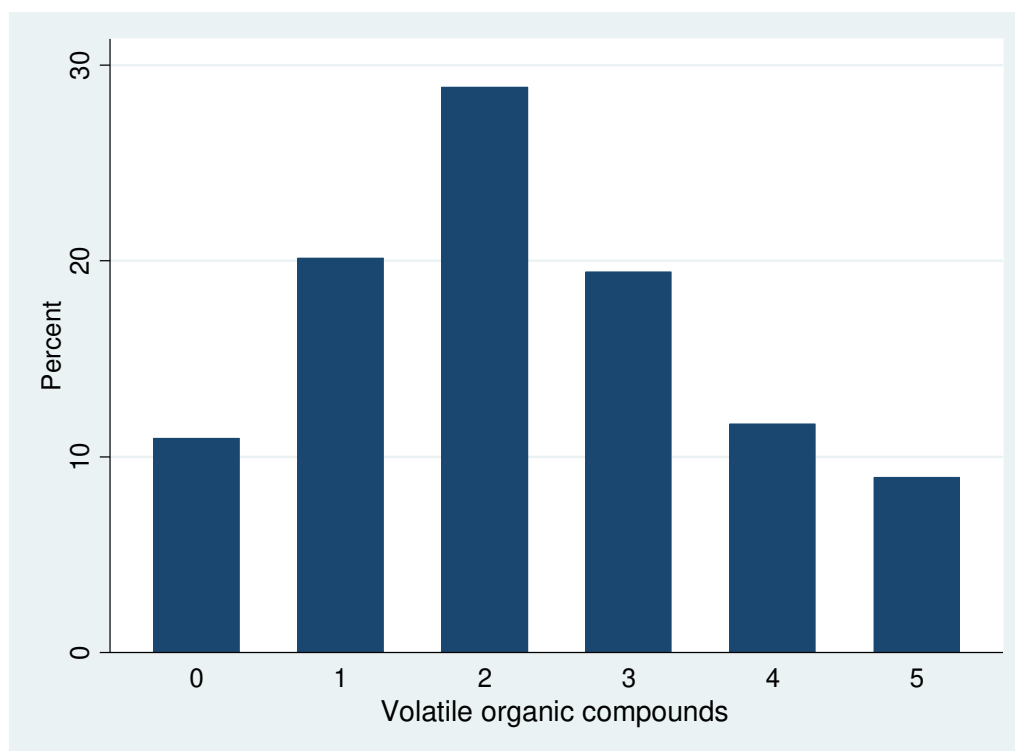
Table 3. Distribution of indoor chemical, physical and comfort parameters among schoolchildren and comparison with existing guidelines (N=5175)

Indoor air pollutants, physical and comfort parameters	Percentile								
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>10th</i>	<i>25th</i>	<i>Median</i>	<i>75th</i>	<i>90th</i>	<i>99th</i>
Benzene ($\mu\text{g}/\text{m}^3$)	4923	4.47	5.94	0.50	1.13	2.39	4.83	11.10	32.56
Naphthalene ($\mu\text{g}/\text{m}^3$)	4171	2.31	5.35	0	0	0.02	1.80	8.11	28.87
Limonene ($\mu\text{g}/\text{m}^3$)	4923	41.12	81.32	1.72	4.83	10.90	42.20	106.05	412.06
Formaldehyde ($\mu\text{g}/\text{m}^3$)	4967	14.50	10.25	5.88	7.61	11.31	17.84	28.20	50.28
Carbon monoxide (ppm)	4925	0.72	5.77	0	0	0.20	0.63	1.30	3.51
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	4715	45.31	34.55	16.67	22.40	38.36	51.31	85.6	187.50
Radon (bq/m ³)	4066	230.19	827.95	30	55.60	113.8	188	315.5	3785.00
Ozone ($\mu\text{g}/\text{m}^3$)	4620	6.93	14.17	0	0.20	3.00	7.61	15.02	52.07
Tetrachloroethylene ($\mu\text{g}/\text{m}^3$)	4655	1.35	5.58	0	0	0	0.63	3.34	11.14
Carbon dioxide (ppm)	4897	1581	903.57	659.88	918	1369.89	1938.60	3073	4158
Relative humidity (%)	4927	42.49	14.34	25.90	35.90	39.60	49.50	66	77
Temperature (°C)	4927	21.53	2.11	17	20	22	23.00	24	25
Ventilation rate (ACH)	4781	0.64	0.72	0.08	0.17	0.40	0.74	1.66	3.50

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812 Figure 1. Percentage of schoolchildren in schools with exposed to VOCs exceeding the
813 median concentration of each pollutant



814

Table 4. Pearson Correlation heatmap of indoor air pollutants, physical and comfort parameters

	Formaldehyde	Benzene	Tetrachloroethylene	Limonene	Ozone	Radon	Naphthalene
Formaldehyde	1	-0.003	0.031	0.173	-0.218	0.260	-0.045
Benzene	-0.003	1	-0.077	0.260	-0.114	-0.165	0.306
Tetrachloroethylene	0.031	-0.077	1	-0.038	0.013	-0.062	-0.053
Limonene	0.173	0.260	-0.038	1	-0.168	-0.103	0.465
Ozone	-0.218	-0.11	0.013	-0.168	1	0.204	-0.063
Radon	0.260	-0.165	-0.062	-0.103	0.2044	1	-0.080
Naphthalene	-0.045	0.306	-0.053	0.465	-0.063	-0.080	1
PM _{2.5}	0.232	0.372	-0.004	0.010	-0.192	-0.004	0.214
Carbon monoxide	-0.025	-0.002	-0.014	-0.019	0.1463	0.101	-0.008
Carbon dioxide	0.078	0.166	0.111	0.077	-0.139	0.092	0.193
Relative humidity	0.186	-0.199	0.101	-0.006	0.4397	0.348	-0.076
Temperature	0.155	0.108	-0.118	0.054	-0.321	-0.106	-0.026
Ventilation rate	-0.094	-0.260	0.099	-0.088	0.1042	-0.304	-0.181

Table 4. Pearson Correlation heatmap of indoor air pollutants, physical and comfort parameters

	PM _{2.5}	Carbon monoxide	Carbon dioxide	Relative humidity	Temperature	Ventilation rate
Formaldehyde	0.232	-0.025	0.078	0.186	0.155	-0.094
Benzene	0.372	-0.002	0.166	-0.199	0.108	-0.260
Tetrachloroethylene	-0.004	-0.014	0.111	0.101	-0.118	0.099
Limonene	0.010	-0.019	0.077	-0.006	0.054	-0.088
Ozone	-0.192	0.146	-0.139	0.440	-0.321	0.104
Radon	-0.004	0.101	0.092	0.348	-0.106	-0.304
Naphthalene	0.214	-0.008	0.193	-0.076	-0.026	-0.181
PM _{2.5}	1	-0.006	0.361	0.037	-0.114	-0.129
Carbon monoxide	-0.006	1	-0.053	0.135	-0.112	0.000
Carbon dioxide	0.361	-0.053	1	0.419	-0.512	-0.268
Relative humidity	0.037	0.135	0.419	1	-0.686	0.074
Temperature	-0.114	-0.112	-0.512	-0.686	1	-0.058
Ventilation rate	-0.129	0.000	-0.268	0.074	-0.058	1

Table 5. Association between health disorders during the past three months and exposure to indoor air pollutants in the SINPHONIE study (N = 5175).

Symptoms		Benzene	Naphthalene	Limonene	Carbon monoxide	Formaldehyde	PM _{2.5}
Eye	Model 1	0.85 (0.55 - 1.32)	1.14 (0.70 - 1.85)	1.37 (0.89 - 2.14)	0.75 (0.48 - 1.17)	0.94 (0.62 - 1.42)	0.57 (0.37 - 0.89)*
	Model 2	0.82 (0.52 - 1.29)	1.23 (0.74 - 2.04)	1.55 (0.98 - 2.45)	0.77 (0.79 - 1.21)	0.98 (0.64 - 1.50)	0.61 (0.38 - 0.96)*
	Model 3	0.74 (0.46 - 1.20)	1.11 (0.68 - 1.82)	1.36 (0.84 - 2.19)	0.72 (0.46 - 1.13)	0.94 (0.62 - 1.42)	0.50 (0.31 - 0.79)*
Skin	Model 1	0.77 (0.56 - 1.06)	0.92 (0.66 - 1.30)	1.10 (0.80 - 1.52)	0.94 (0.68 - 1.29)	1.08 (0.80 - 1.47)	0.82 (0.60 - 1.13)
	Model 2	0.71 (0.51 - 0.99)*	0.95 (0.67 - 1.34)	1.16 (0.84 - 1.62)	0.98 (0.71 - 1.35)	1.08 (0.79 - 1.49)	0.89 (0.63 - 1.24)
	Model 3	0.81 (0.57 - 1.13)	0.96 (0.68 - 1.35)	1.27 (0.90 - 1.80)	0.96 (0.69 - 1.32)	1.09 (0.80 - 1.49)	0.86 (0.62 - 1.20)
Upper airways	Model 1	1.64 (1.29 - 2.09)*	1.19 (0.92 - 1.54)	1.67 (1.30 - 2.14)*	1.26 (1.01 - 1.59)*	1.18 (0.94 - 1.48)	1.37 (1.09 - 1.74)*
	Model 2	1.62 (1.27 - 2.08)*	1.16 (0.89 - 1.51)	1.72 (1.33 - 2.22)*	1.27 (1.01 - 1.60)*	1.18 (0.94 - 1.49)	1.33 (1.04 - 1.69)*
	Model 3	1.51 (1.16 - 1.96)*	1.16 (0.89 - 1.51)	1.59 (1.21 - 2.07)*	1.22 (0.97 - 1.53)	1.20 (0.95 - 1.50)	1.26 (0.99 - 1.62)
Lower airways	Model 1	1.70 (1.29 - 2.24)*	1.07 (0.80 - 1.43)	1.37 (1.04 - 1.82)*	1.11 (0.86 - 1.45)	1.09 (0.84 - 1.41)	1.34 (1.02 - 1.76)*
	Model 2	1.73 (1.30 - 2.31)*	1.04 (0.77 - 1.41)	1.40 (1.05 - 1.88)*	1.16 (0.89 - 1.52)	1.07 (0.82 - 1.39)	1.32 (1.00 - 1.75)**
	Model 3	1.51 (1.12 - 2.05)*	1.05 (0.78 - 1.42)	1.23 (0.91 - 1.68)	1.06 (0.81 - 1.38)	1.08 (0.83 - 1.40)	1.19 (0.90 - 1.59)
Systemic	Model 1	1.41 (1.12 - 1.77)*	0.97 (0.76 - 1.23)	1.72 (1.36 - 2.18)*	1.00 (0.80 - 1.26)	1.06 (0.86 - 1.32)	1.13 (0.91 - 1.42)
	Model 2	1.34 (1.06 - 1.69)*	0.97 (0.76 - 1.25)	1.77 (1.39 - 2.25)*	1.03 (0.82 - 1.28)	1.06 (0.86 - 1.33)	1.12 (0.89 - 1.41)
	Model 3	1.22 (0.95 - 1.56)	0.94 (0.74 - 1.21)	1.57 (1.22 - 2.02)*	0.94 (0.75 - 1.18)	1.05 (0.85 - 1.31)	1.00 (0.79 - 1.26)

Figures are adjusted odds-ratios 95% Confidence interval; exposure to an air pollutant is defined as a dichotomous variable ("low" (variable=0) versus "elevated" (variable=1)), with respect to the median value of the distribution of the pollutants for all classrooms.

Model 1: Adjusted on age, gender, race, maternal education, maternal employment, exposed to tobacco smoke at home, pets, country and family history of allergy.

Model 2: Adjusted on covariates from Model 1 and further adjusted on ventilation rate

Model 3: Adjusted on covariates from Model 1 and further adjusted on CO2

* p-value < 0.05 ** p-value = 0.05

Table 5. (cont.) Association between health disorders during the past three months and exposure to indoor air pollutants in the SINPHONIE study (N = 5175). Bold results show significant associations.

Symptoms		Tetrachloroethylene	Radon	Ozone
Eye	Model 1	0.73 (0.47 - 1.15)	1.26 (0.80 - 2.00)	2.00 (1.28 - 3.12)*
	Model 2	0.88 (0.55 - 1.42)	1.30 (0.80 - 2.10)	2.04 (1.28 - 3.24)*
	Model 3	0.73 (0.46 - 1.16)	1.32 (0.83 - 2.09)	1.98 (1.26 - 3.11)*
Skin	Model 1	1.03 (0.74 - 1.44)	0.87 (0.62 - 1.22)	1.14 (0.83 - 1.54)
	Model 2	1.50 (0.84 - 1.70)	0.85 (0.60 - 1.22)	1.20 (0.87 - 1.65)
	Model 3	1.07 (0.77 - 1.48)	0.90 (0.63 - 1.27)	1.15 (0.84 - 1.57)
Upper airways	Model 1	1.23 (0.97 - 1.57)	1.35 (1.04 - 1.75)*	1.99 (1.58 - 2.51)*
	Model 2	1.28 (0.99 - 1.64)	1.36 (1.04 - 1.78)*	1.99 (1.56 - 2.52)*
	Model 3	1.22 (0.95 - 1.55)	1.35 (1.05 - 1.75)*	1.84 (1.45 - 2.33)*
Lower airways	Model 1	1.18 (0.90 - 1.56)	1.14 (0.85 - 1.52)	2.25 (1.71 - 2.96)*
	Model 2	1.16 (0.87 - 1.56)	1.19 (0.88 - 1.61)	2.24 (1.69 - 2.97)*
	Model 3	1.13 (0.84 - 1.50)	1.11 (0.83 - 1.49)	2.10 (1.58 - 2.78)*
Systemic	Model 1	1.21 (0.96 - 1.52)	1.36 (1.07 - 1.74)*	1.63 (1.32 - 2.04)*
	Model 2	1.28 (1.01 - 1.63)*	1.42 (1.10 - 1.82)*	1.63 (1.30 - 2.04)*
	Model 3	1.18 (0.93 - 1.50)	1.35 (1.06 - 1.72)*	1.52 (1.22 - 1.90)*

Figures are adjusted odds-ratios with 95% Confidence interval; exposure to an air pollutant is defined as a dichotomous variable ("low" (variable=0) versus "elevated" (variable=1)), with respect to the median value of the distribution of the pollutants for all classrooms. Model 1: Adjusted on age, gender, race, maternal education, maternal employment, exposed to tobacco smoke at home, pets, country and family history of allergy.

Model 2: Adjusted on covariates from Model 1 and further adjusted on ventilation rate

Model 3: Adjusted on covariates from Model 1 and further adjusted on CO2

* p-value < 0.05

** p-value = 0.05

Table 6. Association between any of the symptom and exposure to indoor pollutants, physical and comfort parameters during the past three months in the SINPHONIE study. Bold results show significant associations.

	Any of the symptom		
	aOR		
	Model 1	Model 2	Model 3
Air pollutants			
Benzene ($\mu\text{g}/\text{m}^3$)	1.14 (0.96 - 1.35)	1.08 (0.91 - 1.29)	0.98 (0.82 - 1.17)
Naphthalene ($\mu\text{g}/\text{m}^3$)	0.95 (0.79 - 1.14)	0.95 (0.79 - 1.14)	0.94 (0.78 - 1.13)
Limonene ($\mu\text{g}/\text{m}^3$)	1.34 (1.13 - 1.50)*	1.40 (1.17 - 1.68)*	1.22 (1.02 - 1.47)*
Carbon monoxide (ppm)	0.96 (0.81 - 1.31)	0.98 (0.82 - 1.16)	0.93 (0.78 - 1.10)
Formaldehyde ($\mu\text{g}/\text{m}^3$)	1.02 (0.87 - 1.20)	1.02 (0.86 - 1.20)	0.99 (0.84 - 1.17)
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	0.96 (0.81 - 1.14)	0.96 (0.81 - 1.14)	0.81 (0.68 - 0.98)*
Tetrachloroethylene ($\mu\text{g}/\text{m}^3$)	1.03 (0.87 - 1.23)	1.12 (0.93 - 1.35)	1.00 (0.83 - 1.20)
Radon (Bq/m ³)	1.10 (0.91 - 1.32)	1.12 (0.93 - 1.37)	1.13 (0.94 - 1.36)
Ozone ($\mu\text{g}/\text{m}^3$)	1.53 (1.29 - 1.80)*	1.53 (1.29 - 1.81)*	1.47 (1.24 - 1.74)*
Carbon dioxide (ppm)	1.17 (0.99 - 1.39)	1.10 (0.92 - 1.31)	-
Relative humidity (%)	1.14 (0.97 - 1.35)	1.20 (1.01 - 1.42)*	1.08 (0.91 - 1.28)
Temperature °C	0.45 (0.30 - 0.68)*	0.47 (0.30 - 0.72)*	0.44 (0.29 - 0.67)*
Ventilation rate (ach)	0.95 (0.81 - 1.13)	-	0.99 (0.84 - 1.17)

Figure are adjusted odds-ratio (aOR) of being exposed to the air pollutant with 95% Confidence interval; exposure to an air pollutant is defined as a dichotomous variable ("low" (variable=0) versus "elevated" (variable=1)), with respect to the median value of the distribution of the pollutant for all classrooms.

Model 1: Adjusted on age, gender, race, maternal education, maternal employment, exposed to tobacco smoke at home, pets, country and family history of allergy.

Model 2: Adjusted on covariates from Model 1 and further adjusted on ventilation rate

Model 3: Adjusted on covariates from Model 1 and further adjusted on CO2

* p-value < 0.05

Table 7. Association between disorders among schoolchildren during the past three months and VOC score

	Eye	Skin	Upper airways	Lower airways	Systemic
VOC Score	aORs				
0	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
1	1.37 (0.62 - 3.06)	0.88 (0.48 - 1.62)	0.94 (0.56 - 1.59)	0.55 (0.31 - 0.96)*	0.98 (0.61 - 1.58)
2	1.08 (0.49 - 2.38)	1.13 (0.65 - 1.97)	1.31 (0.81 - 2.12)	0.91 (0.56 - 1.48)	1.46 (0.94 - 2.26)
3	0.95 (0.41 - 2.18)	0.89 (0.49 - 1.60)	1.51 (0.92 - 2.45)	0.76 (0.46 - 1.27)	1.36 (0.87 - 2.14)
4	0.86 (0.34 - 2.18)	1.11 (0.57 - 2.14)	1.78 (1.06 - 2.98)*	1.39 (0.83 - 2.34)	2.00 (1.25 - 3.21)*
5	1.49 (0.57 - 3.88)	0.80 (0.36 - 1.79)	2.73 (1.61 - 4.66)*	1.83 (1.06 - 3.18)*	2.11 (1.26 - 3.52)*

Figures are odds-ratios and 95% Confidence interval adjusted on age, gender, race, maternal education, and maternal employment, exposed to tobacco smoke at home, pets, country and family history of allergy.

* p-value < 0.05

** p-value = 0.05

Table 8. Association between health outcomes during the past three months and exposure to indoor air pollutants in the SINPHONIE study

	<i>CO₂</i>	<i>Relative humidity</i>	<i>Temperature</i>	<i>Ventilation rate</i>
<i>Symptoms</i>	<i>aOR</i>			
Eye	1.27 (0.83 - 1.95)	1.35 (0.88 - 2.06)	0.38 (0.10 - 1.50)	0.67 (0.46 - 0.98)*
Skin	0.86 (0.62 - 1.17)	1.06 (0.78 - 1.44)	0.49 (0.22 - 1.08)	0.68 (0.51 - 0.89)*
Upper airways	1.38 (1.09 - 1.74)*	1.23 (0.98 - 1.55)	0.30 (0.16 - 0.57)*	0.93 (0.78 - 1.11)
Lower airways	1.52 (1.16 - 2.00)*	1.63 (1.25 - 2.14)*	0.56 (0.30 - 1.09)	0.96 (0.79 - 1.16)
Systemic	1.52 (1.21 - 1.90)*	1.30 (1.05 - 1.63)*	0.68 (0.38 - 1.23)	0.91 (0.78 - 1.08)

Figures are odds-ratios of being exposed to the air pollutant and 95% Confidence interval adjusted on age, gender, race, maternal education, maternal employment, exposed to tobacco smoke at home, pets, country and family history of allergy. CO₂: Carbon dioxide; exposure to an air pollutant is defined as a dichotomous variable ("low" (variable=0) versus "elevated" (variable=1)), with respect to the median value of the distribution of the pollutants for all classrooms.

* p-value < 0.05

Table A.1. Definition of respiratory and allergic outcomes by organs in schoolchildren

Symptom/disease by organ (3 months)	Question: "During the past three months, has your child had any of the following during the past three months?"
Eye	Eye irritation (redness, dryness, itching) Swollen eyes
Skin	Skin rash on hands or forearms Skin rash on face or neck Eczema Itching on hands or forearms Itching on face or neck
Upper airways	Runny nose/nasal phlegm Nasal obstruction/blocked nose
Lower airway	Dry throat Sore throat Irritative cough Breathing difficulties
Systemic	Feeling like getting a cold Feeling tired or out of sorts Headache

Nausea

Table A.2. Distribution of indoor chemical ($\mu\text{g}/\text{m}^3$), physical and comfort parameters among schoolchildren according to clusters (N=5175)

Indoor air pollutants	Clusters	Percentile								
		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>10th</i>	<i>25th</i>	<i>Median</i>	<i>75th</i>	<i>90th</i>	<i>99th</i>
Benzene ($\mu\text{g}/\text{m}^3$)	Northern Europe	583	2.59	2.55	0.32	0.54	1.89	3.73	7.35	10.31
	Western Europe	785	1.24	0.71	0.50	0.84	1.06	1.58	1.68	3.50
	Central-Eastern Europe	1541	6.23	6.91	0.80	1.60	3.30	9.78	17.30	29.04
	Southern Europe	1515	3.86	2.79	1.30	2.03	3.45	4.74	6.92	17.30
Naphthalene ($\mu\text{g}/\text{m}^3$)	Northern Europe	583	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Western Europe	467	0.54	0.86	0.00	0.00	0.00	0.73	1.83	3.53
	Central-Eastern Europe	1375	4.83	6.44	0.01	0.07	2.40	8.22	12.24	30.82
	Southern Europe	1247	2.15	6.06	0.00	0.00	0.82	1.46	2.60	42.72
Carbon monoxide (ppm)	Northern Europe	583	0.49	0.60	0.00	0.00	0.20	0.80	1.54	1.83
	Western Europe	759	0.16	0.34	0.00	0.00	0.00	0.07	0.80	1.20

Limonene (µg/m³)	Central-Eastern Europe	1569	0.44	0.52	0.00	0.00	0.25	0.60	1.30	2.40
	Southern Europe	1515	1.49	10.34	0.00	0.00	0.20	0.75	3.30	4.50
	Northern Europe	583	12.30	37.03	0.53	2.04	4.50	8.19	20.60	228.95
	Western Europe	785	29.90	42.29	2.40	4.83	8.80	38.48	101.33	163.00
	Central-Eastern Europe	1541	76.94	119.17	1.50	7.70	29.50	80.56	202.17	668.26
	Southern Europe	1515	31.32	58.85	1.90	5.43	13.35	38.00	54.57	430.26
	Northern Europe	583	11.71	8.22	5.91	6.33	8.39	15.41	22.80	38.45
	Western Europe	785	17.51	9.91	8.19	10.00	14.90	19.20	31.40	46.00
Formaldehyde (µg/m³)	Central-Eastern Europe	1585	13.72	8.13	4.87	7.05	11.31	19.40	27.56	33.20
	Southern Europe	1515	9.73	4.48	5.52	6.87	8.73	11.90	14.60	21.37

Table A.2. (cont.) Distribution of indoor chemical ($\mu\text{g}/\text{m}^3$), physical and comfort parameters among schoolchildren according to clusters (N=5175)

Indoor air pollutants	Clusters	Percentile								
		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>10th</i>	<i>25th</i>	<i>Median</i>	<i>75th</i>	<i>90th</i>	<i>99th</i>
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	Northern Europe	583	30.29	14.75	6.35	20.96	31.25	42.20	46.21	61.30
	Western Europe	690	20.57	6.57	14.25	16.90	18.40	23.50	31.10	39.60
	Central-Eastern Europe	1560	59.59	46.15	22.40	30.80	42.10	72.00	123.71	250.10
	Southern Europe	1383	41.08	23.39	15.71	20.83	42.30	51.31	69.78	122.87
Tetrachloroethyl ene ($\mu\text{g}/\text{m}^3$)	Northern Europe	583	4.82	14.51	0.00	0.00	0.00	2.02	10.09	81.16
	Western Europe	785	0.17	0.23	0.00	0.00	0.00	0.33	0.58	0.71
	Central-Eastern Europe	1541	1.28	2.61	0.00	0.00	0.20	0.80	7.47	10.20
	Southern Europe	1247	1.09	1.51	0.00	0.00	0.00	2.45	3.34	4.90
Radon (Bq/m^3)	Northern Europe	563	50.17	27.07	27.50	30.00	46.10	61.60	97.80	119.30

	Western Europe	498	100.90	81.80	0.00	0.00	101.80	170.80	209.00	238.00
	Central-Eastern Europe	1382	168.82	177.10	54.00	84.00	113.80	162.00	339.20	1121.00
	Southern Europe	1624	384.56	1282.79	40.00	67.00	166.10	249.00	386.80	9186.00
	Northern Europe	583	7.42	8.37	2.21	3.00	4.85	7.00	13.95	52.00
	Western Europe	717	1.84	3.28	0.00	0.00	0.00	1.80	6.64	15.93
Ozone ($\mu\text{g}/\text{m}^3$)	Central-Eastern Europe	1865	6.16	17.77	0.00	0.20	1.38	6.04	15.02	131.10
	Southern Europe	1455	10.24	13.23	0.00	2.90	6.73	9.80	30.41	58.07
	Northern Europe	570	1184.86	579.17	679.06	788.27	1089.10	1249.50	2107.70	3194.90
	Western Europe	744	1015.01	359.41	648.00	755.00	918.00	1251.00	1405.00	2320.00
CO ₂ (ppm)	Central-Eastern Europe	1569	1417.70	407.02	889.08	1123.00	1404.90	1682.00	1922.83	2427.00
	Southern Europe	1515	2074.29	1296.86	511.00	761.78	1792.00	3193.00	3783.00	4471.00

Table A.2. (cont.) Distribution of indoor chemical ($\mu\text{g}/\text{m}^3$), physical and comfort parameters among schoolchildren according to clusters (N=5175)

Indoor air pollutants	Clusters	Percentile								
		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>10th</i>	<i>25th</i>	<i>Median</i>	<i>75th</i>	<i>90th</i>	<i>99th</i>
Relative humidity (%)	Northern Europe	570	33.82	17.78	13.70	25.10	29.22	43.10	48.30	98.30
	Western Europe	758	37.04	8.71	24.20	30.50	37.80	43.00	49.30	57.50
	Central-Eastern Europe	1585	37.31	7.65	26.30	32.50	37.30	42.80	47.09	55.10
	Southern Europe	1515	53.97	15.02	33.00	40.00	56.00	68.00	72.50	77.00
Temperature (°C)	Northern Europe	136	20.99	0.90	20.00	20.00	21.00	22.00	22.00	22.00
	Western Europe	185	17.94	1.54	17.00	17.00	17.00	20.00	21.00	21.00
	Central-Eastern Europe	599	21.81	1.38	19.00	22.00	22.00	23.00	23.00	25.00
	Southern Europe	299	23.45	0.76	23.00	23.00	23.00	24.00	24.00	27.00
Ventilation rate	Northern Europe	542	1.10	0.77	0.22	0.30	1.05	1.76	2.11	2.81

(ACH)	Western Europe	717	0.30	0.27	-0.04	0.10	0.27	0.53	0.64	0.86
	Central-Eastern Europe	1569	0.85	0.80	0.19	0.24	0.56	1.27	2.01	3.27
	Southern Europe	1515	0.56	0.68	0.09	0.15	0.40	0.67	0.90	4.30

Table A.3. National and international guidelines for selected pollutants and measured concentrations in SINPHONIE, AIRMEX, and EU schools in $\mu\text{g}/\text{m}^3$

	WHO 2010	GV1	EPHECT	WHO 2006	LCI	ECHA	Sensory irritation	Mean-99 th SINPHONIE	Mean-Max AIRMEX	Mean/Max Salonen et al. 2018
							Eye and upper airways			
Formaldehyde	100	100	100	-	100	-	400-800	15-50	17-50	-
							Not an irritant			
Benzene	1.7 ^a	-	-	-	-	-	Leukemia	5-33	4 - 64	-
							200 ~400			
Naphthalene	10	-	-	-	-	-	Lung effect	2 - 29	n.m.	-
Limonene	1/90--	5000	9000 ^b	-	5000	16600 ^c	8500	41- 412	9 - 186	-
							Pulmonary irritant			
Ozone		1/10 ^d ; 0.1 BV-	-	100	-	-	~160	7-52	-	1-30/8-78
				25 ^{24hr}						
PM2.5 ^e	-	-	-	10 ^{ann}	-	-	-	45-188	-	-
Radon, bq/m3	100 ^f	-	-		-	-	-	230- 785	-	-
Carbon dioxide			General international consensus < 1000 ppm					1581-4158	-	-

a. Life risk for 100.000.

b. Long-term value

c. European Chemicals Agency (ECHA)

d. IJHEH (Peder Wolkoff, 2013); depends subjective vs objective observation

e. Ambient air, not directly compatible with indoor air – will depend on morphology and surface chemistry

f. life risk for 0.6x100.000

GV1, <https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values>

EPHECT, Trantallidi et al. (2015).

Table A.4. Symptoms improve when schoolchildren are away from school (N=5175)

Symptoms improve when away from school			
Eye (N=3090)	No	Yes	p-value
	n (%)	n (%)	
No	2224 (97.33)	767 (95.28)	<0.01
Yes	61 (2.67)	38 (4.72)	
Total	2285	805	
Skin (N=3113)	No	Yes	
	n (%)	n (%)	
No	2193 (95.14)	757 (93.69)	0.11
Yes	112 (4.86)	51 (6.31)	
Total	2305	808	
Upper airways (N=3134)	No	Yes	
	n (%)	n (%)	
No	2079 (89.81)	670 (81.81)	<0.01
Yes	236 (10.19)	149 (18.19)	
Total	2315	819	
Lower airways (N=3129)	No	Yes	
	n (%)	n (%)	
No	2136 (92.67)	708 (85.92)	<0.01
Yes	169 (7.33)	116 (14.08)	
Total	2305	824	
Systemic (N=3137)	No	Yes	
	n (%)	n (%)	

No	1320 (57.59)	315 (38.75)	<0.01
Yes	972 (42.41)	498 (61.25)	
Total	2292	813	

Indoor air parameters and respiratory and allergic symptoms among European schoolchildren

