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

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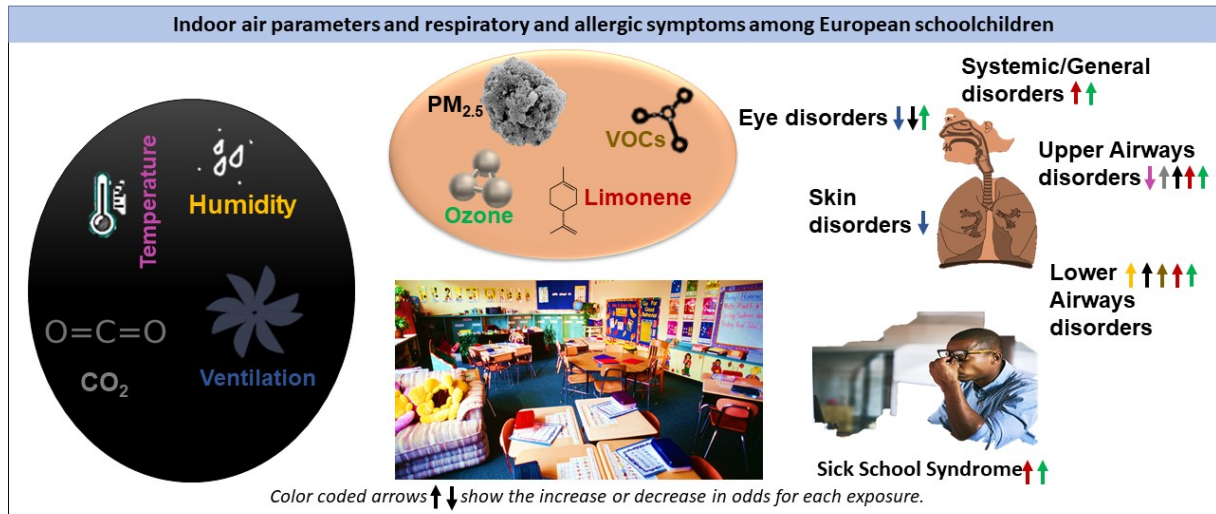
130 None

131 **Abbreviations**

132

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

151



152

153 **Highlights**

- 154 • Indoor air physical and comfort parameters in 114 schools across 23 European countries
- 155 were measured.
- 156 • PM_{2.5}, radon and carbon dioxide concentrations were higher compared to air quality
- 157 guidelines.
- 158 • VOCs, particulate matter and physical parameters were positively and negatively
- 159 associated with different disorders.

160

161 **Abstract**

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

184

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

186 parameters

187

188 1. Introduction

189 Children are more vulnerable than adults to environmental risks because of a number of factors:
190 children are constantly growing, they breathe more air, consume more food, and drink more
191 water than adults do, in proportion to their weight (*WHO | Environmental Risks*, n.d.). Their
192 developing respiratory and immune systems and different responses to environmental exposure
193 puts children at increased risk of developing various diseases including respiratory and allergic
194 symptoms compared to adults (Scientific Committee on Health and Environmental Risks
195 (SCHER), 2007). Many studies have reported that the overall indoor environment in schools can
196 cause or contribute to acute and chronic health problems such as rhino conjunctivitis, and other
197 allergic and general symptoms (Annesi-Maesano et al., 2012; Daisey et al., 2003; Hulin et al.,
198 2012; Ramachandran et al., 2005; Siskos et al., 2001). In industrialized countries, people spend
199 around 90% of their time indoors, where both the number and the concentrations of air
200 pollutants can be higher than those outdoors (Klepeis et al., 2001; C.-Y. Lu et al., 2018).
201 Additionally, surrounding outdoor air pollution is also a matter of concern indoors as it can
202 contribute to the indoor environment by entering through windows, doors and other openings
203 (Jantunen et al., 2011), thus compromising the indoor air quality (IAQ) further.

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

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

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

225 **2. Material and Methods**

226 *2.1. Overview and study design*

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

232 *2.2. Study Population*

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

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

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

245 *2.3. Sampling*

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

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

266 2.4. Sample analysis, quality assessment and quality control

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

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

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

287 Carbon dioxide (CO₂) concentrations, temperature and relative humidity were measured
288 continuously using an IAQ-CALC monitor (model 7545, TSI, Inc.). The ventilation rate (ACH)
289 was estimated based on decay of the indoor CO₂ concentration when classrooms were
290 occupied. The ventilation rate values were estimated using the average outdoor CO₂
291 concentration over the 5-day measurement period. The estimated final ventilation rate in the
292 classroom is the time-weighted average of the ventilation rates obtained during the school
293 week. The ACH was calculated based on the ASTM E 741-00 (2006) and ASTM D 6245-98
294 (2002) standards. All instruments were calibrated each year at the factory.

295 2.5. Health outcomes at the period of the survey

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

299 The questionnaire was based on previous studies conducted in Europe among schoolchildren
300 that investigated children's health. These studies include the ISAAC (International Study of
301 Asthma and Allergies in Childhood) (M Innes Asher et al., 2006), HESE (Health Effects of
302 School Environment) (*Health Effects of School Environment (HESE) - Final Scientific Report*,
303 2006) and the SEARCH (School Environment and Respiratory Health of Children) study
304 (Csobod et al., 2010).

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

312 3 months were related to the school environment, the parents/guardians were queried on
313 whether children' symptoms improved during the weekend (Table A.3.).

314 2.6. *Confounders*

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

319 2.7. *Statistical analysis*

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

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

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

347 3. Results

348 3.1. *Description of population, health outcomes and air pollutants, physical and comfort* 349 *parameters*

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

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

362 During the past three months, systemic disorders (11.77%) and upper airways symptoms
363 (10.82%) were the most frequently reported health outcomes among schoolchildren followed by
364 lower airways symptoms, skin and eye symptoms respectively (Table 2). The reporting of skin
365 disorders and upper airways symptoms differed significantly across gender.

366 Table 3 shows distributions of the concentrations of air pollutants. A quarter of schoolchildren
367 were exposed to elevated indoor PM_{2.5}, benzene, radon and CO₂ levels according to the EU
368 Commission and WHO standards (European Environment Agency, 2019; WHO Regional Office
369 for Europe, 2010; European Commission, 2008). Summary statistics of indoor air pollutants
370 according to geographic clusters are reported. Indoor air concentrations of benzene,
371 naphthalene, PM_{2.5}, ozone and radon were significantly higher in Southern and Central Eastern
372 Europe. No significant difference in concentrations of CO was observed between clusters and
373 values were below WHO guidelines. CO₂ concentrations were also below the WHO indoor air
374 quality and/or EU guidelines in the Western Europe region (WHO Regional Office for Europe,
375 2010). The lowest median temperature and ventilation rates were observed in Western Europe
376 (Table A.2). A comparison between different guidelines and sources and SINPHONIE is
377 described in Table A.3.

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

387 3.2. *Relationship of indoor air pollutants to past 3-month health disorders*

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

405 3.3. *Relationship of physical and comfort parameters to past 3 month health disorders*

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

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

416 **4. Discussion**

417 *4.1. Key Findings*

418 The main objective of our study was to investigate the relationship between indoor air quality
419 and comfort conditions in classrooms and health among European schoolchildren. In our
420 sample, schoolchildren were excessively exposed to elevated concentrations of several air
421 pollutants. Of note, the mean concentrations of benzene, limonene, PM_{2.5} and CO₂ exceeded
422 the WHO and/or EU air quality guidelines (World Health Organization, 2010; World Health
423 Organization. Occupational and Environmental Health Team, 2006). Furthermore, 28.87%,
424 19.43%, 11.68% of children were co-exposed to 2, 3 and 4 VOCs known to be dangerous for
425 health, respectively. Additionally, in our study, we found the median temperature to be over the
426 90% acceptability limit according to ASHRAE guidelines on thermal environmental conditions for
427 human occupancy (American Society of Heating et al., 2004).

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

434 *4.2. Comparison of findings with other published work*

435 Several studies have suggested a potential relationship between multi-pollutant exposures and
436 adverse health outcomes including respiratory and/or allergic symptoms, headaches, skin
437 symptoms, and nausea in children (Annesi-Maesano et al., 2012; *Health Effects of School*
438 *Environment (HESE) - Final Scientific Report*, 2006; Rumchev et al., 2002; G. Smedje et al.,
439 1997; G Smedje & Norbäck, 2001; Zhao et al., 2008). Further, both indoor and outdoor air
440 pollution along with indoor environmental factors, including temperature and relative humidity
441 have been shown to be associated with occurrence of any symptom or sick building syndrome
442 (sick school syndrome in schools) (Deng et al., 2016; Jiang et al., 2018; C. Lu et al., 2016).
443 Although PM_{2.5} has been associated with several health outcomes, impacts from PM_{2.5} levels
444 specifically in classrooms has only been described in (Annesi-Maesano et al., 2007, 2012). In
445 the current study, elevated levels of benzene in classrooms were significantly associated with
446 upper airways, lower airways and systemic symptoms in schoolchildren. These findings are in
447 agreement with earlier studies (Annesi-Maesano et al., 2012; *Health Effects of School*
448 *Environment (HESE) - Final Scientific Report*, 2006; Rumchev et al., 2002; G. Smedje et al.,
449 1997; G Smedje & Norbäck, 2001; Zhao et al., 2008). Our study also found no significant
450 association between formaldehyde and allergic symptoms as observed by Ezratty et al., 2007.
451 The difference in outcomes among the studies might be due to different exposure levels, which
452 could blur the real association with benzene (Peder Wolkoff & Nielsen, 2010).
453 For the first time, we observed an adverse effect of limonene in schoolchildren. Limonene
454 measured in classrooms can be introduced through the use of cleaning products, air fresheners
455 and perfumes (Peder Wolkoff & Nielsen, 2017; Steinemann et al., 2011; Nazaroff & Weschler,
456 2004). Limonene is generally considered a harmless substance and the most significant health
457 effects associated with limonene are irritation of eyes, nose, throat and skin (Kotzias et al.,
458 2005). However, a recent Canadian study provides evidence that household exposure to
459 limonene may increase the prevalence of asthma at the general population level overall in
460 children (Dales & Cakmak, 2019). Our study also found a significant relationship between upper

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

463 Formaldehyde was seen to have no effect in our study, which is contrary to previous work
464 (Mendell, 2007). A recent meta-analysis on formaldehyde exposure in children calculated a
465 pooled odds ratio (OR) of 1.03 (95% CI: 1.02 -1.04) for an increase of 10 µg/m³ (McGwin et al.,
466 2010). Two other studies focusing on respiratory symptoms in relation to formaldehyde also
467 found increased risk of sensory irritation with higher indoor concentrations (Rumchev et al.,
468 2002; G Smedje & Norbäck, 2001). Although, it is not excluded that such studies were flawed by yet
469 to be unidentified confounding variables, a formaldehyde indoor air limit of 0.1 ppm should protect even
470 particularly susceptible individuals from both irritation effects and any potential cancer hazard (Golden
471 2011).

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

482 Our analysis showed statistically significant associations between elevated concentrations of
483 radon and upper airways and systemic disorders on which extreme caution is needed. It is well
484 known that elevated radon concentrations increase the risk of lung cancer (Baysson et al.,
485 2004; Darby et al., 1998; Field et al., 2000; Krewski et al., 2006), however, other adverse effects
486 of radon have been observed, namely in the case of chronic obstructive pulmonary disease

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

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

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

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

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

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

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

549 4.3. *Possible mechanisms*

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

556 4.4. *Strength and limitations*

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

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

577 4.5. Public health policy implications

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

586 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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803 *Environmental Health Perspectives*, 116(1), 90–97. <https://doi.org/10.1289/ehp.10576>
- 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 (%)	(n = 2557) n (%)	(N=5175) 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 n (%)	Male n (%)	Total 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)

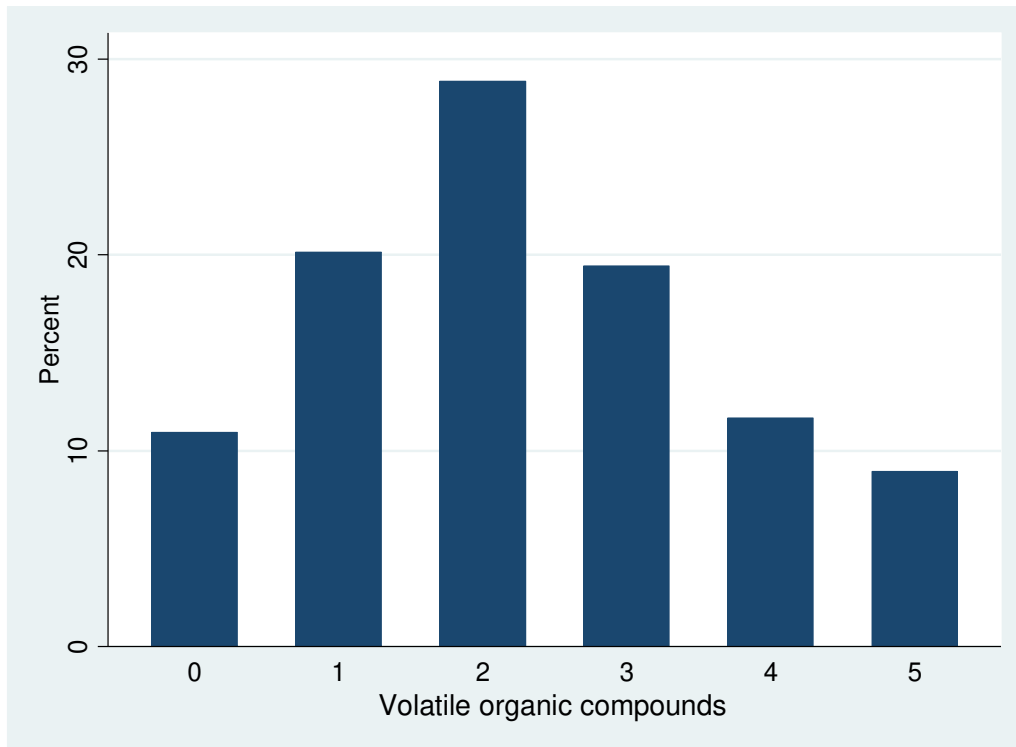
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Table 3. Distribution of indoor chemical, physical and comfort parameters among schoolchildren and comparison with existing guidelines (N=5175)

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

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>	aOR			
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

	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
Limonene ($\mu\text{g}/\text{m}^3$)	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
Formaldehyde ($\mu\text{g}/\text{m}^3$)	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
	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
Tetrachloroethylene ($\mu\text{g}/\text{m}^3$)	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	190 ^a	5000	9000 ^b	-	5000	16600 ^c	8500	41- 412	9 - 186	-
							Pulmonary irritant			
Ozone		10 ^d	-	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 (%)	
<i>No</i>	2224 (97.33)	767 (95.28)	<0.01
<i>Yes</i>	61 (2.67)	38 (4.72)	
<i>Total</i>	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

