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Association of subjective health symptoms with indoor air quality in European office buildings: The OFFICAIR project

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Abstract

The aim of this study was to explore the association between the building-related occupants' reported health symptoms and the indoor pollutant concentrations in a sample of 148 office rooms, within the framework of the European OFFICAIR research project. A large field campaign was performed in 37 office buildings among eight countries, which included (a) 5-day air sampling of volatile organic compounds (VOCs), aldehydes, ozone, and NO₂ (b) collection of information from 1299 participants regarding their personal characteristics and health perception at workplace using online questionnaires. Stepwise and multilevel logistic regressions were applied to investigate associations between health symptoms and pollutant concentrations considering personal characteristics as confounders. Occupants of offices with higher pollutant concentrations were more likely to report health symptoms. Among the studied VOCs, xylenes were associated with general (such as headache and tiredness) and skin symptoms, ethylbenzene with eye irritation and respiratory symptoms, α-pinene with respiratory and heart symptoms, d-limonene with general symptoms, and styrene with skin symptoms. Among aldehydes, formaldehyde was associated with respiratory and general symptoms, acrolein with respiratory symptoms, propionaldehyde with respiratory, general, and heart symptoms, and hexanal with general SBS. Ozone was associated with almost all symptom groups.

KEYWORDS

aldehydes, health perception, office workers, ozone, sick building syndrome, volatile organic compounds

1 | INTRODUCTION

During the last years, there has been an increasing interest in understanding interaction of the built environment and human occupants in terms of health and well-being.¹ Especially health problems having a potential association with indoor environment raise both the public concern and the construction industry. As the proportion of people working in office buildings is high and increasing worldwide, the progressively reported health symptoms related to indoor environment and their causality should be further examined.

Sick building syndrome (SBS) was defined by World Health Organization (WHO) in 1983,² and it describes work-related non-specific symptom complexes for which the cause is not always known while most of the occupants report relief soon after leaving the building.^{3,4} The SBS symptoms include eye, nose and throat symptoms, fatigue, headache as well as skin and respiratory irritations. Other reported symptoms are cough, tight chest, wheeze, and difficulty in breathing.⁵ The SBS symptoms can be influenced by both personal and environmental factors. Common personal factors associated with SBS symptoms include age, gender, allergy medical history, smoking status, anxiety, interpersonal conflicts, type of occupation, amount of work, and psychosocial work stress.^{6–10} The SBS symptoms are also related to physical environment especially linked to indoor air quality (IAQ). In general, IAQ changes are immediately reflected in sensory perception (sometimes instantaneously) while occupants cannot detect pollutant concentrations.^{2,11} The coupled analysis of self-reported perceived IAQ through questionnaires and field measurements of chemical compounds can provide insights to better understand relation between health perception and IAQ. The IAQ in an office building can be significantly affected by several parameters, such as inappropriate selection of indoor materials, electronic equipment, heating, ventilation and air conditioning (HVAC) systems. In particular, workplace conditions such as the use of carpets as floor covering, recently painted walls, dust and dirt, unpleasant odors as well as crowded offices and noise appeared to be risk factors related to SBS.^{6,12}

A number of studies conducted in office buildings tried to investigate relation of pollutant concentrations connected both with indoor emissions and ventilation rates,¹³ with the prevalence of SBS symptoms. In 1988, a large-scale project in Northern Sweden recorded occupants' health perception. By analyzing these data, Stenberg et al found that female gender, asthma/rhinitis, pieces of paper, work on video monitor, outdoor airflow rates, and presence of photocopiers were related to an increased prevalence of SBS symptoms.^{14,15} A study conducted in university offices located in Mauritania revealed that symptoms of SBS (eg, headache, nervousness, nausea, irritated sore eyes, and sneezing) were significantly

Practical Implications

- This study provides further insight in the association between indoor pollutant concentrations and the possible effect on office occupants' health perception.
- These findings could be useful for recommendations to construction industry/building managers, regarding the design-maintenance-replacement of building/furnishing materials/electronic equipment as well as use and maintenance of HVAC systems, to improve IAQ in office buildings, and thus improve well-being and work conditions for office occupants.

higher among occupants of buildings with mechanical ventilation than those of naturally ventilated ones, while carbon dioxide, carbon monoxide, nitrogen dioxide determination for monitoring of IAQ were not found to be reliable predictors of SBS.¹⁶ Analysis of Building Assessment Survey and Evaluation (BASE) study data in 100 US offices provided a strong evidence that ambient ozone concentrations (the dominant source of indoor ozone is ambient ozone that penetrates indoors) are related to the upper respiratory, dry eyes, neurological, and headache symptoms—highlighting the role of building ventilation systems.⁵ Investigation of health symptoms perception in two office buildings in Rio de Janeiro (Brazil) showed no association among its prevalence and total VOCs (TVOCs), benzene, or toluene concentrations—except for the association between the running nose prevalence and exposure to a higher concentration of total particulate matter (TPM).¹⁷ Eye irritation and upper respiratory symptoms were found to be related with indoor CO₂ concentration greater than 800 ppm in an office building in Taiwan.¹⁸ Further to CO₂ concentration, a study in Taiwan¹⁹ revealed that eye irritation, stuffy nose and dry throat, difficulty breathing, skin dryness, irritability, and dizziness were slightly associated with TVOCs. In a comparison study of two office buildings in Malaysia (new vs old), results indicated a significant association between prevalence of SBS and indoor air pollutants—CO₂, CO, TVOC, PM₁₀, and PM_{2.5}.²⁰ Also, in the same area, results of another study suggested that some indoor air pollutants (CO, formaldehyde, TVOCs, and dust) were related to adverse health symptoms.²¹ In a recent study, Azuma et al²² examined the correlation between IAQ and SBS of office workers in 17 air-conditioned office buildings in Japan and showed a significant correlation of upper respiratory symptoms with increased indoor concentration of suspended particles (especially particle size >0.3 µm) as well as with several irritating VOCs such as formaldehyde, acetaldehyde, ethylbenzene, toluene, and xylenes.

Health perception and symptoms attract wide attention and public concern while more and more people focus on the conditions at the work environment as well as poor IAQ. High prevalence of reported SBS complaints in office buildings as well as lack of a confirmed direct cause-effect relationship between them and exposure to typical indoor pollutants raise the interest for new studies in this scientific area. Especially, studies which combine simultaneous monitoring of occupants' perception by questionnaire and IAQ field measurements in European level seem to be very limited.

The aim of the present study was to investigate association of subjective occupants' health symptoms with IAQ in a large number of European office buildings (148 office rooms of 37 buildings). For the scope of the study, measurements of major indoor air pollutants and recording of occupants' health complains on questionnaires were simultaneously performed. The present analysis follows and extends our previous work²³⁻²⁵ in the aspect of occupant health perception in "modern" office buildings in the frame of OFFICAIR project.²⁶ Using the OFFICAIR cross-Europe survey database, this study aims to investigate for the first time the possible associations between chemical compounds and the occupants' perceived health symptoms in office buildings considering the examined personal characteristics as potential confounders.

2 | MATERIAL AND METHODS

The EU-financed OFFICAIR project focused on modern office buildings and tried to increase knowledge on indoor environment quality (IEQ) through databases, modeling tools, and other methods toward an integrated approach in assessing health risks. In the survey, 167 office buildings in eight European countries (Portugal, Spain, Italy, Greece, France, Hungary, the Netherlands, and Finland) participated in three consecutive monitoring campaigns (ie, general survey, detailed field campaign, and intervention study). The detailed objectives have been described elsewhere.²⁵ Briefly, it involved building/workspace characterization, monitoring of physical and chemical parameters, and occupant-related information, by gathering questionnaires and checklists. Further details on the project study design and findings are reported in project-related publications.^{23-25,27-34}

2.1 | Data collection

One of the main objectives of the OFFICAIR project was to characterize the IAQ in office buildings and assess the associated health effects with the simultaneous monitoring of indoor pollutants and information provided by occupants in questionnaires. From a preliminary campaign in 167 office buildings (characterized as "general survey"), a subgroup was selected for further investigation, namely the "detailed study," applying a unified quantitative ranking score based on health symptoms and ERI (effort-reward imbalance), which were reported in the previous campaign as positive factors, building facility manager willingness to participate, sufficiently number

of occupants (ie, at least 40) and diversity in building location. In the subsequent "detailed study" or field campaign, 148 office rooms of 37 office buildings (4 offices per building) in eight countries were investigated during two campaigns (from summer 2012 to winter 2013). The participating countries and the number of buildings were as follows: Finland = 3 buildings, France = 9, Greece = 5, Hungary = 5, Italy = 4, the Netherlands = 3, Portugal = 5, and Spain = 3. In total, 3045 office occupants were invited to participate.

2.2 | Questionnaire study

A questionnaire was delivered online to the occupants, including personal data, work data, psychosocial environment/characteristics, physical effects (IAQ perception, comfort, and health-related symptoms), and online tests (Ocular Surface Disease Index [OSDI], Self-Reported Break-Up Time [SBUT], and memory and performance). The questionnaire was translated to each country's local language, the study was anonymous, and the participants gave their consent prior to participation. The study was approved by the competent local/national ethics committees. The questionnaire was proposed to the occupants, in offices of which there were IAQ measurements in progress. When answering the questionnaire, occupants were not informed about the results of the measurements.

The "personal data" and the "physical effects (health-related symptoms)" sections of the questionnaire were used in this study. The occupants were asked to report their SBS symptoms by answering to the following questions: "Have you ever experienced any of the following symptoms while working in this building (or workstation)?" (a least one day per week including today) and "Was it better on days away from the office (eg, holidays, weekend)?" The questionnaire asked about the following symptom groups: eye irritation (dry eyes, watering or itchy eyes, burning or irritated eyes), respiratory (blocked or stuffy nose, runny nose, dry/irritated throat, cough, sneezing, phlegm/mucus, wheezing, chest tightness, or breathing difficulty), heart (tachycardia, irregular heartbeats, bradycardia), skin (dry skin, rash, or irritated skin), and general symptoms (headache, flu-like symptoms, lethargy, unusual tiredness). The questionnaires were filled once in the same week as the IAQ measurements were in progress in the offices by occupants whose workplace was located in these offices. The invitations were sent by the building managers and one reminder was sent during the survey.

2.3 | IAQ measurements

Chemical and physical measurements at 5 locations per building: 4 indoor and 1 outdoor were carried out continuously for 5 working days (Monday to Friday). The indoor air pollutants measured in OFFICAIR buildings were chosen because of a potential association with health effects³⁵ and were as follows: particulate matter (PM_{2.5}), ozone (O₃), nitrogen dioxide (NO₂), aldehydes (formaldehyde, acetaldehyde, acrolein, propionaldehyde, benzaldehyde, glutaraldehyde,

and hexanal), and VOCs (benzene, toluene, xylenes, ethylbenzene, n-hexane, trichloroethylene (TCE), tetrachloroethylene (PCE), α -pinene, d-limonene, 2-butoxyethanol, 2-ethylhexanol, and styrene). Air was sampled using diffusive air samplers placed approximately at the height of breathing zone of seated occupants for 5 weekdays. Detailed information regarding study design, sampling strategy, applied analytical procedures, and quality assurance/quality control methods is provided by Mandin et al and Campagnolo et al.^{28,31,32} PM_{2.5} sampling was performed at one location per building (one out of the four with gaseous pollutant sampling) using low-volume aerosol samplers.

2.4 | Statistical analysis

A combined database has been produced from the questionnaire survey and the IAQ measurements by assigning each occupant's questionnaire to the respective indoor concentrations using the building and office code. In addition, for analysis robustness, data from the two campaigns were merged and all questionnaires were treated as a unified sample. Such an approach has been further enforced by the fact that only 35% of the participants took part in both campaigns. Statistical analysis of the dataset was performed following four main steps (Figure 1):

1. Descriptive results about the survey, symptom prevalence, and pollutant concentrations were obtained.
2. A stratified analysis using non-parametric Mann-Whitney U test was applied in order to reveal the pollutant concentration variation among the several SBS groups.

3. Toward identifying new or verify potential confounders of personal characteristics on the occupants' health perception, a step-by-step logistic regression was applied for each personal characteristic vs the prevalence of any SBS symptom. A wide range of participants' personal and lifestyle data, home activities, personal and family medical history work/workstation, and psychosocial environment data were considered. Afterward, variables with $P < .2$ were entered in a multivariable logistic regression model. Parameters from the final model, after eliminating parameters with $P > .2$ were selected to be inserted as confounders in the subsequent steps of the analysis.
4. To analyze associations between SBS group symptoms (dependent variable) and pollutant concentrations, a set of three models were used. Following Chao et al and Takigawa et al, chemical concentrations were classified into four groups at quartiles, and afterward, they were inserted in the models and treated as continuous variables.^{9,36} The degree of multicollinearity between independent variables was checked by the variance inflation factor (VIF). VIF values ranged from 1.5 to 4.6, that is, were below 10; therefore, multicollinearity was not an issue.³⁷ In the first model (crude), a stepwise multiple logistic regression (backward Wald, $P < .10$ as inclusion criteria) was applied by including only chemical factors. In the second model, factors of personal characteristics (identified previously) were forced inserted into the model as adjusted variables and chemical factors were inserted into a backward stepwise model according to Takigawa et al.³⁶ In the third and final step, a multilevel model was applied to take into account the two-level structure of our data (level 1—occupant, level 2—building) which suits best for this survey sample size. The

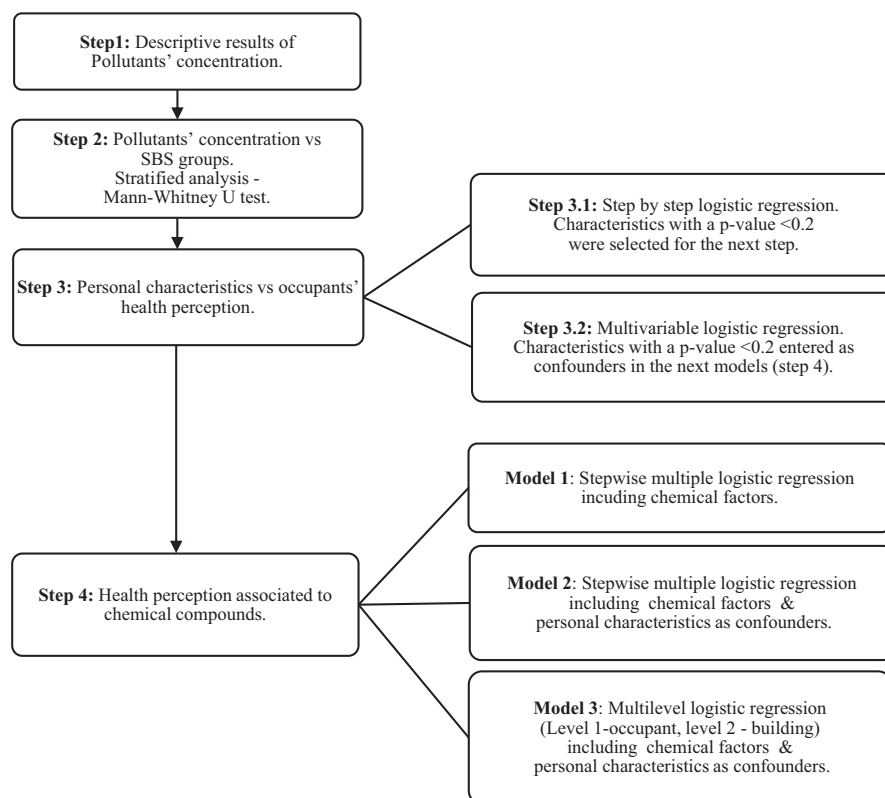


FIGURE 1 Schematic overview of the methodology used

TABLE 1 Characteristics of the study population

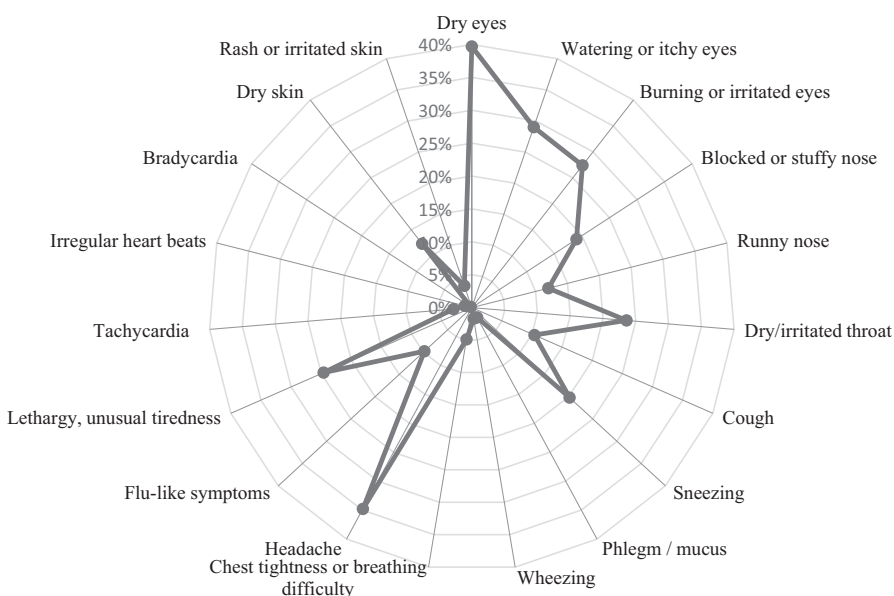
Characteristics	n	(%)
Participants per country		
Total	1299	100
The Netherlands	125	9.6
Italy	295	22.7
Portugal	156	12.0
Spain	84	6.5
Greece	152	11.7
Finland	103	7.9
Hungary	182	14.0
France	202	15.6
Gender		
Men	541	41.6
Women	758	58.4
Age (years), mean (SD)	39.8	9.7
Level of education		
Master PhD or specialization	338	26.0
University college or equivalent	425	32.7
Professional	70	5.4
Secondary school	187	14.4
Primary school or lower	6	0.5
Smoking status		
Current	258	19.9
Former	288	22.2
Never	753	58.0
Alcohol consumption		
Yes	596	45.9
No	433	33.3
Effort-reward ratio—ERI (mean, SD)	0.51	0.27

multilevel logistic regression analysis was selected using building as random effect and the covariates as fixed effects. Significant chemical factors from the previous step were entered, together with all personal factors, irrespectively if the personal environmental factors were significant or not.³⁸ The final model was obtained by eliminating variables associated with a p-value distinguishably above 0.20. Results were reported in odds ratios (OR) calculated for quartile range change in individual chemical concentrations and 95% confidence interval (CI) with the two-tailed test significance values of $P < .05$ and marginal significance of $P < .1$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS).³⁹

3 | RESULTS

3.1 | Participation, characteristics of the study population, and symptoms

The total number of submitted questionnaires was 1356, out of the approximately 3250 invited occupants (response rate 42%). The response rate ranged from 27% (Portugal) to 83% (Italy) (France and Spain: 28%; Finland: 33%; Greece: 51%; Hungary: 55%; the Netherlands: 59%). After clearing the database for erroneous identification codes, the study population resulted in 1299 occupants. Table 1 presents the characteristics of the studied population. About 60% of the occupants were women. The mean age of respondents for all countries was 39.9 (± 9.7) years old (range 21–64) and up to 59% had a graduate or postgraduate education. Concerning their lifestyle, 22% were smokers while 46% consumed alcohol. The ERI ranged from 0.2 to 3.4 (mean: 0.51, ± 0.27), and in general, 4.5% of the investigated occupants had an ERI greater than 1, implying an imbalanced reward toward their effort in work.⁴⁰

**FIGURE 2** SBS symptoms prevalence

The SBS generic group (SBS vs non-SBS) and the SBS subgroups (eg, eye irritation group) were created. If any participant reported at least one symptom from a specific SBS subgroup, he was classified in that group and also to the SBS generic group. About 77.7% of the subjects suffered from at least one SBS symptom. More specifically, the most frequently reported SBS symptoms were eye irritation (58.3%), respiratory (45.3%), and general (47%) and then heart (3.8%) and skin (13.9%). Figure 2 shows the prevalence of the SBS symptoms. The most reported symptoms related to eye irritation and respiratory subgroup were dry eyes (40%) and blocked or stuffy nose (19%). For the general symptoms subgroup, the most reported symptom was headache (35%), while for the skin subgroup was dry skin (12.3%). The least frequent ones were related to heart symptoms bradycardia (>1%) and irregular heartbeats (1%), respiratory phlegm/mucus (2%), and wheezing (2%).

3.2 | Potential confounders—personal characteristics

Table 2 presents all personal characteristics with a *P*-value lower than 0.2 against the prevalence of at least one SBS symptom (SBS

generic group) from the multivariable logistic regression. Results in our study revealed that the occupants' health perception seems to be significantly ($P < .05$) affected by gender, age, smoking status/smoking habits at home, type of work contract, and medical history, for example, migraine or family history of high blood pressure and anxiety. Age was categorized into three groups: under 35 years; 36-45; and more than 46 years considering a balanced sample distribution among them (ie, 38.7%, 32.9%, and 28.3% of occupants, respectively).

3.3 | Indoor air pollutant concentrations in offices

Descriptive data of indoor VOCs, aldehydes, O_3 , NO_2 , and $PM_{2.5}$ concentrations are shown in Figure 3. Among VOCs, the highest median concentrations were measured for d-limonene $5.9 \mu g m^{-3}$ (max: $81 \mu g m^{-3}$), toluene $3.7 \mu g m^{-3}$ (max: $63 \mu g m^{-3}$), and α -pinene $3.2 \mu g m^{-3}$ (max: $68 \mu g m^{-3}$) while formaldehyde showed the highest indoor concentration among the investigated aldehydes, with median value equal to $10 \mu g m^{-3}$ (max: $48 \mu g m^{-3}$). Median concentration for O_3 was $3.0 \mu g m^{-3}$ (max: $42 \mu g m^{-3}$) and for NO_2 was $17 \mu g m^{-3}$ (max: $39 \mu g m^{-3}$).

TABLE 2 Associations between personal characteristics and SBS generic group (SBS vs none)

Personal characteristics	Binary logistic regression analysis	
	OR (95% CI)	P-value
Gender: Men (vs Women)	0.58 (0.42-0.8)	.001**
Age ^a : Under 35 (vs More than 46)	1.46 (0.98-2.17)	.060*
36-45 (vs More than 46)	1.81 (1.21-2.69)	.004**
Use of video monitor at work: Yes (vs No)	1.43 (0.94-2.17)	.094*
Contract type: Permanent vs Fixed-term	1.92 (1.24-2.97)	.003**
Smoking status: Current (vs Never)	1.58 (1.05-2.36)	.027**
Former (vs Never)	1.2 (0.77-1.89)	.422
Smoking at home (anyone): Yes (vs No)	1.63 (1-2.67)	.050**
Use of Candles/incense at home at least once a week: Yes (vs No)	1.46 (0.98-2.19)	.065*
Use of contact lenses: Yes (vs No)	1.52 (0.94-2.44)	.086*
Alcohol consumption: Yes (vs No)	0.8 (0.57-1.11)	.175
Migraine confirmed by a doctor: Yes (vs No)	2.53 (1.24-5.16)	.011**
Respiratory diseases confirmed by a doctor: Yes (vs No)	4.66 (0.6-36.2)	.141
Eczema among close relatives (parents, sisters/brothers, children) confirmed by a doctor: Yes (vs No)	0.67 (0.38-1.18)	.165
High lipids in the blood (ie, cholesterol, triglycerides) among close relatives (parents, sisters/brothers, children) confirmed by a doctor: Yes (vs No)	1.49 (0.99-2.22)	.054*
High blood pressure among close relatives (parents, sisters/brothers, children) confirmed by a doctor: Yes (vs No)	1.64 (1.15-2.34)	.006**
Anxiety among close relatives (parents, sisters/brothers, children) confirmed by a doctor: Yes (vs No)	5.22 (2.03-13.47)	.001**
Effort-Reward Ratio (ERI)	3.84 (1.84-8.02)	<.001**

Note: *P*-values in bold (**) are significant at 5% and in italic (*) are marginal significant at 10%. Characteristics with a *P* value lower than 0.20 are presented. OR: odd ratio, CI: confidence interval 95%.

^aThree balanced distributed age-groups.

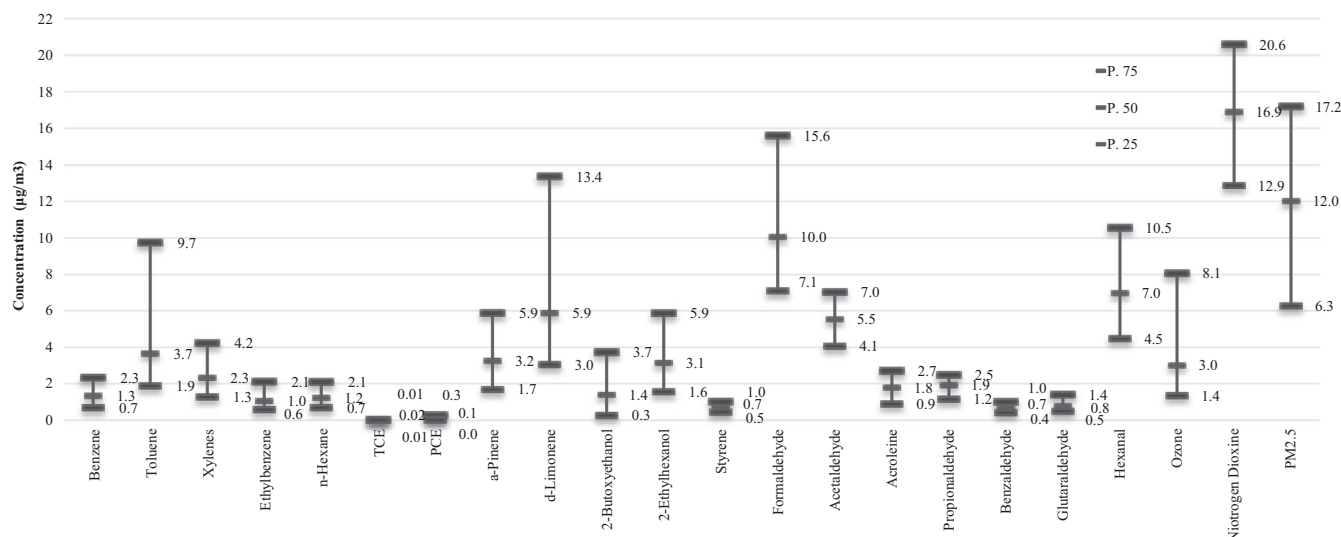


FIGURE 3 Quartiles of indoor pollutants' concentrations (25%, 50%, 75%) ($\mu\text{g}/\text{m}^3$)

3.4 | Associations between indoor concentrations and SBS symptoms

The differences in concentrations between the occupants belonging to the SBS generic group and the ones from the non-SBS group are indicated in Table 3. Almost all VOCs showed higher mean values in the SBS generic group. Significant differences were observed in toluene, xylenes, and ethylbenzene with $P < .05$. Regarding aldehydes, occupants who reported SBS symptoms were exposed to higher values with significant difference in acrolein $P = .027$.

In order to explore deeper the indoor concentration variations, tests were performed for each SBS symptom subgroup. Significant results with a P -value below 0.2 are shown in Table 4. For occupants who reported eye irritation, toluene, xylenes, and ethylbenzene concentrations were higher in their offices than in those of occupants without symptoms. For occupants with respiratory symptoms, besides VOCs (xylenes, ethylbenzene, and styrene), aldehyde concentrations were also higher (formaldehyde and acetaldehyde). For general symptoms, mean concentration values of benzene, toluene, 2-butoxyethanol, formaldehyde, and acetaldehyde were significantly higher. For the group of heart and skin symptoms, few chemicals showed higher concentrations in the offices of participants. More specifically, $\text{PM}_{2.5}$ seems to be higher in offices of the heart group while TCE, $\text{PM}_{2.5}$, and styrene concentrations were higher in offices of the skin group.

3.5 | Indoor concentration associations with health perception

In Table 5, results of the three step-by-step models are presented. Influence of each air pollutant on perceived health was examined and results are expressed in odd ratios (OR) and adjusted OR (aOR) with their confidence interval (CI) at 95%, by applying a stratified

analysis among the SBS groups. In the SBS generic group, acrolein was associated only with the first model, while ozone and hexanal only with the second. Ethylbenzene showed significant association in the first and third models. Styrene was negatively associated with all models. Ethylbenzene was also found to be correlated with eye irritation. Ozone was also significantly associated with the first model. Acrolein and formaldehyde identified to have association with respiratory health reports (model 3). In the other models in respiratory subgroup, positive association was also revealed for propionaldehyde, ethylbenzene, a-pinene, and ozone. Xylenes had a marginally significant association with respiratory symptoms. Ozone, d-limonene, and formaldehyde were associated significantly to general symptoms subgroup. Xylenes have presented a positive effect in general symptoms (model 1), while NO_2 showed a marginal significant positive association. Heart symptoms were associated with increasing concentration of propionaldehyde (model 1), and a-pinene and ozone (model 2). Finally, skin symptoms were associated with xylenes (model 1) and styrene (models 2 and 3). Also, in this subgroup some negative associations were reported for propionaldehyde, 2-ethylhexanol, O_3 , and NO_2 . Among the SBS subgroups were indicated some marginally significant associations with chemical compounds ($P < .10$).

4 | DISCUSSION

4.1 | Occupants' perceived health and IAQ

This study examined the association between IAQ measurements and office occupant self-reported health symptoms. Dry, watering or itchy, burning or irritated eyes and headache, lethargy, unusual tiredness were the most commonly reported symptoms among occupants. As reported in detail in our previous study by Mandin et al.,³² the indoor concentrations were in general below indoor air quality guidelines and in the same order of magnitude than the ones

TABLE 3 Differences in indoor concentrations ($\mu\text{g}/\text{m}^3$) between SBS and non-SBS generic group

Compounds	SBS					Non-SBS					P-value
	25%	50% (Median)	Mean	75%	95%	25%	50% (Median)	Mean	75%	95%	
Benzene	0.7	1.9	2.2	3.5	5.8	0.7	1.9	1.9	2.5	4.1	.206
Toluene	3.3	8.0	9.5	9.7	32.4	3.5	5.3	7.3	9.0	23.2	.001**
Xylenes	1.5	3.2	4.2	6.5	10.7	1.3	3.2	3.0	4.1	7.4	.003**
Ethylbenzene	0.9	1.4	1.7	2.7	3.7	0.8	1.1	1.3	1.5	3.7	.002**
n-Hexane	0.7	1.1	1.8	2.0	6.5	0.7	0.9	1.4	2.0	3.3	.083*
TCE	<0.1	<0.1	0.1	<0.1	1.4	<0.1	<0.1	0.2	<0.1	1.5	.108
PCE	<0.1	0.1	4.3	0.5	1.8	0.1	0.2	8.5	0.5	58.2	.141
a-Pinene	1.5	5.5	4.9	7.4	10.5	1.4	3.1	4.3	6.7	10.6	.892
d-Limonene	3.9	9.3	17.2	32.6	48.0	3.3	10.9	17.9	36.4	40.2	.332
2-Butoxyethanol	1.8	4.0	9.5	6.1	52.8	0.6	2.9	8.4	5.2	52.1	.098*
2-Ethylhexanol	2.0	3.5	4.4	6.2	16.8	1.7	2.4	3.4	4.2	9.6	.260
Styrene	0.5	0.7	0.8	1.0	2.2	0.4	0.6	0.7	1.0	1.5	.777
Formaldehyde	7.6	10.1	11.2	14.0	20.5	7.2	8.0	10.8	14.0	24.0	.086*
Acetaldehyde	4.7	5.7	5.6	6.9	9.1	3.3	5.2	5.3	7.1	9.2	.071*
Acrolein	0.8	1.6	1.7	2.2	4.3	0.5	0.7	1.4	2.4	4.4	.027**
Propionaldehyde	1.1	2.1	2.2	2.4	6.6	0.9	1.3	1.8	2.1	6.6	.181
Benzaldehyde	0.5	0.8	1.0	1.1	2.9	0.4	0.5	0.7	1.1	1.6	.128
Glutaraldehyde	0.5	0.7	1.2	1.4	2.9	0.5	0.7	1.0	1.4	2.8	.503
Hexanal	4.3	6.7	8.3	10.6	29.7	4.0	5.3	7.0	9.5	19.0	.126
Ozone	2.4	5.8	7.9	9.8	31.7	1.7	4.4	7.2	9.1	31.7	.199
NO ₂	18.1	21.15	22.4	28.3	39.4	17.5	19.5	21.3	23.7	39.4	.381
PM _{2.5}	8.7	11.4	12.0	15.9	20.6	6.9	9.9	12.9	17.7	32.3	.386

Note: Mann-Whitney U test. P-values in bold (**) are significant at 5% and in italic (*) are marginal significant at 10%. Concentrations are expressed in $\mu\text{g}/\text{m}^3$.

measured in past studies in offices, for example, AIRMEX.⁴¹ Most of these chemical compounds were detected at relative low concentrations although results showed that SBS groups were exposed to significant ($P < .05$) higher ones.

The occupant personal characteristics as a contributor on health perception were examined. Our results revealed that gender, age, smoking status/alcohol consumption, and psychological work stress remain significant. This is in compliance with previous studies conducted in offices as well as other type of microenvironments.^{7,8,42-44} Activities that are not directly linked with work environment seemed to amplify the SBS. For example, it was revealed that smoking habits and usage of candles/incense at home affects occupants' perception in their workplace. Participants with these habits in their homes could be more sensitive to the IAQ conditions and therefore prone to develop symptoms. It is remarkable that not only personal occupant's medical history but also their family history played a significant role. In our study, except for participant's personal experienced migraine and respiratory diseases, also eczema, high lipids in the blood, high blood pressure (ie, cholesterol, triglycerides), and anxiety from close relatives (parents, sisters/brothers, children) should be taken into consideration as

confounding factors. Similar studies such as that of Lim et al.⁴⁵ investigated associations between SBS symptoms, selected personal factors, office characteristics, and indoor office exposures among office workers from a university in Malaysia and has concluded that a combination of allergies (cat or house dust-mites) is a risk factor for SBS. Also, the aspect of parental diseases such as asthma/allergy, and their effect on the prevalence of SBS was raised by Zhang et al.⁴⁶

There are a limited literature data on the association between IAQ and health symptom prevalence especially in office buildings. In a recent review,¹ it has been highlighted that SBS contains a collection of factors that could affect physical health. These factors include physical contributors in a building environment such as temperature, relative humidity, ventilation, light, noise, electromagnetic radiation, biological factors, IAQ/chemical compounds, as well as personal characteristics. In this analysis, we tried to give insights for the association of SBS symptoms with specific indoor concentrations of chemical air pollutants. VOCs, aldehydes, and ozone present significant associations with health symptoms after adjustment for personal characteristics and when considering the effect of multilevel structure of data. In our study, results revealed that some chemical

TABLE 4 Differences in indoor concentrations ($\mu\text{g}/\text{m}^3$) between SBS and non-SBS among symptom subgroups

Symptoms subgroup	Compounds	SBS	Non-SBS	P-value
		Mean	Mean	
Eye irritation	Benzene	1.7	1.5	.103
	Toluene	6.7	6.1	.009**
	Xylenes	3.4	3.2	.018**
	Ethylbenzene	1.5	1.4	.025**
Respiratory	Xylenes	3.5	3.2	.014**
	Ethylbenzene	1.5	1.4	.005**
	TCE	0.0	0.1	.114
	PCE	1.9	3.1	<.001**
	Styrene	0.9	0.8	.040**
	PM _{2.5}	13.2	11.9	.150
	Formaldehyde	12.2	11.5	.026**
	Acetaldehyde	5.8	5.5	.024**
	Acrolein	2.1	2.0	.092*
	Propionaldehyde	2.07	2.08	.110
General	Benzene	1.67	1.52	.050**
	Toluene	6.6	6.2	.012**
	Xylenes	3.3	3.4	.170
	n-Hexane	1.5	1.5	.166
	d-Limonene	11.6	11.1	.051*
	2-Butoxyethanol	6.0	5.5	.038**
	2-Ethylhexanol	4.1	3.9	.179
	PM _{2.5}	13.6	11.6	.006**
	Formaldehyde	12.1	11.5	.042**
	Acetaldehyde	5.8	5.5	.048**
	Acrolein	2.1	2.0	.091*
	Propionaldehyde	2.1	2.0	.069*
	Benzaldehyde	0.9	0.8	.099*
Heart	2-Butoxyethanol	6.58	5.69	.095*
	PM _{2.5}	18.47	12.35	.033**
	Propionaldehyde	2.16	2.07	.195
Skin	Xylenes	3.76	3.27	.175
	TCE	0.07	0.05	.043**
	2-Butoxyethanol	4.99	5.84	.082*
	2-Ethylhexanol	3.36	4.12	.007**
	Styrene	0.92	0.85	.063*
	Ozone	5.02	7.38	<.001**
	PM _{2.5}	15.03	12.05	.027*
	Benzaldehyde	0.77	0.86	.015*
	Hexanal	8.19	8.37	.194

Note: Mann-Whitney *U* test. *P*-values in bold (**) are significant at 5% and in italic (*) are marginal significant at 10%. Concentrations are expressed in $\mu\text{g}/\text{m}^3$.

substances could be associated with reported SBS, even though in low concentrations. This is in compliance with Azuma et al studies, who reported that irritating VOCs were correlated with upper respiratory symptoms below their guideline levels.^{22,47} The estimated

ORs of SBS symptoms were calculated using quartile range change of each pollutant.

Xylenes were associated with general symptom and skin subgroup, while ethylbenzene was associated with generic SBS, eye

TABLE 5 Models for associations between indoor concentrations ($\mu\text{g}/\text{m}^3$) and SBS generic group and SBS subgroups

Symptoms group	Compounds	Logistic regression analysis				Multilevel logistic regression analysis	
		Model 1 ^a : OR (95% CI)	P-value	Model 2 ^b : aOR (95% CI)	P-value	Model 3 ^c : aOR (95% CI)	P-value
SBS generic	Benzene			0.84 (0.67-1.06)	.142		
	Xylenes			1.24 (0.91-1.69)	.176		
	Ethylbenzene	1.42 (1.2-1.68)	<.001**	1.29 (0.92-1.82)	.141	1.26 (1.01-1.57)	.042**
	Styrene	0.77 (0.66-0.9)	.001**	0.7 (0.57-0.87)	.001**	0.81 (0.66-0.99)	.043**
	Acrolein	1.22 (1.01-1.47)	.035**				
	Hexanal	1.12 (0.95-1.33)	.188	1.31 (1.06-1.61)	.011**	1.17 (0.95-1.43)	.134
	Glutaraldehyde	0.88 (0.74-1.05)	.154				
	Ozone			1.2 (1.01-1.42)	.043**		
Eye irritation	Ethylbenzene	1.34 (1.16-1.55)	<.001**	1.44 (1.21-1.72)	<.001**	1.15 (0.98-1.36)	.096*
	n-Hexane	0.87 (0.75-1.01)	.062*	0.87 (0.73-1.04)	.123		
	Propionaldehyde	0.91 (0.79-1.04)	.165				
	2-Butoxyethanol			1.13 (0.96-1.33)	.137	1.14 (0.96-1.36)	.123
	Styrene			0.86 (0.74-1.01)	.074	0.9 (0.77-1.06)	.202
	Glutaraldehyde	0.9 (0.78-1.04)	.163				
	Ozone	1.14 (1.01-1.28)	.035**				
	NO ₂	0.9 (0.79-1.02)	.088*				
Respiratory	Toluene	0.78 (0.64-0.95)	.015**	0.71 (0.56-0.91)	.006**	0.88 (0.73-1.07)	.203
	Xylenes	1.21 (0.97-1.52)	.091*				
	Ethylbenzene	1.2 (0.97-1.49)	.101	1.3 (1.06-1.59)	.011**		
	a-Pinene			1.18 (1-1.4)	.046**		
	2-Butoxyethanol	0.91 (0.79-1.05)	.198	0.87 (0.73-1.05)	.139		
	Formaldehyde	1.25 (1.04-1.51)	.02**	1.26 (1.05-1.52)	.014**	1.16 (0.98-1.38)	.083*
	Acrolein			1.13 (0.95-1.34)	.168	1.19 (1.01-1.41)	.040**
	Propionaldehyde	1.25 (1.04-1.5)	.015**				
	Benzaldehyde	0.88 (0.75-1.03)	.106				
	Hexanal	0.82 (0.69-0.98)	.029**				
	Ozone	1.14 (1.01-1.3)	.033**	1.17 (1.01-1.35)	.04**		
General	Xylenes	1.31 (1.03-1.65)	.027**				
	Ethylbenzene	0.84 (0.68-1.03)	.092*	0.84 (0.73-0.98)	.028**	0.88 (0.75-1.04)	.131
	a-Pinene	0.86 (0.74-1)	.057*				
	d-Limonene	1.22 (1.06-1.4)	.006**	1.24 (1.07-1.43)	.004**	1.25 (1.08-1.45)	.003**
	2-Butoxyethanol	0.85 (0.72-1)	.049**				
	2-Ethylhexanol	1.11 (0.98-1.27)	.099*	1.11 (0.96-1.29)	.164		
	Formaldehyde	1.14 (0.96-1.35)	.138	1.18 (1-1.39)	.045**	1.28 (1.09-1.49)	.002**
	Propionaldehyde	1.17 (0.99-1.39)	.07*				
	Glutaraldehyde	0.9 (0.78-1.05)	.178				
	Ozone	1.19 (1.05-1.35)	.007**	1.28 (1.12-1.46)	<.001**	1.21 (1.04-1.4)	.012**
	NO ₂	1.14 (0.99-1.31)	.063*				

(Continues)

irritation, and respiratory symptoms showing higher OR values. Norbäck et al³⁸ reported that higher concentrations of xylenes indicated associations with fatigue and of ethylbenzene with rhinitis and tiredness. a-Pinene concentrations were associated with respiratory

and heart subgroups. Saijo et al studied newly constructed buildings and stated that among other VOCs, xylene, ethylbenzene, and a-pinene were significantly responsible for respiratory symptoms.⁴⁸ Further to these compounds, in our analysis d-limonene

TABLE 5 (Continued)

Symptoms group	Compounds	Logistic regression analysis				Multilevel logistic regression analysis	
		Model 1 ^a : OR (95% CI)	P-value	Model 2 ^b : aOR (95% CI)	P-value	Model 3 ^c : aOR (95% CI)	P-value
Heart	Benzene			0.77 (0.53-1.12)	.172	n.a.	n.a.
	n-Hexane	0.78 (0.56-1.1)	.155				
	a-Pinene			1.61 (1.12-2.3)	.009**	n.a.	n.a.
	d-Limonene	1.32 (0.94-1.84)	.106				
	Styrene	1.29 (0.93-1.78)	.135				
	Acetaldehyde			1.44 (0.91-2.28)	.115	n.a.	n.a.
	Propionaldehyde	1.74 (1.14-2.64)	.01**				
	Hexanal	0.7 (0.46-1.06)	.701	0.69 (0.44-1.07)	.099*	n.a.	n.a.
	Glutaraldehyde	0.79 (0.56-1.11)	.174				
	Ozone	1.32 (0.99-1.76)	.054*	1.49 (1.02-2.18)	.038**	n.a.	n.a.
Skin	Xylenes	1.42 (1.05-1.91)	.022**				
	Ethylbenzene	0.82 (0.61-1.11)	.199	0.81 (0.64-1.03)	.091*	0.8 (0.62-1.03)	.084*
	2-Ethylhexanol	0.84 (0.71-0.99)	.040**				
	Styrene	1.13 (0.95-1.34)	.163	1.31 (1.03-1.67)	.027**	1.29 (1-1.66)	.050**
	Propionaldehyde			0.64 (0.44-0.93)	.020**	0.62 (0.41-0.92)	.017**
	Benzaldehyde	0.81 (0.69-0.97)	.020**	0.76 (0.59-0.99)	.040**	0.77 (0.59-1.02)	.064*
	Hexanal			1.3 (0.91-1.86)	.154	1.33 (0.91-1.95)	.137
	Ozone	0.83 (0.7-0.99)	.036**				
	NO ₂	0.84 (0.71-0.99)	.039**	0.81 (0.65-1.01)	.066*	0.83 (0.65-1.06)	.129

Note: P-values in bold (**) are significant at 5% and in italic (*) are marginal significant at 10%. OR: odd ratio. CI: confidence interval 95%. OR calculated for quartile range change. Variables with a P value lower than 0.20 are presented. n.a.: not available due to limited samples.

PM_{2.5} concentrations not included due to the limited samples as well as TCE and PCE due to limited number of samples above detection/quantification limit.

^aModel 1: Crude model only with chemical compounds (backward regression Wald statistics, $P < .1$).

^bModel 2: aOR: adjusted OR for gender, age-groups, smoking status, alcohol consumption, effort-reward ratio, use of video monitor at work, use of contact lenses, job's contract type, smoking at home, use of candles/incense at home, migraine/respiratory diseases, eczema/ high lipids/high blood pressure/anxiety among close relatives. (Forced adjusted variables and chemical compounds entered in a backward regression Wald statistic, $P < .1$).

^cModel 3: aOR: adjusted OR as in model 2. Variables with $P < .2$ from model 2 were entered in a 2-level multilevel model (Level 1—occupant level, Level 2—building level). Reported aORs after eliminating variables with p-value distinguishably above 0.20.

was associated positively with general symptoms and styrene found to have association with skin symptoms. In our study, a number of VOCs seem to be associated with the prevalence of health symptoms and are in compliance with other studies which examined TVOC concentration.^{20,49,50}

Formaldehyde was associated with respiratory and general symptoms. Norbäck et al³⁸ found an association between indoor formaldehyde and ocular symptoms, throat symptoms, and tiredness. In a study in dwellings, aldehyde concentrations were associated with mucosal symptoms.^{51,52} Acrolein was associated with SBS generic group and respiratory symptom subgroup. For formaldehyde and acrolein, there is evidence supporting they have a causative association with eye and/or airway irritation.^{53,54} Results also reveal that propionaldehyde was associated with respiratory, general, and heart symptoms while hexanal with SBS generic group. Concentrations were in accordance with previous measurements in offices.^{41,55} We found no previous study on associations between

health symptoms reports and propionaldehyde and hexanal concentrations in offices.

Ozone was found to be the pollutant that had affected the most symptom groups. Specifically, it was positively correlated with the SBS generic group as well as with eye irritation, respiratory, general, and heart symptom subgroups. Similar findings were also reported in a study conducted in offices by Apte et al.,⁵ where ozone concentrations showed a positive association with the prevalence of upper respiratory, dry eyes, and headache symptoms. In the case of NO₂, only a marginal significant ($P < .1$) positive association with general symptoms subgroup was observed. Norbäck et al reported that NO₂ could be risk factor of throat and tiredness symptoms. Our finding about the marginal significance is more in compliance with another study about nitrous acid (HONO) which is produced indirectly by absorption of NO₂. The HONO concentrations are associated with decrements in lung function and possibly with more respiratory symptoms; however, a direct

association between respiratory symptoms and NO_2 was not verified despite the fact that the measurements of indoor NO_2 were highly correlated with HONO ($r = .77$).⁵⁶

Finally, it was observed that some pollutants were negatively associated ($P < .05$) with SBS symptoms. Such cases were styrene (OR:0.81) in the SBS generic group, hexanal (OR:0.82) and toluene (OR:0.71) in respiratory symptom subgroup, 2-butoxyethanol (OR:0.85) and ethylbenzene (OR:0.84) in general symptoms subgroup, and finally ozone (OR:0.83), 2-ethylhexanol (OR:0.84), propionaldehyde (OR:0.62), benzaldehyde (OR:0.81), and NO_2 (OR:0.84) in skin symptom subgroup. We have no explanation to this negative association. However, as Norbäck et al also reported, this is likely due to residual confounding with some other indoor exposures.³⁸ These findings should be further examined.

4.2 | Strengths and limitations

This study is the frame of an innovative systematic study of this kind in newly built or recently retrofitted offices in Europe, which provided a large dataset of monitoring data. Furthermore, it tries to expand further our understanding of indoor pollutant concentrations and the possible relations with commonly reported health complaints. This study through the geographical variability of the studied buildings and the extended number of chemical measurements of IAQ, tried to give insight to the scientific literature, which is very limited especially in a wide Europe level, about the current status of IAQ and its association with occupants' health. Results of the current study could be useful for recommendations to construction industry/building managers, regarding the design-maintenance-replacement of building/furnishing materials/electronic equipment and on use and maintenance of HVAC systems, to improve IAQ in office buildings, and thus improve well-being and work conditions for office occupants, and further to develop public health policies. In the analysis, we consider the participants of subjects as cluster and as independent from each other by analyzing the data using both single-level logistic regression analysis and multilevel analysis.

There are some limitations to our study. Results reveal associations between SBS symptoms and chemical pollutants, but it is difficult to determine these associations until further toxicological tests are done. It is noticed that the statistical associations found in this study should be interpreted with caution. The possibility that an association is found by chance may not be excluded. In general, the higher the number of tested associations, the larger the risk of identifying statistically significant associations by chance. This caution should be particularly taken in the interpretation of the marginally significant associations found in the study. Based on the Bradford Hill criteria,^{57,58} the likelihood of a causal association is bigger when consistency of similar effect is found in multiple studies with different populations and designs, when there is a plausible biological mechanism for the effect, if similar relations/effects are found in experimental studies. Also, it should be noted that not all air

compounds were sampled and analyzed, while some pollutants (eg, $\text{PM}_{2.5}$) were monitored in a limited number of offices. In addition, measurements of the IAQ during the working hours would better characterize the occupant's exposure. Furthermore, a more systematic seasonal study would offer more sufficient data of high temporal and spatial scale. A potential limitation could be that health data were collected by an online self-reported questionnaire. Another limitation could be the cross-sectional design of survey; therefore, no causality of the identified relations can be confirmed. Moreover, the participation in the survey was voluntary and selected occupants were invited, whose workplace was in offices where measurements took place, which might have inserted biased answers in the questionnaire. Furthermore, the response rates could be considered low when comparing with surveys with hard-copy questionnaires collected by an investigator. Despite these limitations, the results provide useful indications to potential causes, and thereby an essential basis for further dedicated experimental studies. The response rate is in line with other recent online surveys²⁵ and no statistically significant relation between response rate and SBS prevalence was found (Spearman correlation $P = .277$). In this first approximation, the respiratory system was considered as a unified system to work with an adequate number of data. Similarly, flu-like symptoms were categorized in the "general symptoms" group to have an adequate number of data in subgrouping and considering that reporting such symptoms may not correspond to having a real flu. All these aspects, as well as the found negative associations should be addressed in a future study.

5 | CONCLUSIONS

This study suggests that indoor chemicals in office buildings can be associated with SBS symptoms. It was reported that office workers commonly complain about eye irritation (dry, watering or itchy, burning or irritated eyes) and general symptoms such as headache, lethargy, unusual tiredness. Personal characteristics as well as occupants' and family medical history may affect their health perception at their workplace. The analysis found that in office buildings across Europe, there is an identifiable population of occupants who report SBS symptoms. Occupants in offices with higher concentrations are more likely to report health complaints. Xylenes, ethylbenzene, α -pinene, d-limonene, styrene, formaldehyde, acrolein, propionaldehyde, hexanal, and ozone could contribute to a greater prevalence of symptoms. Air pollutants were associated with self-reported health symptoms although their concentrations were below indoor air quality guidelines. Future study in this topic is still necessary to deeper understand and enlighten the complex relations between IAQ and health symptoms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Ioannis A. Sakellaris: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (equal); Methodology (lead); Writing-original draft (lead); Writing-review & editing (lead). **Dikaia E. Saraga:** Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Corinne Mandin:** Conceptualization (equal); Investigation (equal); Methodology (equal); Supervision (equal); Writing-review & editing (lead). **Yvonne Kluizenaar:** Investigation (equal); Writing-review & editing (equal). **Serena Fossati:** Investigation (equal); Writing-review & editing (equal). **Andrea Spinazzè:** Investigation (equal); Writing-review & editing (equal). **Andrea Cattaneo:** Investigation (equal); Writing-review & editing (equal). **Victor G. Mihucz:** Investigation (equal); Writing-review & editing (equal). **Tamás Szigeti:** Investigation (equal); Writing-review & editing (equal). **Eduardo O Fernandes:** Investigation (equal); Writing-review & editing (equal). **Krystallia Konstantinos Kalimeri:** Investigation (equal); Writing-review & editing (equal). **Rosanna Mabilia:** Investigation (equal); Writing-review & editing (equal). **Paolo Carrer:** Investigation (equal); Writing-review & editing (equal). **John G Bartzis:** Conceptualization (equal); Funding acquisition (lead); Methodology (equal); Project administration (lead); Supervision (lead); Writing-review & editing (equal).

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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