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Mucous membrane and lower respiratory building related symptoms in relation to indoor carbon dioxide concentrations in the 100-building BASE dataset

Abstract Indoor air pollutants are a potential cause of building related symptoms and can be reduced by increasing ventilation rates. Indoor carbon dioxide (CO_2) concentration is an approximate surrogate for concentrations of occupant-generated pollutants and for ventilation rate per occupant. Using the US EPA 100 office-building BASE Study dataset, we conducted multivariate logistic regression analyses to quantify the relationship between indoor CO_2 concentrations (dCO_2) and mucous membrane (MM) and lower respiratory system (LResp) building related symptoms, adjusting for age, sex, smoking status, presence of carpet in workspace, thermal exposure, relative humidity, and a marker for entrained automobile exhaust. In addition, we tested the hypothesis that certain environmentally mediated health conditions (e.g., allergies and asthma) confer increased susceptibility to building related symptoms. Adjusted odds ratios (ORs) for statistically significant, dose–dependent associations ($P < 0.05$) for combined mucous membrane, dry eyes, sore throat, nose/sinus congestion, sneeze, and wheeze symptoms with 100 p.p.m. increases in dCO_2 ranged from 1.1 to 1.2. Building occupants with certain environmentally mediated health conditions were more likely to report that they experience building related symptoms than those without these conditions (statistically significant ORs ranged from 1.5 to 11.1, $P < 0.05$).

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Key words: BASE study, Carbon dioxide; Indoor environmental quality; Building related symptoms; Sick building syndrome; Ventilation

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Practical implications

These results suggest that provision of sufficient per-person outdoor ventilation air, could significantly decrease prevalence of selected building related symptoms. The observed relationship between indoor minus outdoor CO_2 concentrations and mucous membrane and lower respiratory symptoms suggests that air contaminants are implicated in the etiology of building related symptoms. Levels of indoor air pollutants that are suspected to cause building related symptoms could be reduced by increasing ventilation rates, improving ventilation effectiveness, or reducing sources of indoor air pollutants, if known.

Introduction

Building related symptoms (BRS), sometimes called sick building syndrome (SBS) symptoms, are a set of symptoms with unidentified etiology frequently reported by building occupants, especially occupants of office buildings. The individuals who suffer from BRS report that the symptoms occur when they spend time indoors and that the symptoms lessen while away from the building (Levin, 1989). Understanding the etiology of BRS in office buildings has been a major challenge. Evidence supporting the hypothesis that building characteristics and related indoor environmental quality affects symptom occurrence in building occupants continues to accumulate (Mendell, 1993, Fisk, 2000; Chao et al., 2003). BRS include symptoms of allergies, asthma, and respiratory illnesses. Indoor air quality also appears to influence absenteeism, work performance, and health care costs (Fisk, 2000).

Abbreviated symptom phrasing is used throughout the paper. ''Dry eyes'' abbreviates ''dry, itching, irritated eyes''. ''Sore throat'' abbreviates ''sore or dry throat''. ''Nose/sinus'' abbreviates ''stuffy or runny nose, or sinus congestion''. ''Sneeze'' abbreviates ''sneezing''. ''Tight chest'' abbreviates ''chest tightness''. ''Short breath'' abbreviates ''shortness of breath''.

Carbon dioxide and building related symptoms (BRS)

The primary source of carbon dioxide (CO_2) in office buildings is the respiration of building occupants. At concentrations occurring in most indoor environments, steady state indoor carbon dioxide (CO_2) concentration above that outdoors can be considered a surrogate for concentrations of other occupant-generated pollutants, particularly bioeffluents, and for ventilation rate per occupant, but not as a causal factor in human health responses (ASHRAE, 2001; ACGIH, 1991). That is, higher indoor CO_2 concentrations reflect a lower per occupant ventilation rate, and lower indoor CO_2 concentrations reflect a higher per occupant ventilation rate. CO_2 concentrations in office buildings typically range from 350 to 2500 p.p.m. (Seppänen et al., 1999). The threshold limit value for 8-h time-weighted-average exposures to CO_2 is 5000 p.p.m. (ACGIH, 1991), thus CO_2 concentrations encountered in the normal operation of buildings are not expected to cause health symptoms directly. Currently, the American Society of Heating, Refrigeration, and Air-conditioning Engineers (ASHRAE) recommends a minimum office building ventilation rate in offices of 10 l/s/person, corresponding to an approximate steady state indoor CO_2 concentration of 870 p.p.m. (ASHRAE, 2001), based on the assumptions that outdoor CO_2 is 350 p.p.m and indoor CO_2 generation rate is 0.31 l/min/person.

In an extensive review of mostly cross-sectional studies (Seppänen et al., 1999), one half of 18 studies of BRS in office buildings reported that increased indoor CO_2 concentrations levels were associated with a statistically significant increase in the prevalence of one or more BRS. Symptoms that were associated with CO_2 levels included headache, fatigue, eye symptoms, nasal symptoms, respiratory tract symptoms, and total symptom scores. When limiting the review to mechanically ventilated and air-conditioned buildings only (i.e., excluding naturally ventilated buildings), the proportion of studies reporting a statistically significant association between indoor CO_2 and BRS increased to 70% (Seppänen et al., 1999, Apte et al., 2000). A previous analysis of the 41-building 94–96 BASE dataset (cross-sectional design) found statistically significant dose–response relationships between indoor minus outdoor CO_2 levels (dCO_2) and the following symptoms: sore throat, nose/sinus, combined mucous membrane symptoms, tight chest, and wheeze; the adjusted odds ratios for these symptoms ranged from 1.1 to 1.5 per 100 p.p.m. increase in dCO_2 levels (Apte et al., 2000).

In a longitudinal study using a modified version of the BASE questionnaire, Chao et al. (2003) found that upper respiratory symptoms (''sore/dry throat'', ''sinus congestion'', ''cough'', ''sneezing'') were associated with indoor CO_2 levels (OR = 1.49; 95% CI, 1.09–2.03); eye irritation and non-specific symptoms (e.g., ''headache'', ''unusual tiredness'', ''tension'', ''dizziness'') were not related to indoor CO_2 levels. Not surprisingly, the relationship between CO_2 concentrations and upper respiratory symptoms in this study was no longer statistically significant after adjusting for the number of people in the office, since people are the main source of CO_2 in office buildings.

In this paper, we focus on building-related upper respiratory and mucous membrane (MM) symptoms (i.e., dry eyes, sore throat, nose/sinus, and sneeze) and lower respiratory (LResp) symptoms (i.e., tight chest, short breath, cough, and wheeze). We examine the relationship of the MM and LResp symptoms to indoor building ventilation as inferred from occupant-generated indoor CO_2 concentrations, while controlling for potentially confounding individual-level and environmental variables. The analyzes presented here expand those presented in Apte et al. (2000) to the full 94–98 BASE Study dataset collected in 100 US office buildings.

Methods

The BASE study

The data analyzed in this paper were collected in 100 randomly selected, non-complaint, large US office buildings from 1994 to 1998 by the US Environmental Protection Agency for the Building Assessment Survey and Evaluation (BASE) study (Girman et al., 1995, Womble et al., 1996). These buildings were all at least partially mechanically ventilated, and all but one was air-conditioned. BASE buildings were studied during 1-week periods either in winter or summer. Environmental data were collected during the same week that the questionnaire was administered. The BASE protocol has been discussed fully elsewhere (Womble et al., 1993; BASE Website).

The BASE questionnaire confidentially collected occupant information, including sex, age, smoking status, job characteristics, perceptions about the indoor environment, and health and well-being. The questionnaire inquired about occurrence of the following symptoms: dry eyes, nose/sinus, sore throat, sneeze, tight chest, short breath, cough, wheeze, fatigue, headache, eyestrain, back pain, nausea, hand pain, dizziness, depression, difficulty concentrating, and dry or itchy skin. In this study, we restrict our analyses to the mucous membrane (dry eyes, nose/sinus, sore throat, and sneeze) and lower respiratory (tight chest, short breath, cough, and wheeze) symptoms. A symptom was considered ''building related'' if the occupant reported that the symptom occurred at least 1–3 days per week during the previous month and that the symptom improved when the occupant was away from the building. Symptoms were analyzed both

individually and in the following combined categories: Mucous Membrane (MM) = at least one of dry eyes, nose/sinus, sneeze, or sore throat; Lower Respiratory (LResp) = at least one of tight chest, short breath, cough, or wheeze.

In addition, BASE questionnaire responses were used to test the hypothesis that subpopulations with certain environmentally mediated health conditions are more likely to experience and/or report BRS. The variables used for this purpose include previously diagnosed dust allergy, mold allergy, hayfever, eczema, asthma, and migraine. Self-reported sensitivity to (environmental) tobacco smoke and chemical sensitivity also were considered. The health condition variables were included individually in some models and were combined in other models (i.e., the health conditions variables were combined into a general "susceptibility" variable for some models). It is thought that individuals with these conditions may have a lower threshold in terms of responding to factors that are associated with the symptoms of interest.

At each BASE office building, CO_2, temperature, relative humidity, and volatile organic compounds (VOCs) were measured at three indoor locations and outdoors. CO_2 and indoor temperature were collected as 5-min averages. VOC samples using both canister and multisorbent tube collection methods were collected and analyzed by gas chromatograph-mass spectrometry for up to 73 VOC species. Spatial-average pollutant concentrations and average temperatures were calculated based on data from the three measurement sites. One-day average concentrations of dCO_2, 19 VOCs, formaldehyde, carbon monoxide, temperature, and relative humidity were calculated for all 100 buildings.

Time-averaged workday (defined as 08.00–17.00) difference between indoor and outdoor CO_2 concentrations (dCO_2) was calculated and served as a surrogate measure of ventilation rate per occupant for each building. Only Wednesday measurements were used since that day had a complete set of measurements. dCO_2 was calculated as follows:

$$dCO_2 = \overline{CO}_{2indoor} - \overline{CO}_{2outdoor} \quad (1)$$

where, $\overline{CO}_{2indoor}$ = the time-averaged indoor workday CO_2 concentration, and $\overline{CO}_{2outdoor}$ = the time average outdoor workday CO_2 concentration.

A thermal exposure (THEMEXP) variable (°C-hours) was calculated as the integrated difference between 5-minute-average-temperature and 20°C, duration-normalized in to 8.5 h of exposure. The indoor workday-average relative humidity (RH) was calculated. Climatic and season variables were entered into a subset of enhanced models, including heating degree-days for the building site (HDD,°C-days), cooling degree-days for the building site (CDD,°C-days), and the season (summer or winter) during which the building was studied.

One VOC, 1,2,4 trimethylbenzene (1,2,4-TMB), was selected as a covariate in the regression models to adjust for the potential affects of ambient automotive sources on BRS. Previous analyzes have shown 1,2,4-TMB to have statistically significant associations with a number of MM and LResp symptoms (Apte and Daisey, 1999). 1,2,4-TMB is found in infiltrating outdoor air and originates from automotive sources. Other sources of 1,2,4-TMB in office buildings may include carpet, undercarpet, and building materials (Apte and Daisey, 1999).

Statistical methods

Prevalence odds ratios (OR) and Wald Maximum Likelihood (WML) statistics were calculated using multivariate logistic regression procedures in SAS Release 8.2 (SAS, 1989). Crude and adjusted multivariate models were constructed using continuous dCO_2 as the independent variable and each of the BRS variables as dependent variables. Covariates used in all of the multivariate models to control for potential confounding were age, sex, presence of carpet in workspace, smoking status, THEMEXP, RH, and 1,2,4-TMB concentration. Heating degree-days (HDD), cooling degree-days (CDD), and season variables were added in enhanced models to account for variability possibly caused by climate during the study. Additional details regarding model building with the BASE dataset can be found in Apte et al. (2000).

To evaluate the "dose–response" relationship between the CO_2 metric (dCO_2) and BRS, additional analyzes were conducted where dCO_2 was divided into five exposure categories. The dCO_2 categories reflect the 10th and 90th percentiles of the dCO_2 distribution across all 100 buildings and three bins evenly split between these percentiles. To evaluate the dose–response trends in the associations between dCO_2 levels and BRS, an analysis of covariance approach was used (Selvin, 1995). Dummy variables representing the four highest dCO_2 bins were constructed and used in regression models in place of the continuous dCO_2 variable. The bottom 10th percentile category served as the referent. This approach also was used in the previous analysis of the 94–96 BASE dataset (Apte et al., 2000).

Additional logistic regression models used a single categorical dCO_2 variable with five interval levels as defined above. These levels were coded using the bin-mean dCO_2 for each dCO_2 level. The WML statistic and associated *P*-value for this categorical variable was used as a measure-of-fit of the dose–response relationship for the adjusted associations between categorical dCO_2 measures and BRS.

To estimate the proportion of BRS prevalence that potentially could be avoided through improved building ventilation or elimination of indoor air pollutants, the percent risk reduction (PRD) was calculated for symptoms with statistically significant odds ratios. The PRD statistic was described by Apte et al. (2000) and is an adaptation of the attributable risk percent statistic for situations where the rare disease assumption does not apply. A simple formula used to calculate attributable risk percent (AR%) is

$$AR\% = [(RR - 1)/RR] \times 100 \quad (2)$$

where RR is the relative risk estimate for the effect of interest (e.g., dCO_2 and BRS). RR may be a risk ratio or rate ratio (Miettinen, 1974; Jekel et al., 2001). Alternatively, an odds ratio, which is an approximation of the risk ratio, may be used if the disease or health outcome of interest is rare (Cole and MacMahon, 1971, Jekel et al., 2001). To obtain the PRD for symptom prevalences between 5% and 10% and an odds ratio less than 10, Apte et al. (2000) recommended that a correction of less than −10% be applied to the simple AR% calculation. For a symptom prevalence of 30% and an odds ratio less than 10, the recommended correction is less than −20%. The application of these corrections gives an approximate PRD in these situations. For these analyzes, the PRD is interpreted as the percent reduction of individuals reporting BRS that would be expected if a given dCO_2 level were reduced to the dCO_2 level in the referent group (i.e., the lowest dCO_2 concentration observed among the BASE buildings, 40 p.p.m). This interpretation assumes that dCO_2 concentrations represent concentrations of causal agents.

Table 1 Summary statistics for environmental covariates, individual-level covariates, and BRS dependent variables in the 100 building 94–98 BASE Study dataset

Variable	n	Percent	Mean	SD	Min	Max
Environmental covariates						
dCO_2 (p.p.m./100)	100		2.6	1.3	0.40	6.1
THERMEXP (°C-hours w/T > 20°C)	100		25*	6.8	2.2	43
1,2,4-TMB (p.p.b)	100		0.98	1.1	0.05	6.7
Smoking building	100	25%				
Winter season	100	49%				
Average RH < 20%	100	16%				
Heating degree-days (°C-days)	100		2200	1163	114	4616
Cooling degree-days (°C-days)	100		801	583	22	2243
Individual-level covariates						
Current smoker	4304	15%				
Carpet in workspace	4292	89%				
Female	4295	66%				
Age ≥ 40 years	4294	55%				
Dust allergy (diagnosed)	4158	32%				
Mold allergy (diagnosed)	4093	25%				
Hay fever (diagnosed)	4073	29%				
Combined allergy	4208	42%				
Migraine (diagnosed)	4099	21%				
Asthma (diagnosed)	4032	12%				
Eczema	3972	9%				
Sensitivity to tobacco smoke	4263	56%				
Sensitivity to chemicals in the air	4276	49%				
Sensitivity to tobacco or chemicals	4311	67%				
Any allergy, migraine, eczema, or sensitivity	4316	81%				
BRS dependent variables						
MM	4315	29%				
dry eyes	4245	19%				
sore throat	4258	7%				
nose/sinus	4197	13%				
sneeze	4201	11%				
LResp	4319	8%				
tight chest	4302	2%				
short breath	4287	2%				
cough	4260	5%				
wheeze	4301	2%				

*The geometric mean 1,2,4-TMB concentration across the 100 BASE buildings was 0.6 p.p.b and the geometric standard deviation was 2.5.

Results

Comparison of results from the 94–96 and 94–98 BASE datasets

Table 1 provides summary statistics for environmental covariates, individual-level covariates, and BRS dependent variables for the participants in the full 100 building 94–98 BASE survey. Prior to development of new models, the results of the analysis of dCO_2 association with BRS in the 94–96 dataset were compared to those in the full 100 building 94–98 dataset. This initial comparison did not include climatic/season or the environmentally mediated health condition variables. Table 2 compares the earlier 94–96 dataset with the full 94–98 dataset using multivariate logistic regression models that were unadjusted and then adjusted for SEX, AGE, CARPET, SMOKER, THERMEXP, RH, and 1,2,4-TMB. These same covariates were used in previously published analyses using the smaller 94–96 dataset (Apte et al., 2000). The dCO_2 odds ratios (ORs) are reported in units per 100 p.p.m. The larger 94–98 BASE dataset analysis yielded similar but weaker findings compared with the smaller 94–96 dataset, with smaller adjusted ORs ranging from 1.15 to 1.21 per 100 p.p.m. increase in dCO_2 for sore throat and wheeze. The effect for dry eyes, nose/sinus, and MM observed in the 94–96 dataset was not apparent in the 94–98 dataset. As stated above, this paper focuses on MM and LResp symptoms. However, for completeness we report that none of the associations of dCO_2 with other symptoms reported in the BASE dataset were statistically significant. This finding is consistent with those reported in Apte et al. (2000) for the 94–96 BASE dataset.

Enhanced modeling

Differences in climate may affect regional variability in building codes, design, construction, and operation and, thus, could influence the environmental conditions inside office buildings. In an attempt to account

Table 2 Crude and adjusted* prevalence odds ratios† (OR) for the association of dCO_2 with selected MM and LResp BRS symptoms for both the 94–96 and 94–98 BASE dataset analyzes

BRS Symptom	94–96 BASE Dataset dCO_2 OR (per 100 p.p.m)		94–98 BASE Dataset dCO_2 OR (per 100 p.p.m)	
	Crude	Adjusted	Crude	Adjusted
MM	**1.10 (1.03–1.18)‡**	**1.11 (1.02–1.20)**	1.04 (0.99–1.09)	1.05 (0.98–1.11)
Dry eyes	**1.11 (1.03–1.20)**	**1.13 (1.03–1.24)**	1.06 (1.00–1.12)	1.06 (1.00–1.12)
Sore throat	**1.30 (1.16–1.47)‡**	**1.39 (1.19–1.62)‡**	**1.14 (1.05–1.25)‡**	**1.15 (1.05–1.26)‡**
Nose/sinus	**1.11 (1.02–1.22)**	**1.15 (1.03–1.28)**	1.05 (0.98–1.12)	1.05 (0.98–1.13)
Sneeze	1.03 (0.94–1.14)	1.03 (0.92–1.16)	1.04 (0.97–1.11)	1.04 (0.97–1.12)
LResp	1.10 (0.98–1.22)	1.10 (0.97–1.26)	1.03 (0.95–1.12)	1.03 (0.94–1.12)
Tight chest	1.11 (0.90–1.37)	1.27 (0.99–1.65)	1.03 (0.89–1.20)	1.09 (0.93–1.28)
Short breath	1.08 (0.87–1.34)	1.18 (0.90–1.56)	1.05 (0.89–1.24)	1.09 (0.91–1.29)
Cough	1.04 (0.90–1.19)	1.02 (0.86–1.20)	0.97 (0.88–1.08)	0.96 (0.86–1.07)
Wheeze	**1.37 (1.12–1.68)‡**	**1.42 (1.09–1.85)**	**1.22 (1.04–1.42)**	**1.21 (1.03–1.43)**

*Adjusted for age, sex, presence of carpet in workspace, smoking status, THERMEXP, RH, and 1,2,4-TMB. These models did not include environmentally mediated health condition variables (e.g., asthma, allergies, chemical sensitivity, etc.).
†Values in parentheses are the 95% confidence interval (CI). ORs and CIs given in bold are statistically significant at the 95% confidence level or higher.
‡$P \leq 0.005$.

for the variance due to climatic differences, SEASON, heating degree-days (HDD), and cooling degree-days (CDD) variables were added to further refine the initial models. For simplicity of presentation, Table 3 lists the basic set of variables used in all the models described below. Additionally, variables representing the following selected environmentally mediated health conditions, or ''susceptibilities'', were added into these enhance models: dust allergy, mold allergy, hayfever, eczema, asthma, migraine, sensitivity to (environmental) tobacco smoke, and chemical sensitivity. All of the health condition variables showed some statistically significant relationships with symptoms, thus supporting the hypothesis that individuals with these conditions are more susceptible to experiencing BRS than those without these conditions. In particular, diagnosed asthma and self-reported chemical sensitivity were consistent predictors of lower respiratory and all symptoms, respectively. Statistically significant ORs for BRS ranged from 1.52 (95% CI, 1.14–2.01) to 11.13 (95% CI, 2.72–45.53) comparing individuals with one or more susceptibility with those without any susceptibility.

Table 3 Descriptions of covariates included in all enhanced models

Variable	Description
SEX	0: male; 1: female
AGE	0: age < 40 years; 1: age ≥ 40 years
CARPET	0: no carpet at workstation; 1: carpet on most or all of floor at workstation
SMOKER	0: never or former smoker; 1: current smoker
THERMEXP	8.5 h workday normalized degree Celsius hours above 20°C
RH	0: mean RH < 20%; 1: mean RH ≥ 20%
1,2,4-TMB	indoor canister 1,2,4-Trimethylbenzene; automobile exhaust marker
SEASON	0: summer; 1: winter
CDD	Cooling degree-days (°C-days)
HDD	Heating degree-days (°C-days)

After including the health condition variables, the dCO_2 variable was no longer statistically significant with the exception of sore throat (data not shown). An inspection of the model output suggested that this might be due to reduced statistical power; many observations had missing values for the health condition variables, reducing the sample size to about 3700 observations. To create a more parsimonious model, a new variable was defined such that any individual who reported having one or more of the environmentally mediated health conditions was considered to be ''susceptible'' (SUSCEPT). The increase in sample size achieved by combining the health condition variables resulted in fewer observations being dropped due to missing values, yielding a sample size of about 4200. In these models, adjusted odds ratios per 100 p.p.m. increases in dCO_2 were statistically significant for MM (OR = 1.08; 95% CI, 1.02–1.15), dry eyes (OR = 1.09; 95% CI, 1.02–1.17), sore throat (OR = 1.21; 95% CI, 1.09–1.34), nose/sinus (OR = 1.11; 95% CI, 1.02–1.20), sneeze (OR = 1.09; 95% CI, 1.00–1.19), and wheeze (OR = 1.23; 95% CI, 1.01–1.48) symptoms (Table 4). Table 4 provides a comparison between the crude and adjusted models and also provides the ORs and 95% confidence intervals for the FEMALE and SUSCEPT variables. Other statistically significant covariates in these models were AGE (OR range: 1.2–1.4), SMOKER (OR range: 1.4–2.2), RH (OR range: 1.6–2.0), 1,2,4-TMB (OR = 1.3 for short breath), and CDD (OR range: 0.96–0.98 per 100°C-days).

CO_2 dose–response

Figure 1 presents the results of the analysis of the trend between increasing dCO_2 levels and reported symptoms after adjustment for all of the covariates listed in Table 3 plus SUSCEPT. The data from buildings in the

Table 4 Crude and adjusted prevalence odds ratios* (OR) for the association of dCO_2, sex, and any environmental susceptibility with MM and LResp BRS symptoms for the 94–98 BASE dataset analyzes

BRS Symptom	94–98 BASE Dataset			
	dCO_2 OR (per 100 p.p.m.)		Individual risk factors	
	Crude	Adjusted†	FEMALE§	SUSCEPT¶
MM	1.04 (0.99–1.09)	**1.08 (1.02–1.15)**	**2.07 (1.78–2.42)‡**	**1.88 (1.55–2.29)‡**
Dry eyes	1.06 (1.00–1.12)	**1.09 (1.02–1.17)**	**2.18 (1.80–2.63)‡**	**2.14 (1.66–2.74)‡**
Sore throat	**1.14 (1.05–1.25)‡**	**1.21 (1.09–1.34)‡**	**2.12 (1.56–2.89)‡**	**2.21 (1.46–3.35)‡**
Nose/sinus	1.05 (0.98–1.12)	**1.11 (1.02–1.20)**	**1.80 (1.45–2.24)‡**	**2.34 (1.73–3.16)‡**
Sneeze	1.04 (0.97–1.11)	**1.09 (1.00–1.19)**	**1.99 (1.58–2.52)**	**1.52 (1.14–2.01)**
LResp	1.03 (0.95–1.12)	1.08 (0.97–1.19)	**1.75 (1.34–2.29)‡**	**2.69 (1.81–4.01)‡**
Tight chest	1.03 (0.89–1.20)	1.07 (0.90–1.28)	**1.84 (1.10–3.07)**	**11.13 (2.72–45.53)‡**
Short breath	1.05 (0.89–1.24)	1.07 (0.87–1.32)	**3.00 (1.53–5.89)‡**	**5.53 (1.72–17.80)‡**
Cough	0.98 (0.88–1.08)	1.03 (0.91–1.16)	**1.80 (1.29–2.51)‡**	**1.90 (1.22–2.95)‡**
Wheeze	**1.22 (1.04–1.42)**	**1.23 (1.01–1.48)**	1.69 (0.97–2.92)	**2.44 (1.10–5.40)**

*Values in parentheses are the 95% confidence interval (CI). ORs and CIs given in bold are statistically significant at the 95% confidence level or higher.
†Adjusted for covariates listed in Table 3 and the susceptible population variable SUSCEPT‡.
‡$P \leq 0.005$.
§Adjusted odds ratio for females vs. males of having the BRS symptoms.
¶One or more of the following susceptibilities: dust allergy, mold allergy, hay fever, eczema, asthma, migraine, sensitivity to (environmental) tobacco smoke, chemical sensitivity.

lowest dCO_2 bin served as the referent. Total sample size for each symptom also is shown (n range: 4108–4225). Visually, the plots suggest possible dose–response relationships, but usually with the odds ratio in one exposure category deviating from the expected dose–response pattern. Based on the WML tests for statistically significant trends, the following symptoms or symptom groups were found to have a statistically significant dose–response relationship with dCO_2 ($P < 0.05$): MM, dry eyes, sore throat ($P < 0.005$), nose/sinus, sneeze, and wheeze.

Potential for BRS risk reduction

Using the percent risk reduction (PRD) statistic (Apte et al., 2000), we estimated the maximum potential reduction in BRS that could be achieved if dCO_2 were reduced from 608 p.p.m. (the highest dCO_2 concentration among the BASE buildings) to 40 p.p.m. (the lowest dCO_2 concentration among the BASE buildings). Based on the adjusted regression models reported in Table 4, the calculated ORs corresponding to a dCO_2 concentration of 608 p.p.m. for dry eyes, sore throat, nose/sinus, sneeze, and wheeze are 6.19, 6.87, 6.30, 6.19, and 6.99, respectively. In BASE buildings with the highest dCO_2 concentrations, the implied potential maximum reduction in prevalence of these symptoms is roughly 64%, 75%, 64%, 74%, and 85%, respectively. As discussed above and in Apte et al. (2000), a correction can be applied when the prevalence of the outcome of interest is 5% or greater to give a more conservative estimate. Since the prevalence of wheeze was less than 5%, no correction was applied. Prevalences for dry eyes, sore throat, nose/sinus, and sneeze were higher (see Table 1), thus, corrections of −20%, −10%, −20%, and −10%, respectively, were applied.

Discussion

dCO_2 analyses

It should be re-emphasized here that there is no direct causal link between exposure to CO_2 and BRS, but rather dCO_2 is a surrogate measure of ventilation rate per occupant and is approximately correlated with other indoor pollutants that may cause BRS. The results of these analyses suggest that there is an association between elevated dCO_2 levels and increased prevalence of certain mucous membrane and lower respiratory building related symptoms in the 100 building 94–98 BASE dataset. These findings were evident in crude regression models and persisted through adjustment for a number of potential confounders.

Analysis of trend indicates that in the fully adjusted model (i.e., the model that include dCO_2, the covariates listed in Table 3, and SUSCEPT), a statistically significant dose–response trend is apparent for the relationship between dCO_2 and MM, dry eyes, sore throat, nose/sinus, sneeze, and wheeze symptoms in the 94–98, 100 building BASE dataset. This is consistent with the findings for the 94–96 BASE dataset as discussed in Apte et al. (2000); however, the 95% confidence intervals around the odds ratio point estimates are considerably tighter using the 94–98 BASE dataset as would be expected given the larger sample size.

The odds ratios for the associations of symptoms with the highest average observed difference between indoor and outdoor CO_2 concentrations may indicate

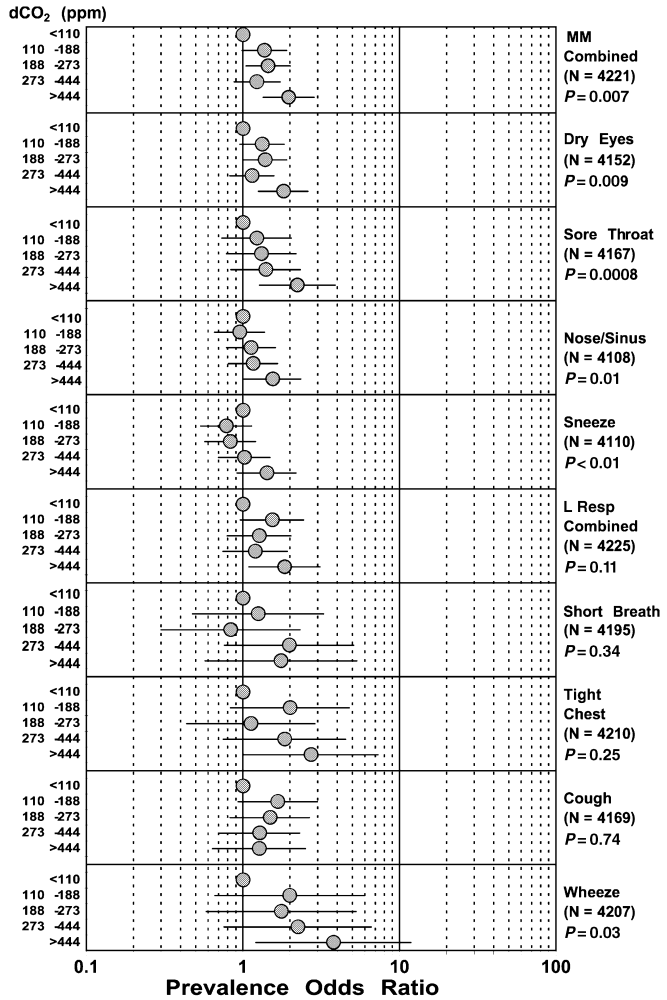

Fig. 1 Dose–response relationship between binned dCO_2 and MM and LResp symptoms in 100 building 94–98 BASE dataset. Odds ratios and 95% confidence intervals are the results of adjusted models that included covariates listed in Table 3 and the SUSCEPT variable. dCO_2 bins reflect the 10th and 90th percentiles of the dCO_2 distribution across all 100 buildings and three bins evenly split between them. The *P*-values reflect the fit of the dose–response model with smaller *P*-values indicating a better fit

the maximum potential to reduce selected symptoms in BASE office buildings, which are thought to be representative of typical US office buildings. Based on the assumption that dCO_2 concentrations are correlated with concentrations of BRS causal agents, the implied potential maximum reductions in BRS prevalence that could be achieved by reducing dCO_2 concentrations in the BASE buildings are on average roughly 64%, 75%, 64%, 74%, and 85% for dry eyes, sore throat, nose/sinus, sneeze, and wheeze, respectively. The reader should be aware that these reductions are based on logistic regression models using the entire BASE building dataset, not just the extreme cases. However it may be impractical in most cases to supply sufficient ventilation to buildings to achieve the greatest reduction in prevalence of these symptoms. Practical approaches to achieve reductions in dCO_2 and correlated indoor air pollutants could come through increases in ventilation rates, improved effectiveness in providing fresh air to the occupants' breathing zone, or through identification of the symptom-causing agents in the indoor air and control of their sources. In no case in this study were the indoor average or the peak indoor CO_2 concentrations extraordinarily high; only two buildings had peak indoor (absolute) CO_2 concentrations routinely above 1000 p.p.m.

Susceptible population

The subpopulation of the office buildings with environmentally mediated health conditions appears to play a strong role in driving the prevalence of BRS. The SUSCEPT variable was a consistently strong and statistically significant predictor of symptoms in the full 94–98 BASE dataset. The lowest adjusted odds ratios observed in this study of BRS risk for individuals with any of the environmental susceptibilities (i.e., allergies, asthma, migraine, eczema, hayfever, chemical and/or tobacco sensitivity) were around 1.9. The odds of a susceptible individual having short breath in their office building were 5.5 times greater than those of a nonsensitive individual – the odds were 11.1 times greater for tight chest. Interestingly, the prevalence of SUSCEPT in the BASE study building population is very high (81%), although the prevalences of the lower respiratory symptoms were on the order of a few percent.

Epidemiological considerations

Epidemiological considerations regarding these analyses were discussed in detail in Apte et al. (2000). We refer the reader to that paper for a discussion of bias and confounding, biological plausibility, and consistency of findings in BASE study analyses. One statistical concern is the potential impact of cross-level bias. This issue has not been addressed in the analyses presented here. The concern relates to the fact that the individual level observations within a building are not truly independent as the environments of the occupants are shared. The extent to which this bias might lead to error in the estimates of the true relationships is thought to be small, but more sophisticated methods would be needed to verify the assumption.

Conclusion

The BASE dataset is a valuable source of information about the US building stock, providing an opportunity for identification of causal factors of building related symptoms and for developing solutions to lower their prevalence in buildings. After adjusting for selected covariates, we found statistically significant

associations of mucous membrane (MM) and lower respiratory (LResp) building related symptoms (BRS) with increasing dCO_2. Covariate-adjusted odds ratios per 100 p.p.m. increases in dCO_2 were statistically significant for dry eyes, sore throat, nose/sinus, sneeze, and wheeze symptoms and ranged from 1.1 to 1.2. The data indicate that in the most highly ventilated buildings (lowest dCO_2) these symptoms may be reduced by a maximum of 64–85% depending upon the symptom, compared to buildings that just meet the ASHRAE minimum ventilation standard. These results suggest that reducing indoor CO_2 levels to approximately outdoor levels through increases in the ventilation rates per person among typical office buildings will reduce the prevalence of several symptoms, even when these buildings meet the existing ASHRAE ventilation standard for office buildings. The magnitude of the reduction depends on the magnitude of the increase in ventilation rates, improvement in ventilation effectiveness, and whether sources of BRS-causing agents are eliminated or reduced.

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