Respiratory performance of humans exposed to moderate levels of carbon dioxide

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Abstract

In a business-as-usual scenario, atmospheric carbon dioxide concentration (CO_2) could reach 950 parts per million (ppm) by 2100. Indoor CO_2 concentrations will rise consequently, given its dependence on atmospheric CO_2 levels. If buildings are ventilated following current standards in 2100, indoor CO_2 concentration could be over 1,300 ppm, depending on specific ventilation codes. Such exposure to CO_2 could have physiological and psychological effects on building occupants. We conducted a randomized, within-subject study, examining the physiological effects on the respiratory functions of 15 persons. We examined three exposures, each 150 minutes long, with CO_2 of: 900 ppm (reference), 1,450 ppm (decreased ventilation), and 1,450 ppm (reference condition with added pure CO_2). We measured respiratory parameters with capnometry and forced vital capacity (FVC) tests. End-tidal CO_2 and respiration rates did not significantly differ across the three exposures. Parameters measured using FVC decreased significantly from the start to the end of exposure only at the reduced ventilation condition (p<0.04, large effect size). Hence poor ventilation likely affects respiratory parameters. This effect is probably not caused by increased CO_2 alone and rather by other pollutants - predominantly human bioeffluents in this work - whose concentrations increased as a result.

Practical implications

Rising atmospheric CO_2 levels have raised concerns regarding the negative effects on humans and consequently the future of building ventilation. It has been discussed whether it would still be possible to guide ventilation requirements by a difference between outdoor and indoor CO_2 levels or if absolute CO_2 levels should be used. We use this study to show that an increase in the CO_2 level with no change to ventilation, did not affect human respiration parameters. However, poor ventilation was shown to affect lung capacity demonstrated in the form of an obstructive breathing pattern most likely caused by an increase in the concentration of other pollutants, primarily bioeffluents, and not only CO_2. This result provides additional confirmation for the health effects in ill-ventilated spaces.

KEYWORDS

Ventilation; Forced vital capacity; End-tidal CO_2; Spirometry; Respiration; Future buildings

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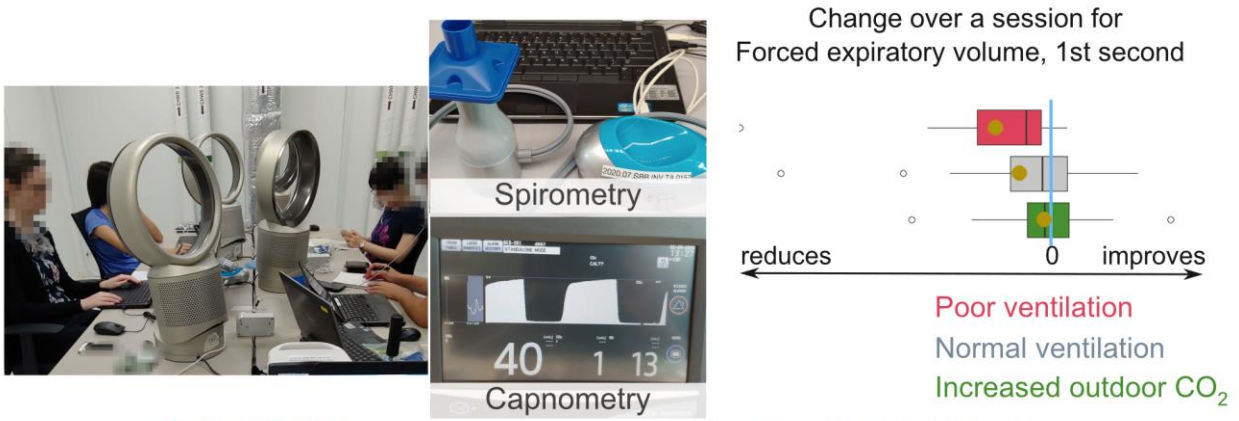
Graphical abstract



Poor ventilation caused obstructive breathing, increased outdoor CO_2 did not.

1 Introduction

Decades of research on indoor air quality (IAQ) has brought us to a point where it is well accepted that IAQ affects people. But, with the rising atmospheric levels of CO_2, we are now faced with a new concern about the outdoor air that we bring in to ventilate indoors. As a long-standing convention, indoor air CO_2 concentration is typically used as an affordable and practical indicator of IAQ. Standards normally recommend a limit of around 1,000 ppm of CO_2 for achieving acceptable IAQ[1]. This limit is based on the CO_2 concentration that corresponds to bioeffluent levels that would result in 20% of unadapted visitors to a space to be dissatisfied with air quality. This limit is a marker of the outdoor air supply rate to the space and is only valid when humans are present indoors. So CO_2 is treated only as a proxy for IAQ and ventilation effectiveness and not a pollutant. The concentration of CO_2 indoors is not considered to be the concern if only it stays below 5,000 ppm which is the occupational exposure limit being a time-weighted average over an eight-hour workday, 40 working hours a week[2]. This level is rarely reached indoors over long durations[1]. The ceiling limit for CO_2 was set at 30,000 ppm for a 10-minute period[2] and is never expected to occur indoors under normal conditions.

Global CO_2 levels are on a rising path. Earth species, including humans, have not encountered CO_2 levels in excess of 300 ppm throughout its evolutionary history, until the early 1900s. Average levels during October 2020 were at 411 ppm at Mauna Loa Observatory[3] and much higher around urban agglomerations[4]. Without significant measures leading to reduced emissions, in the worst-case scenario, these levels can reach about 950 ppm during the next 80 years[5]. Given the history of our species, it is reasonable to assume that the perspective of human beings having to be perpetually in an atmosphere of about 1,000 ppm of CO_2 and higher raises considerable concerns[6]. As a result, during the past 15 years, several studies have been conducted to examine the impact of pure CO_2 on occupants at the levels typically occurring in buildings[7,8]; they do not however provide systematic and consistent information regarding the

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effects of pure CO_2 on humans. Some of these studies have reported a decline in cognitive functions for the exposure to CO_2 as low as 1,000-1,500 ppm[9–11], but others have not[12–16]. The length of exposure to CO_2 has been shown additionally to affect the magnitude of cognitive decline[11,17]. Changes in physiological reactions have also been reported at CO_2 levels higher than 2,500 ppm[16–18]. Two studies with humans neutrophils and mice suggested physiological responses - vascular damage from interleukin-rich microparticles being released - at CO_2 levels of 2,000 ppm and higher[19,20]. There were no results indicating changes in subjective reports of symptoms or air quality.

Currently, there seems to be no obvious physiological mechanism that could explain the observed cognitive decline at the tested levels[7,8]. The studies that have noted physiological impacts did so at CO_2 concentrations >2,500 ppm which are the levels that are not expected to be frequent and prolonged in buildings even in the coming century except for some special conditions such as crowded or tight spaces that are not sufficiently ventilated. There remain nevertheless questions regarding if and how the CO_2 levels in a future building, ventilated as per current standards, would affect occupants physiologically, particularly, their respiration, and that in turn may affect cognitive performance.

Exposure to increased CO_2 levels in inspired air can lead to increased physiological levels of CO_2. This is reflected in arterial CO_2 levels, cerebrovascular activity, and blood and cerebrospinal-fluid pH levels[21,22]. End-tidal CO_2 (ETCO2) can be used as an easy, non-invasive measure of arterial or physiological CO_2 levels, providing an indication of the impact of CO_2 exposure[21]. Some studies have explored how ETCO2 increases with time-length of acute exposure to pure CO_2: 65,000 ppm[23], 50,000 ppm[24], and 30,000 ppm[25]. These studies found that ETCO2 increased initially and then plateaued, within 10 minutes, after having increased 10-40%. A few studies have also performed measurements that provide some indication of how ETCO2 levels of occupants varies over time, when exposed to indoor air under different ventilation conditions and CO_2 concentrations, including a mix of conditions with pure CO_2 and bioeffluents[15,16,26,27]. These studies found that ETCO2 levels plateaued off after nearly an hour, rising by 2-10%. One study even noted a continual decline over a three-hour exposure, without reaching any kind of plateau[26]. This is starkly different from the findings of acute exposure to CO_2, indicating a need for a better understanding of how indoor air impacts physiological CO_2 levels. Similarly, the findings of a recent study suggest that exposure to poorly-ventilated indoors may adversely impact lung capacity, as determined by the forced vital capacity test, performed using spirometry[28].

We aimed to examine whether indoor CO_2 levels impact one specific aspect of human physiology i.e., the respiratory system. We tried to answer the following two questions:

- Is respiration rate, ETCO2, and lung capacity affected by the exposure to two different levels of CO_2 and different ventilation rates?
- Does exposure duration play a role for the effects on respiration rate and ETCO2?

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2 Methods

The study was performed by Berkeley Education Alliance for Research in Singapore (BEARS). The protocol was approved by the University of California Berkeley Ethics Committee (Protocol #2019-04-12042) given that BEARS is a UC Berkeley company in Singapore.

We performed a within-subject experiment in the climate chamber. We studied three exposures, each lasting 150 minutes, and presented randomly to subjects in the design balanced for the order of presentation:

a. CO_2 at 900 ppm - 900-R
b. CO_2 at 1,450 ppm - 1450-V
c. CO_2 at 1,450 ppm - 1450-CO2.

Condition 900-R was achieved with ventilation recommendations from the current standards (reference condition); this level corresponded to a ventilation rate with outdoor air of about 10.4 litres per person per second (L/(p.s)). 1450-V was achieved with reduced ventilation in the presence of people in the chamber corresponding to ventilation rate with outdoor air at about 5 L/(p.s), the -V indicating a change in ventilation from reference condition. 1450-CO2 was achieved by maintaining the same ventilation rate as 900-R, but additionally, pure CO_2 was added to reach indoor CO_2 concentrations of 1,450 ppm. This condition represented a building at the end of this century being ventilated as per current regulations but with outdoor atmospheric CO_2 levels at 950 ppm.

2.1 Facilities and equipment

Experiments were conducted in Singapore over a period of three weeks in July-August 2019. All the sessions were conducted inside a climatic chamber. The layout of the set-up and an image taken during a session are provided in Figs. 1 (a) and 1 (b), respectively. Table S1, in the Supplementary Information (SI), lists the equipment used and their specifications (range and accuracy). In each session, four participants were seated at a workstation equipped with a laptop. Participants used the laptops at their respective stations to provide responses to the subjective questionnaires on the Qualtrics Survey platform. One additional station was kept for the experimenter, the capnometer and the PC connected to the spirometer. The chamber was served by a dedicated air handling unit (AHU) with a variable air volume (VAV) system, both return and supply diffusers being located in the ceiling. The AHU was served by MERV 8 filters, impregnated with activated carbon. To maintain constant ventilation rates, the VAV boxes were set to maximum opening and the supply air temperature was controlled to maintain the indoor temperature.

A recent study[29] discovered that seated occupants, engaged in a range of tasks, may inhale a much higher concentration of CO_2 than the room average. This is due to the formation of a personal cloud (aka, bubble), from a person's exhalation, around a person's breathing zone. The human exhalation chemical concentrations in this bubble can vary based on a variety of factors, including the geometrical and fluid dynamic characteristics of an individual nose and lung.

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Hence, to ensure that all participants during the study were breathing the air of a similar quality as the chamber's average, this bubble was ruptured by an arrangement of desk fans (Fig. 1 (b)). The fans achieved an air velocity between 0.3-0.4 m/s in the breathing zone to achieve this rupture[29]. Participants were informed that they could control the desk fan speeds - as per their comfort needs - so long as they kept the setting above 3 on the fan.

2.2 Study conditions

The actual, measured conditions are given in Table 1. To introduce pure CO_2 into the chamber during days with the 1450-CO2 exposure, we used Brüel & Kjaer, INNOVA 1302 monitor, and 1303 sampler. A cylinder with 99.8% pure CO_2 was connected to the sampler. To keep the subjects blind, the sampler and monitor were kept operational even on days with 900-R and 1450-V exposures though no CO_2 was dosed. The order of presentation of exposure was randomized and balanced across different groups of subjects.

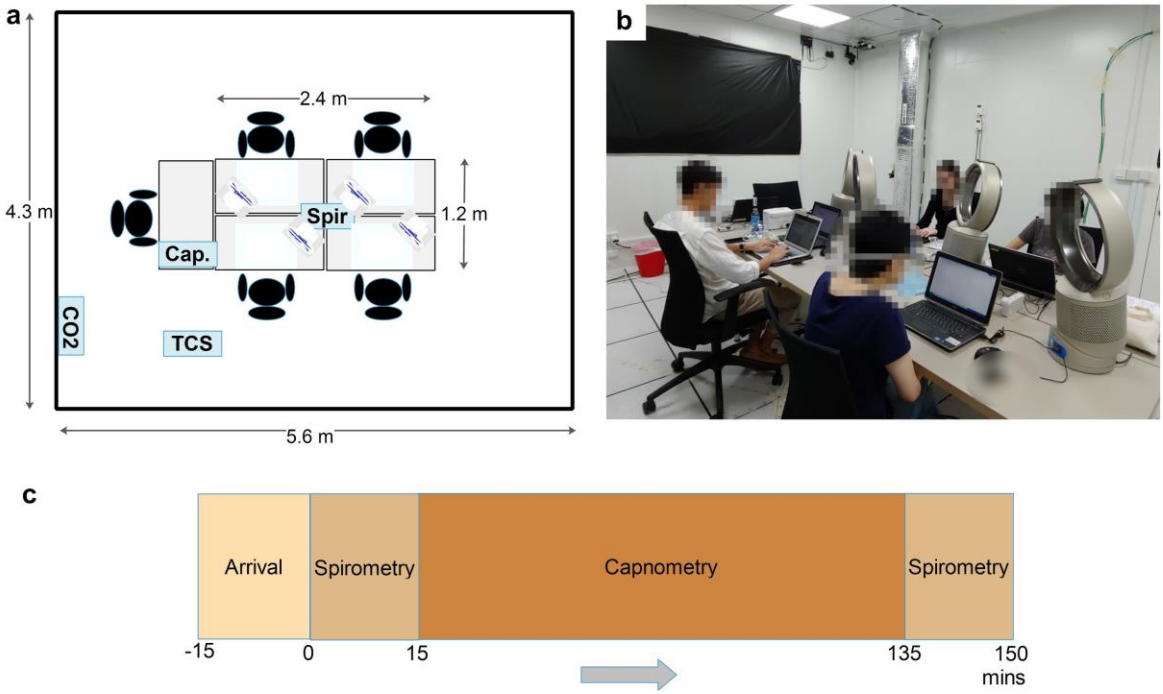

Figure 1. a) A plan section of the chamber layout. 2.6 m ceiling height. b) An image taken during a session. c) Session timeline. All three exposures had the same timeline. In a) Cap. = capnometer, CO2 = wall mounted CO_2 sensor, Spir. = spirometer, TCS = thermal comfort stand

We strove to keep all indoor environmental parameters besides the one relevant to the purpose of this work similar across all three exposure conditions (Table 1). Noise measurements were carried out from minute 15 to minute 135 of the sessions, to avoid the negative effect of the spirometry tests on noise. We kept the VOC monitor active through the entire session duration. The VOC measurements in Table 1 indicate that the levels did not reach instrument detection limit of 15 ppb. Typical indoor chemical human emissions are not expected to be over these limits[30]. The levels may yet have varied for the three sessions, due to difference in ventilation.

https://doi.org/10.1111/ina.12823
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The chamber had only overhead lighting (correlated temperature of ~5000 K). We blacked out the chamber windows so that there would not be any variations from external lighting. The average illuminance was > 500 lux on the horizontal surface where tasks were performed by the subjects.

Table 1. Session conditions. Measured data presented as mean (s.d), except for noise as median (IQR)

Exposures	**1450-V**	**900-R**	**1450-CO2**
Operative temperature (°C)	25.6 (0.5)	25.8 (0.4)	25.8 (0.4)
Relative humidity (%)	56 (2)	55 (1)	54 (1)
Noise (dBA)	41 (3)	43 (3)	44 (2)
VOC (ppm)	Not detectable	Not detectable	Not detectable
CO_2 (ppm)	1400 (110)	930 (20)	1430 (60)

2.3 Participant recruitment and orientation

Participants were recruited through convenience sampling by reaching out to them through posts on social media and student forums. The recruitment criteria included: age between 21 and 55 years old, no history of cardio-respiratory symptoms, ambulatory, no major surgeries (requiring general anaesthesia) during the past year, not pregnant, and not suffering from any sleep disorders. We also required that they had to have lived in Singapore for at least six months prior to the start date of their first session. We did not place an exclusion criterion on smoking or former smokers. However, we asked participant (self-reported) and none of them was a current or former smoker.

Including an initial introduction session of an hour, participants were requested to attend a total of four sessions lasting altogether eight and half hours. During the introduction day, the study process and timeline were explained to the participants, and they were familiarized with the climate chamber. Then, if they were still willing, they gave their written consent to participate. They were then asked to familiarize themselves with the capnometry mask and also completed a practice round during which forced vital capacity (FVC) was measured using the spirometer. The participants were informed that it was the goal to achieve at least three acceptable spirograms during each session to ensure reliable results[31]; acceptable spirograms were determined by the Spirotrac software. Following their introduction to the study, participants were asked to indicate the days on which they could participate in the three experimental sessions. Participants had been advised to maintain relatively regular sleeping habits during this period and to avoid the use of alcohol or other drugs (stimulants or depressants) in the 24 hours prior to sessions. They were also asked not to engage in very strenuous exercise or smoke just before the session. The part regarding smoking is a standard part of the advisory even though in this case, none of the participants were smokers.

Sessions were organized without “washout” days planned between exposure. From previous experimental data[32], we know that the ventilation changes we would be exposing our participants to, would not be perceptible to them. Moreover, subjects are likely to be exposed

https://doi.org/10.1111/ina.12823
https://escholarship.org/uc/item/8qj5v8d1

to similar or worse ventilation in their everyday life, at home or in public transport[33]. Hence, washout days were not scheduled.

While sixteen participants were recruited, one dropped out. Fifteen of them (7 females) attended; one participant completed only two of the exposures (1450-V and 1450-CO2). Using the provided choices, groups of four participants each were formed for each study day after randomizing the exposure order. Five participants started with the condition 900-R, six with 1450-V and four with 1450-CO2. Because of "no shows", there were two days with three participants, and one day with two participants, but the conditions were otherwise not affected. Each participant was compensated with SGD 110 for a total of eight and a half hours of their time. Participant demographics have been provided in Table S2.

The study design was single-blind with "deception". Participants were not made aware of the indoor conditions, the ventilation levels, or even the aim of the experiment. All appearances were kept similar for all three sessions, including operation of the INNOVA system.

2.4 Subjective ratings

Participants assessed indoor environmental quality at the beginning and then again at the end of each session. The questionnaire was administered through the Qualtrics platform[34]. It included questions on thermal sensation; acceptability of thermal environment, humidity, air movement, air quality; thermal preference; air quality specifically odor, stuffiness, and any physical symptoms like dryness or irritation of eyes, skin, throat, or nose, headache, dizziness, etc.; the complete questionnaire is a part of SI. When answering the questions on the questionnaire the context was created by the following sentence: "Read each item and indicate to what extent you feel this way right now, that is, at the present moment." In the analyses, we compared the responses at the end of the session as well as changes in responses over the session duration.

The questionnaire at the onset also asked additional questions on the participants' day before arriving at the experimental session, the mode of transportation to the experimental site, the nature of the last meal, and how well they slept last night.

The questionnaire at the end of the session contained a circumplex model of affects[35,36] additionally to questions related to the indoor environment to get a measure of the participants' emotional state. The circumplex model is a well-accepted and widely used measure of human emotion in psychological research[37]. We decided to include the model as part of subjective feedback since a recent study has found that while the influence of the indoor environment may not be apparent on comfort perception, it may still affect mood[38]. The model divides the current emotional state into eight groups, based on positive and negative emotions and high and low levels of arousal. Twenty-six different adjectives were used to find the participant's location on this multidimensional scale. A representation of the circumplex model and the adjectives under different categories is presented in the Supplementary

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Information, Fig. S1. For analysis, average scores under each of the eight categories were compared.

2.5 Session timeline

We present a session timeline in Fig. 1 (c). At the beginning of each session day, the spirometer was checked against a three liters syringe standard, within a tolerance of ±1%[39]. All sensors used to perform measurements listed in Table 1 were set to logging frequency of one minute. While respiration rate and tidal volume are not known to have a circadian rhythm, metabolism - and consequently ETCO2 - does have a circadian component[40]. We wanted to avoid any confounder due to diurnal variations of the measured parameters. So all sessions, each lasting two and a half hours were held in the afternoon, during the three hours between 1:30 pm and 4:30 pm, local time.

Participants reached the laboratory 15-20 minutes before the scheduled start time and took about 10 minutes to settle into a sedentary condition. Then they moved into the chamber. We had advised the participants to dress for thermal comfort as long as they abide by the safety rules (i.e., full-length trousers, no sleeveless tops, and close-toed shoes). Once inside, they sat down in a relaxed posture. They were reminded that they could control their desk fan to their liking as long as they did not reduce the speed below a certain minimum. The session began with the first round of the FVC test, with each seated participant being asked to use the spirometer, one by one. After that, participants were asked to complete the first round of questions. Once completed by all participants, the period when the capnometer measurements were made was launched and it lasted 120 min. Measurements were done for one participant at a time, moving from one person to the next one; the measurement for one person lasted about three minutes. After two hours, the participants provided answers to the questions (second round) and then completed the FVC tests for the second time, as well. Participants remained seated throughout the session. They could bring their phones or their own books, magazines, paperwork, etc. Capnometry did not require active engagement from the participants, so they were free to do their own work. However, they had to give us their undivided attention during the initial and the final 15 minutes of each session to appropriately conduct the forced vital capacity test. During the sessions, participants were allowed to drink plain water but no food or other drinks. Participants maintained their seated posture throughout the sessions.

Of the three acceptable spirograms obtained, the best results - as indicated by the Spirotrac software - were used for analysis[39]. While an FVC test can yield several parameters, for this study, we focused on the following four, most widely reported parameters[39]:

- FVC - forced vital capacity (liters), amount of air forcibly exhaled by a participant after taking the deepest breath possible
- FEV1 - forced expiratory volume in the first second (liters)
- FEV1/FVC ratio

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- PEF - peak expiratory flow (liters per minute), the maximum flow rate achieved during an FVC test

From the capnometry, we obtained an average ETCO2, the peak CO_2 concentration in exhaled breath, and respiration rate (RR) for every minute of measurement. FVC parameters have inherent variations over a day. For healthy subjects, FVC and FEV1[41], and for PEF[42] these variations are about 5%. Since the FEV1/FVC ratio is a derived quantity, we estimated the variation in it from error propagation in a ratio (5% in each parameter, hence $\sqrt{5^2 + 5^2} \approx 7\%$, in the derived quantity). These variations were used as a reference when analyzing the results, in Fig. 5, to highlight observed differences across the session that were larger than diurnal differences.

2.6 Statistical analysis

We used R[43] for all statistical analyses. We used $\alpha = 0.05$ as the significance level for all tests, 2-tail. For pairwise comparisons of the same parameter between the start and end of a session, the Wilcoxon signed-rank test was used. Effect sizes of Wilcoxon rank tests, Pearson's, r values, were calculated using the Rstatix package[44]; effect sizes were interpreted as $0.1 \leq r < 0.3$ small, $0.3 \leq r < 0.5$ moderate, and ≥ 0.5 large[45].

For comparing a measured parameter across the three sessions we used linear mixed-effects models (LME) using the lme4 package[46]. LME has advantages such as an explicit modelling of fixed and random effects and the ability to include individuals who may not have completed all the exposures. That was the main reason for its selection over repeated measures Anova. In our LME models, the participants were the random effect, while the exposure was the fixed effect. Further, LME models may use random intercepts or random slopes. A random intercepts model corresponds to different individuals having different thresholds when it comes to their respiratory systems' response to the indoor environment. The random slopes model goes further in that not only are individual thresholds different, the slope of response also differs across individuals, for the different exposures, effectively implying different dose-response relations. We tested both model types but, as described in Supplementary Information, the random slopes models were preferentially used.

We used likelihood ratio tests to compare the effect of exposures. We compared a baseline model with only random effects (inter-individual variations) with the model including both random and fixed effects (effect of exposures added in). If, based on *p*-values and log-likelihood ratios, the later model was significantly better, then we concluded that exposures had a significant effect. If exposures turned out to have a significant effect, we then further explored the mixed effects models to understand which exposure(s) led to the differences.

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3 Results

3.1 Model selection

For both RR ($\chi^2(5)=111.9$, $p < 0.0001$) and ETCO2 ($\chi^2(5)=485.9$, $p < 0.0001$), random slopes models gave better fits than random intercepts. Correspondingly, the log-likelihood ratios were higher for the random slopes models: RR (-2401.5 vs. -2457.4) and ETCO2 (-1953.7 vs. -2196.7). In SI (Fig. S2) we show boxplots for the MAE and MSE values generated by the random slopes and random intercepts models for both ETCO2 and RR with a clear indication of error measures being lower for the random slopes model. This means that the dose-response relation varies from subject to subject. We hence selected random slopes models for further analysis. This selection is further supported by Fig. S3 in SI. It shows the ETCO2 and RR values for each individual that are color-coded by the exposure. We use this figure to illustrate the variation that was observed across individuals. For some participants, it may be noted that values are closely clustered while others have a wide range of variations. Thus, to better reflect inter-individual variations, the random-slopes model seems to be a better choice when modelling respiratory parameters.

3.2 Capnometry results

3.2.1 Comparison of capnometry parameters across exposures

Using random slopes models, we compared the ETCO2 and RR data across the three exposures. The comparison of the models with both fixed (exposure) and random (participants) effects with the models that just had the random effects did not show any significant difference for both ETCO2 ($\chi^2(2)=1.6$, $p = 0.45$) and RR ($\chi^2(2)=1.5$, $p = 0.46$), this means that the three exposures did not influence RR and ETCO2. Details for the fixed effects output for the ETCO2 and RR models are provided in Table 2. Fixed effects outputs in the tables provide the model for 900-R as the (Intercept) row while for 1450-V and 1450-CO2, the deviations from 900-R are respectively reported.

Table 2. Mixed effects models comparisons output for ETCO2 and RR data

ETCO2 model				**RR Model**			
Fixed effects				Fixed effects			
	Estimate	Std. Error	t value		Estimate	Std. Error	t value
(Intercept)	40.14	0.82	48.76	(Intercept)	16.8	0.72	23.3
1450-V	0.36	0.33	1.09	1450-V	-0.7	0.53	-1.26
1450-CO2	-0.45	0.85	-0.53	1450-CO2	0.1	0.49	0.12

For ETCO2, the average level for the reference 900-R condition was ~40 mm Hg. The 1450-V exposure was higher than this by ~0.4 mm Hg and 1450-CO2 was lower by ~0.4 mm Hg. For RR, the reference 900-R condition corresponded to ~17 breaths per minute. The 1450-CO2 did not differ much while the 1450-V exposure led to the slowing of breathing by about one breath per min. Overall, none of the differences between the exposures, for ETCO2 and RR, were

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significant. In Fig. 2, we show the violin plots for the distributions of ETCO2 and RR, as recorded for all 15 participants color-coded by the exposure. The plots confirm that there were no obvious differences in ETCO2 and RR between different exposure conditions.

3.1.3 Evolution of ETCO2 and RR over the session duration

One of the goals of the study was to examine whether ETCO2 and RR change along the course of exposure at different conditions. To reach this goal, we used locally estimated scatter-plot smoothing (LOESS). The results are presented in Fig. 3.

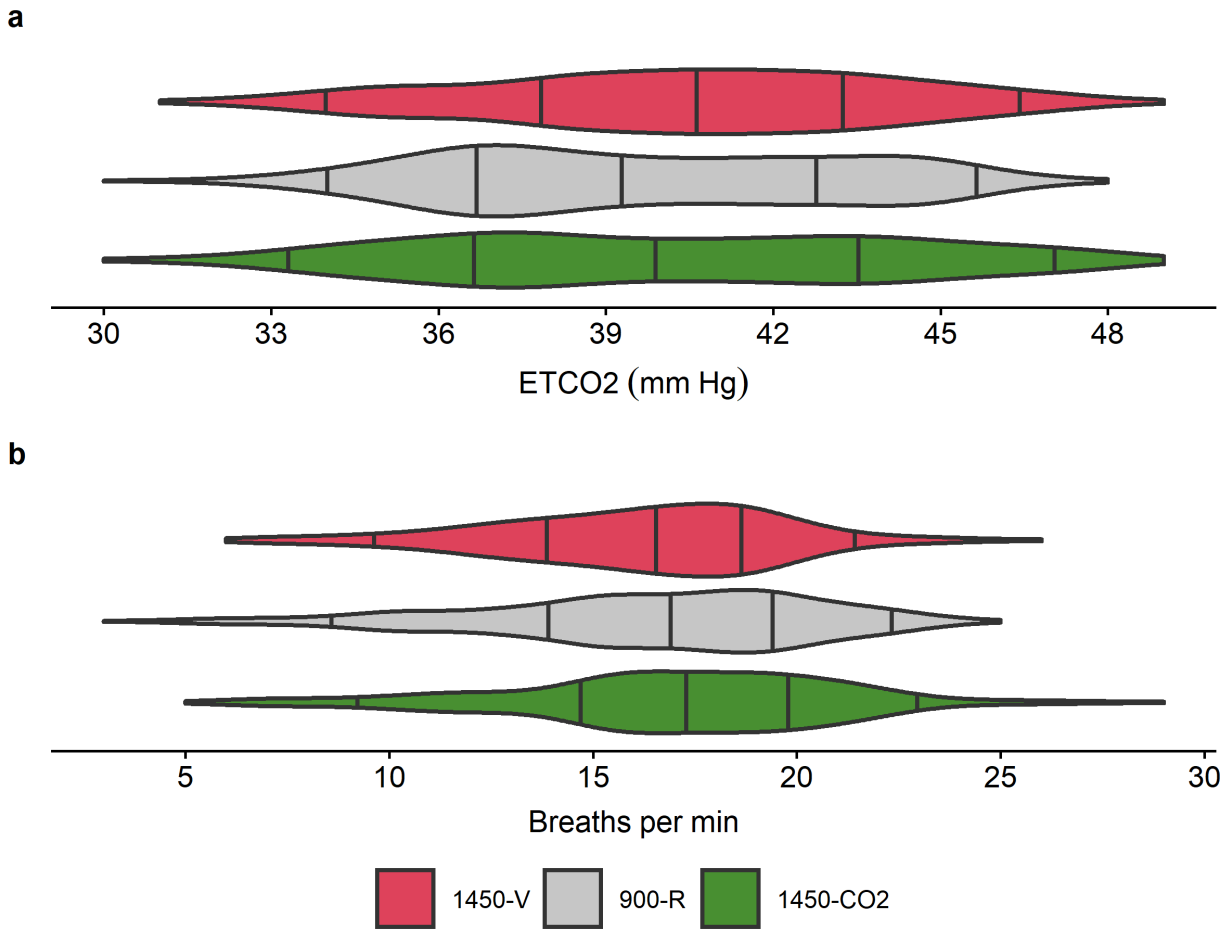

Figure 2. Violin plots for the distribution of (a) ETCO2 and (b) RR for all three exposure conditions, for all participants, taken together. The violin plots have marked lines for 5, 25, 50, 75, and 95th percentiles.

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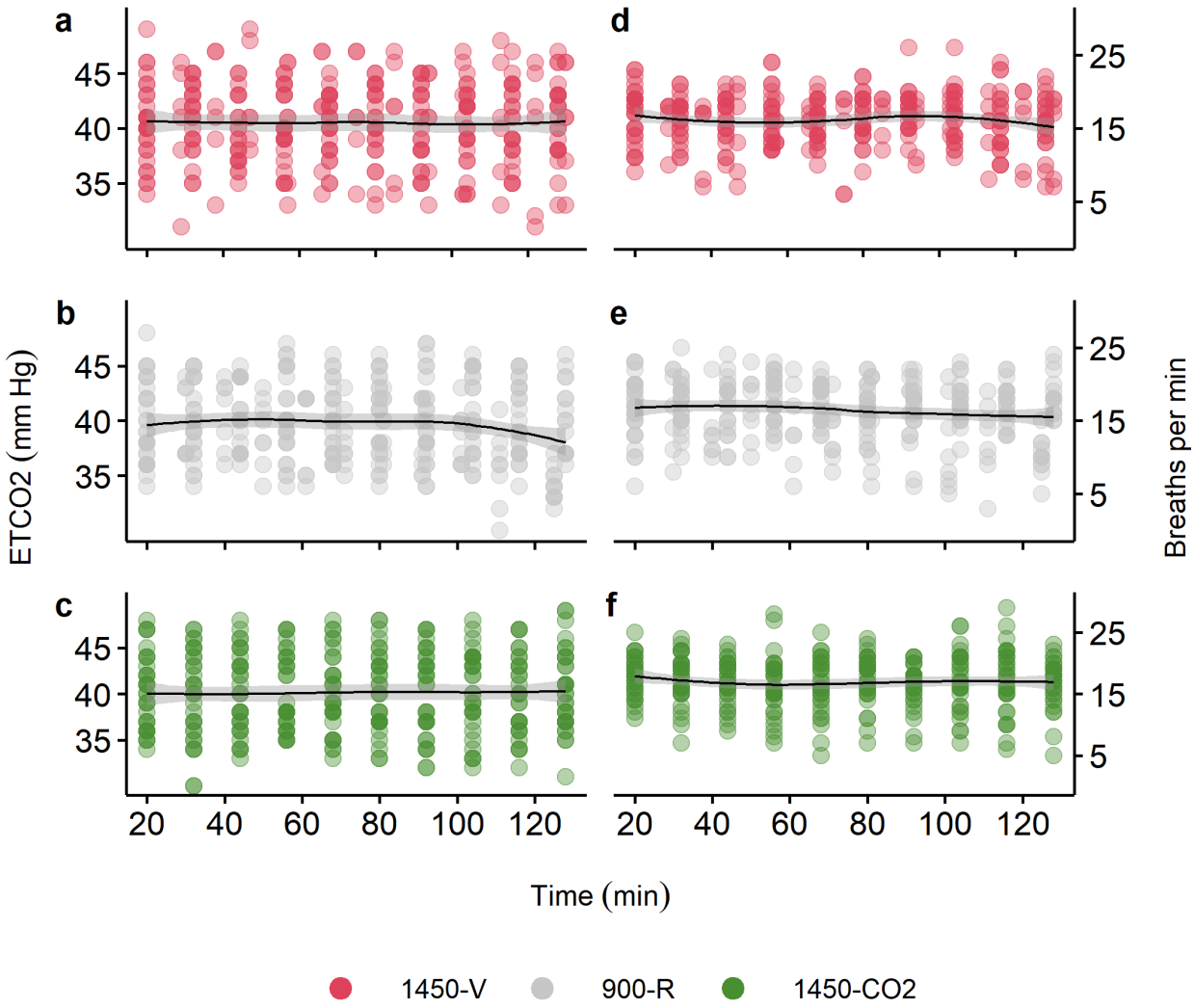

Figure 3. Time series visualization of ETCO2 (a,b,c) and RR (d,e,f) over the course of exposure at three different exposure conditions represented by LOESS plots

Fig. 3 shows no obvious trend either for the ETCO2 and RR. A small reduction in ETCO2 can be noted for the reference 900-R condition towards the very end of the session and a small reduction in RR for the 1450-V condition also towards the end of the exposure.

3.1.4 ETCO2 and RR variation with respect to CO_2 levels

The concentration of CO_2 in inspired air is one of the factors that may affect ETCO2 and correspondingly RR[47]. We examined whether the CO_2 concentration in the chamber recorded at the time point when the capnometric measurement was made could influence ETCO2 or RR values. This is done by plotting ETCO2 and RR against CO_2 in Fig. 4; the LOESS lines do not show any pattern.

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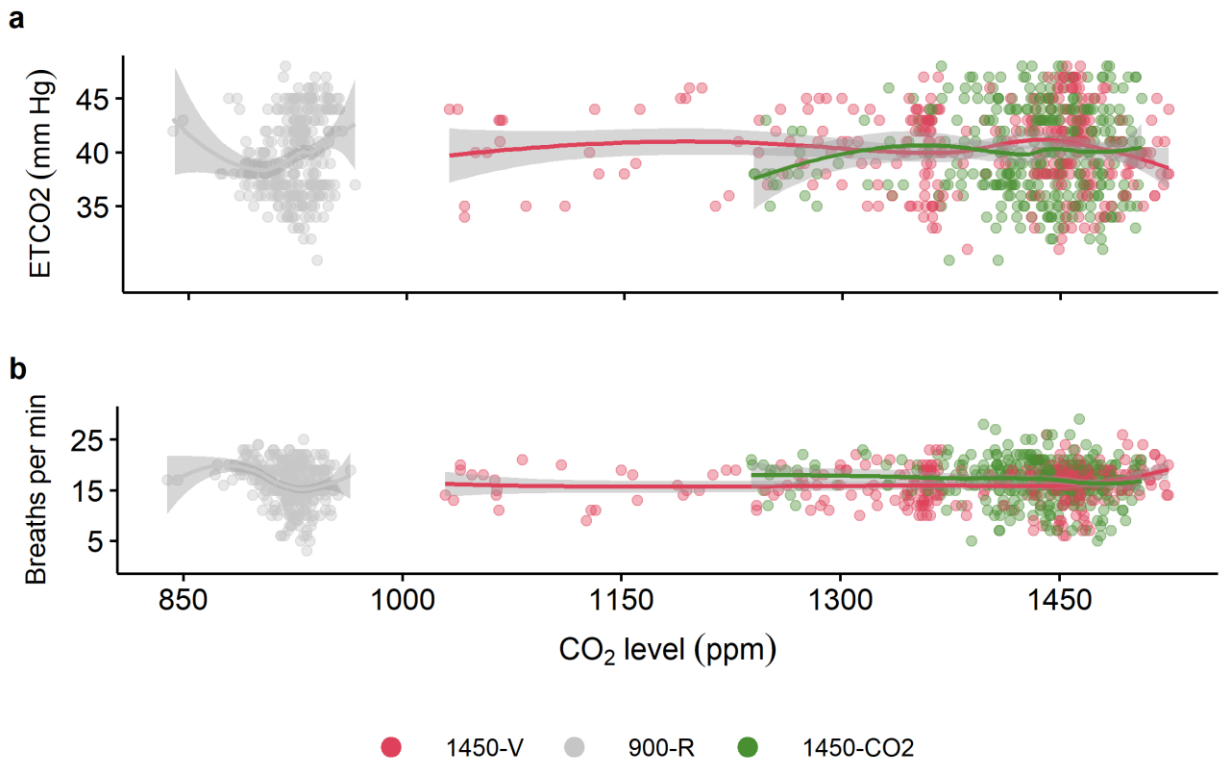

Figure 4. ETCO2 (a) and RR (b) as a function of CO_2 levels recorded in the chamber. The points have been color-coded according to the specific exposure condition.

As can be seen in Fig. 4, there were no obvious trends to ETCO2 and RR values as chamber CO_2 levels varied. For both 1450-V and 1450-CO2 conditions, the LOESS lines are nearly flat. The variation in RR and ETCO2 as seen for the reference 900-R condition was caused by few measurements at the tails of the distribution (extreme values).

3.3 Spirometry results

Unlike capnometry, spirometry is an effort-intensive measurement and hence, instead of continuous measurement data was collected at the beginning and at the end of the sessions. For spirometry results, we made different comparisons. We used the linear mixed mixed-effects on the values obtained at the start of the session and at the end of the session to compare the three exposures. We also compared the values for different FVC parameters from the end of the session against the beginning of the session.

For the FVC test results taken at the beginning of the session, none of the parameters included in the random-effects (i.e. participants only) were significantly different from the mixed-effects (i.e. exposures (fixed effect) and participants (random effect)). For the FVC test results from the end of the session, a significant difference between the random effects and mixed-effects model was found only for PEF ($\chi^2(2)=7.0$, $p = 0.03$). Details for the fixed effects output for the PEF model, at end of the session, are provided in Table S3.

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Table 3. Wilcoxon rank test results for comparison of FVC parameters from the beginning and end of sessions for the three exposures. Results include *p*-value and effect size. Effect size has a qualifier in braces: S - Small, M - Moderate, L - Large. Significant differences and large effect sizes have been put in **bold**.

	1450-V			**900-R**			**1450-CO2**		
	p-value	Eff. Size	Median diff.	*p*-value	Eff. Size	Median diff.	*p*-value	Eff. Size	Median diff.
FVC	0.09	0.44 (M)		0.14	0.40 (M)		0.60	0.15 (S)	
FEV1	**0.004**	**0.75 (L)**		0.36	0.26 (S)		0.64	0.13 (S)	
FEV1/FVC	**0.039**	**0.54 (L)**		0.70	0.11 (S)		0.73	0.10 (S)	
PEF	**0.041**	**0.53 (L)**		0.38	0.24 (S)		0.50	0.18 (S)	

Table 3 shows additionally that FEV1, FEV1/FVC, and PEF changed significantly between the start and the end of sessions and only for the 1450-V exposure; all changes showed a reduction in these parameters and the size of the effect was large. For the 900-R and 1450-CO2 exposure conditions, no significant changes were observed.

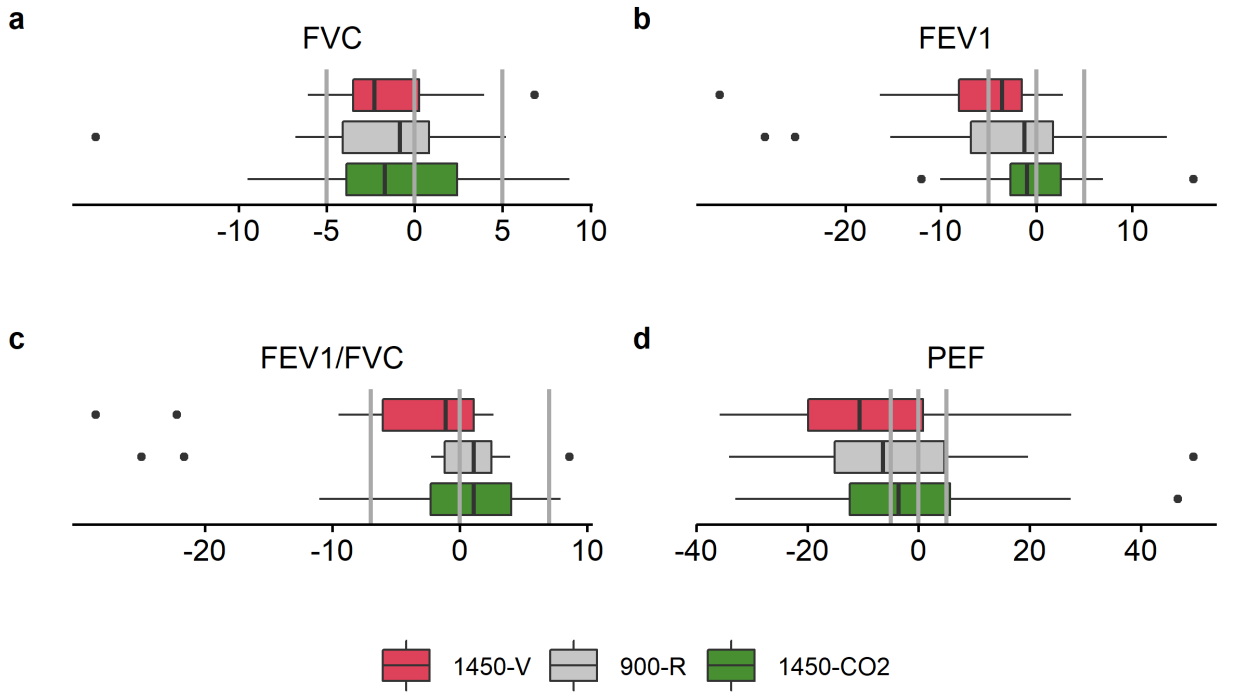

Figure 5. Percentage change in spirometry parameters between the end and the beginning of the session, with respect to the mean value during the session. Change is measured as Session end - Session beginning (a) FVC (b) FEV1 (c) FEV1/FVC (d) PEF. The grey reference lines are provided at the zero line and the fractional diurnal variations expected for a healthy individual.

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Fig. 5 shows the fractional changes of FVC, FEV1, FEV1/FVC, and PEF, from the beginning of the sessions to the end, relative to the values measured at the beginning. In Fig. 5, we hence provide reference horizontal lines for these variations, in each of the plots for FVC, FEV1, FEV1/FVC, and PEF. While for 900-R and 1450-CO2 exposure, points generally lie within the boundaries of normal diurnal variations, for 1450-V negative deviations, outside these boundaries are observed.

3.3 Subjective responses

Self-reported last-night's sleep quality did not differ across the three exposure conditions ($\chi^2(2)=2.0$, $p = 0.37$). The ratings of the eight dimensions of affects at the end of the sessions were not significantly different among the three exposures, both for the random-effects model and the mixed-effects model. The affect dimension that came closest to a significant difference was the High Arousal-Positive ($\chi^2(2)=4.1$, $p = 0.13$).

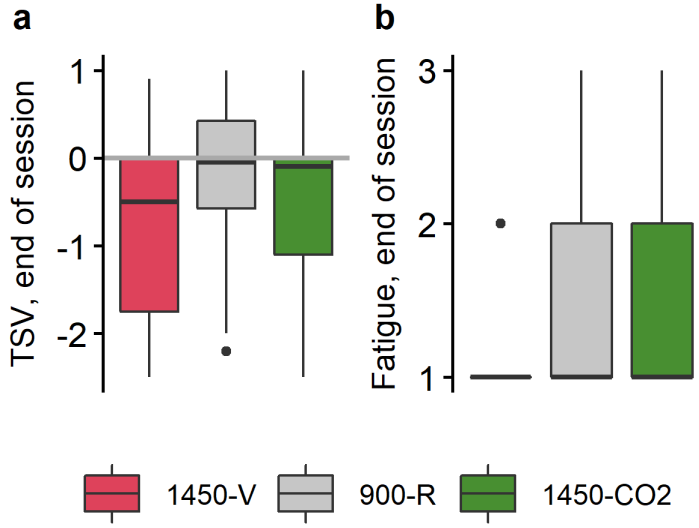

Figure 6. a) Thermal sensation vote (TSV) and b) Fatigue votes, at the end of the sessions, for all three exposures.

Subjective responses obtained at the end of the sessions were compared for different exposure conditions. The results of modeling showed that thermal sensation vote (TSV) ($\chi^2(2)=7.4$, $p = 0.025$) and the rating of fatigue ($\chi^2(2)=6.2$, $p = 0.044$) were significantly different (details of the respective LME models provided in Table S4 in SI). A comparison of the thermal sensation and fatigue votes, at the end of the sessions, for all three exposures, has been provided in Fig. 6. At the end of the session, the mean TSV of participants for the 1450-V condition was closer to slightly cool and for 1450-CO2 and 900-R conditions, it was about mid-way between neutral and slightly cool and neutral respectively. The lower TSV for 1450-V, even though the temperature was unchanged, could relate to the lowered metabolic rate of the participants. The mean vote on Fatigue scale was slightly lower for the 1450-V condition than the other two; but for all three exposures, fatigue mostly remained between "No" and "Light".

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4 Discussion

While the climate impact of rising atmospheric CO_2 levels has been extensively studied and discussed over the past decade and a half, the direct impact on respiration of the higher levels of CO_2 has not received adequate attention. There are four parameters that affect ETCO2, which in turn, is a reflection of body CO_2 levels: activity (metabolic rate), CO_2 concentration in inhaled air, the gas exchange time constant for lungs, and alveolar air exchange[47]. To keep body CO_2 within relatively narrow limits, as metabolism and inspired CO_2 varies, breathing volume is adjusted[48]. Our investigation aimed to investigate how 2.5-h exposure in a chamber, with different CO_2 concentrations, affects respiratory parameters measured by capnometry and spirometry.

4.1 Body CO_2 levels and breathing elevated levels of pure CO_2

ETCO2 and RR values did not differ significantly across the three different exposures, and they also did not show any pattern of variation with respect to the CO_2 levels we examined, i.e., between 800 and 1,500 ppm. Studies that looked at acute exposures to high concentrations of CO_2 showed that ETCO2 generally stabilizes within a matter of minutes. Contrary to this, the few studies that have been done with typical indoor CO_2 levels showed a stabilization time of over 100 min. We summarize them in Table 4, including the current study.

From Table 4, some basic patterns get clear. Acute exposure to high CO_2 concentrations leads to much more substantial and faster change in ETCO2 than CO_2 levels that may be found indoors. Exposures involving both CO_2 and bioeffluent tend to cause larger changes in ETCO2 than exposure to just CO_2. And at levels of exposure under 2000 ppm, changes in ETCO2 are either not noticed or are less than 5%, so, possibly within ranges of instrument accuracy. Our results do not show any apparent evolution of ETCO2 with time (Fig. 3), for both the exposure to added pure CO_2 and the exposure to CO_2, along with bioeffluents. If any adjustment occurred after the participants came inside the climate chamber, it likely took place within the first 15 minutes, when they were engaged in the FVC test, like the timelines from acute exposures. This could mean that the CO_2 concentrations experienced by participants were not enough to change ETCO2.

One difference between our work and the other studies regarding ETCO2 in indoor environments was the presence of localized air movement - from desk fans - in our study. The desk fans ensuring a consistent value of CO_2 in the breathing zone (without variations and a value consistent with the chamber average concentration[29]) could be a reason why our results are more in line with the results from acute exposures that were delivered via masks/Douglas bags. A further reason could also be that in the other indoor exposures, participants were either engaged in actual office work or cognitive tasks simulating a work stress, which could have led to higher metabolism and hence a more discernible change in ETCO2. In our study, participants were not asked to engage in any cognitive tasks and could choose to utilize their time as they pleased.

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Table 4. ETCO2 evolution from exposure to bioeffluents and elevated CO_2

Study reference	CO_2 exposures (ppm)	Change in ETCO2 from start(%)	Duration to ETCO2 plateauing (min)
Indoor CO_2 levels			
(Vehviläinen et al., 2016)[27]	500-1000, 500-4500 (CO_2+bioeffluents)	~6-11	180, keeps rising
(Zhang et al., 2016)[15]	500, 5000	~2	~140
(Liu et al., 2017)[26]	400, 3000	~4-10	180, keeps decreasing
(Zhang et al., 2017a)[16]	400, 1000, 3000 (CO_2 and CO_2+bioeffluents)	~4-8	~120, greater rise in ETCO2 for exposures with bioeffluents at both 1000 & 3000 ppm
(Zhang et al., 2017c)[32]	500, 1600 (CO_2+bioeffluents)	NA	240, no notable changes
Current study	900, 1450, 1450 (CO_2 and, CO_2+bioeffluents)	NA	150, no notable changes
Acute exposures to CO_2			
(Shephard, 1955)[24]	50,000	22	~5
(Boning et al., 1983)[49]	65,000	40	~10
(Sayers et al., 1987)[23]	80,000	40	~15

Since the elevated levels of pure CO_2 did not affect ETCO2 levels, and hence, body CO_2 levels, studies looking at cognitive effects of moderately elevated CO_2 would need to examine in greater detail any possible mechanism for cognitive impacts. We also did not observe any change in the ETCO2 levels with time, implying any impacts due to extended exposure may not be related to changes in body CO_2 levels. Additionally, it would be advisable for future studies examining psychophysiological or cognitive effects of CO_2 or CO_2+bioeffluents to have a mechanism (like a small desk fan) for dealing with personal CO_2 clouds of participants.

4.2 Poor ventilation

Exposure with added pure CO_2 (1450-CO2) did not show an impact on any of the measured respiratory parameters using capnometry and spirometry, compared to exposure with current, recommended ventilation (900-R). However, for reduced ventilation (1450-V), a 150-minute exposure significantly lowered several measured FVC parameters, in particular, FEV1 and FEV1/FVC. Also, spirometry measurements at the end of sessions showed that compared to the

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https://escholarship.org/uc/item/8qj5v8d1

other two exposures, the poor ventilation exposure led to a lower average PEF. We reiterate here that these adverse impacts were found for sedentary, relaxed participants. It would not be far fetched to assume that effects could be worse for active indoor occupants.

Unlike the study by Shriram et al.[28], we did not notice a significant change in FVC and FEV1 across the exposures though essentially, our results mean the same: exposure to poor ventilation adversely affects pulmonary functions determined using the FVC test. Different from the current work, Shriram et al. compared the spirometry performance under ambient conditions with that obtained in progressively lower ventilation in occupied space and were not examining change caused by exposure to specific ventilation over a two-hour-plus period.

The lowering of FEV1 for 1450-V indicates an obstructive breathing pattern[31]. Obstructive breathing pattern means difficulty in exhalation, reducing the body's ability to get rid of metabolic CO_2. We did not see any clear indication of ETCO2 being affected. This could possibly mean that over exposure of this length (~2 hours), the body's compensatory mechanisms kept ETCO2 stable. We note in Section 3.1.2 that compared to the other exposures, for 1450-V, there was a small, but statistically insignificant, rise in ETCO2 (~0.4 mm Hg). This points to the possibility that we may see a clearer difference with larger sample sizes.

In Section 3.1.2, we also saw that for 1450-V, RR slowed down by ~1 breath per min, though not rising to statistical significance. In Section 3.3, we saw that the TSV at the end of the sessions was on the average cooler for 1450-V, even though thermal conditions were similar. It is difficult to explain these two observations, individually. Taken together though, the findings seem to support the analysis of Bako-Biro et al.[50] wherein, they posited that when exposed to poor air quality, metabolism and breathing slow down, in what may be a defensive mechanism. The lowered metabolism could explain the cooler TSV. The slower respiration is a consequence of the body lowering its metabolism and trying to take in less of the polluted air. No significant changes in ETCO2 were noted. This could be because, within this short exposure duration, our body's regulatory mechanisms are able to maintain physiological CO_2 levels consistent[51].

We did not notice any change in the subjective perception of air quality though, implying, the physiological effects of air quality in a poorly-ventilated space are apparent even before occupants perceive the poor ventilation. The 1405-V exposure led to slightly lower fatigue at the end of exposure duration compared to the other two conditions. The difference was less than half a scale unit and could be just a random effect. It is difficult for us to provide a compatible explanation for this variation.

Multiple epidemiological studies show the adverse effects of chronic exposure to outdoor air pollution on human lung[52,53]. Our findings were related to exposure to indoor air pollutants for a duration of just two hours though. The study that comes closest to our finding was by Rice et al.[54]. They observed that after a day of exposure to outdoor air that falls even in the moderate range on EPA's Air Quality Index (AQI)[55], FEV1 and FVC were compromised, compared to a day of exposure to AQI in the good range, even for subjects from the normal, healthy population.

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https://escholarship.org/uc/item/8qj5v8d1

4.3 Limitations

We recruited only healthy participants for this study. Thus, we are unable to ascertain how these conditions could have impacted participants who have pulmonary issues - say, asthmatics or people with COPD. The reference condition had a CO_2 concentration of 900 ppm. It could be informative to have a reference condition closer to current atmospheric levels of CO_2 and examine any differences in participant responses. In addition to the physiological measures we used, it would be pertinent to have some more, chief among them, heart rate variability (breathing cues from the central nervous system).

We had designed the experiment to understand how the future, elevated, atmospheric CO_2 levels would affect building occupants. But one of our most concerning findings came for current buildings that are ill ventilated. It is not uncommon for people to spend a part of their life in badly ventilated buildings, like classrooms and even their own homes and bedrooms[6,33]. Thus, the impacts we saw of poor ventilation on lungs raise an immediate concern. It would emerge as a pressing concern that the impact of poor ventilation on respiratory health be studied in similar, future endeavors, with larger pools of participants. Investigations would also need to examine different levels of ventilation to determine a threshold where pulmonary functions start getting affected and a possible, dose-response relation. From the current work, it is indicated that any ventilation rate that leads to 1450 ppm or more of CO_2 inside an occupied space - keeping in mind that the exposure is to CO_2 and other bioeffluents taken together - is concerning for health. Further follow-up studies would help us determine exactly how flexible ventilation requirements can be for buildings, without compromising occupant pulmonary functions.

5 Conclusions

With a view of gaining a better understanding of how building ventilation must respond to rising atmospheric CO_2 levels, we examined in laboratory conditions how the respiratory system of 15 healthy persons is affected by spending two and half hours in a well-ventilated building (current atmosphere), a poorly-ventilated building, with about half the ventilation of the well-ventilated building (current atmosphere), and a well-ventilated building in the future with the worst-case rise in atmospheric CO_2 levels.

We did not find any effect on end-tidal CO_2 (ETCO2) and respiration rate, either from increased pure CO_2 levels (scenario of a future building, increased atmospheric CO_2 levels) or from the combined effect of increased CO_2 and increased bioeffluents (current building, with poor ventilation). Poor ventilation, with human bioeffluents as the main source of pollution, impacted the forced vital capacity (FVC) parameters of the participants, breathing additional CO_2, with the ventilation as per current regulations, did not. We saw that after spending two and a half hours in the chamber during the poor ventilation exposure, participants were demonstrating reductions in FVC test parameters that are seen as indicators of obstructive breathing.

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The absence of impact on the measured respiratory parameters from added CO_2 to the breathing air indicates that with rising atmospheric CO_2 levels, as long as current ventilation guidelines are being followed, occupant respiration would not be impacted. Also, studies that find an impact on cognitive performance from elevated CO_2 would need to ascribe a physiological reason to it that does not likely stem from the respiratory system being affected. On the other hand, the large negative impact of poor ventilation on FVC parameters reinforces the need for more studies focusing on the physiological impact of living in badly ventilated indoor environments. No effects as yet have been seen at these levels for other outcomes such as cognitive performance or physiological symptoms, indicating a careful monitoring of building ventilation is needed, irrespective of atmospheric CO_2 levels. This finding is of immediate concern given that buildings with poor ventilation are not rare.

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The authors have no conflict of interest to declare.

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Supplementary Information

Instrument specifications and demographics

Table S1. Instrument specifications

Instrument	Parameter measured	Range	Accuracy
Environmental parameters			
Sensor Electronics, ThermCondSys5500 (Thermal comfort stand)	Air temperature	-10 ... 50 °C	± 0.1 °C
	Air velocity	0.05 ... 5 m/s	± (0.02 m/s + 1 %)
	Humidity	10 ... 90%	± 2%
	Globe temperature	-10 ... 50 °C	± 0.1 °C
Vaisala, GMW84	CO_2	0 ... 2,000 ppm	± (30 ppm + 3 %)
Extech SDL600-NIST	Noise	30 … 130 dBA	±1.4 dBA
VOC-TRAQ® II	VOC	0.0015 … 20 ppm	±3%
Physiological parameters			
Nihon Koden, OLG3800 and cap-TEN CO_2 monitor	Respiration rate	0 … 150 breaths/min	-
	End-tidal CO_2	0 … 40 mm Hg	± 2 mm Hg
		40 … 70 mm Hg	± 5%
Vitalograph Pneumotrac Spirometer (with Spirotrac Software 7000)	Flow volumes	0 … 6 L	± 3%
	Flow rates	0.02 … 16 L/s	± 5%

Table S2. Participant demographics [mean(s.d.)]:

	Male (n=8)	Female (n=7)	All participants (n=15)
Height, cm	175 (7)	160 (7)	168 (10)
Weight, kg	70.2 (13.8)	55.2 (7.3)	63.2 (13.3)
BMI, kg/m^2	22.6 (2.5)	21.6 (3.1)	22.1 (3.2)
Age, years	29 (7)	25 (4)	27 (6)

Most of the participants (*n*= 11) were of Chinese ethnicity, the other four being Indonesian, mixed, Caucasian, and Latino respectively.

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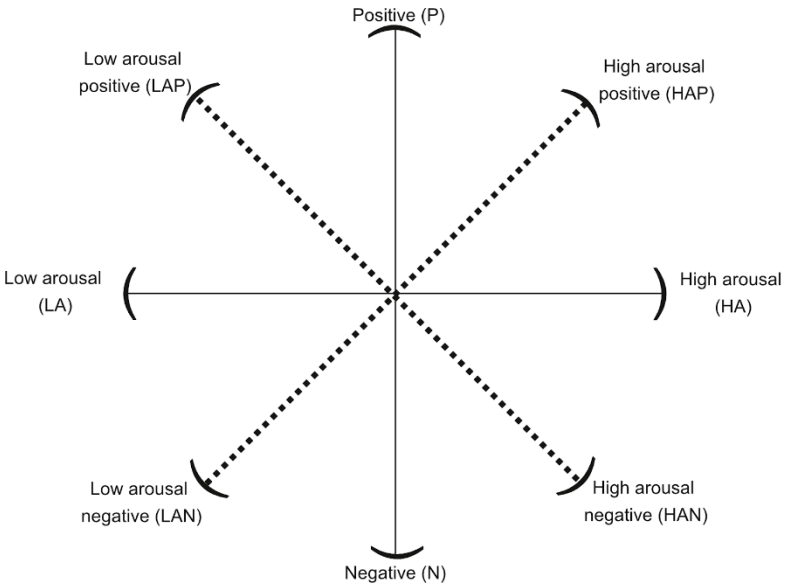
The circumplex model of affects



Category	Adjectives
HA	Aroused, Astonished, Alert, Surprised
HAN	Fearful, Hostile, Nervous, Stressed
HAP	Elated, Enthusiastic, Excited
LA	Passive, Quiet, Still
LAN	Drowsy, Dull, Sleepy
LAP	Calm, Peaceful Relaxed
N	Lonely, Sad, Unhappy
P	Content, Happy, Satisfied

Figure S1. An illustration of the circumplex model of affects with the eight categories having been depicted. In the adjoining table, we also provide the adjectives related to emotion that come under each category, form the questionnaire.

Results

Random intercepts vs random slopes models

Since, to the best of our knowledge, this is the first application of LME to respiratory parameters measured under different indoor conditions, we tried both the random intercepts and by-subject random slopes models for the capnometry parameters. We used k-folds cross-validation (k=10, typical value used in data analysis) to test both random slopes and random intercepts models, thus obtaining distribution for the variables used to assess the accuracy of the models used to predict end-tidal CO_2 (ETCO2) and respiration rate (RR): mean absolute error (MAE) and mean square error (MSE). Fig. S2 presents the mean absolute error (MAE) and mean square error (MSE) values, compared for the random slopes and random intercepts models for ETCO2 and RR. We tested the models on the collected data using k-fold cross validation. The boxplots show a clear tendency for both MAE and MSE to be lower for the random slopes models. The spirometry measurements and participants' ratings do not provide enough data points for a random slopes model and hence random intercepts models were used when analyzing the results from the questionnaires.

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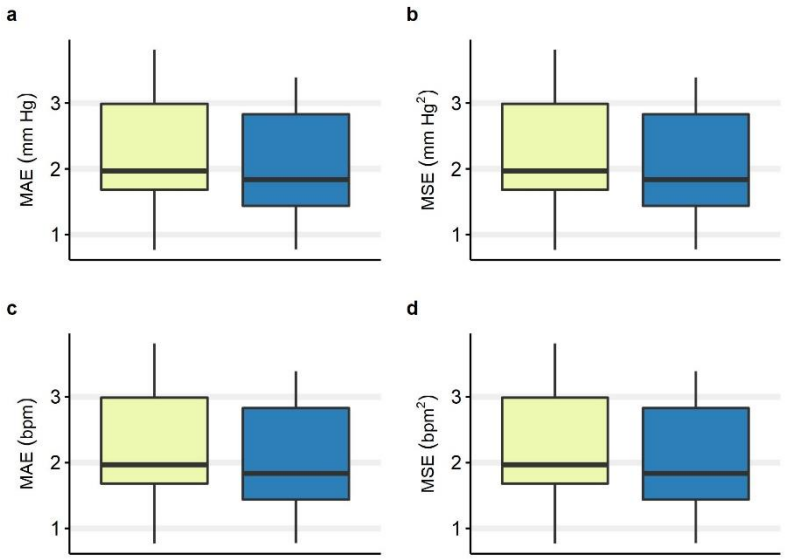

Figure S2. Box-plots of errors associated with random slopes (blue) and random intercepts (yellow) models. (a) MAE, (b) MSE for ETCO2. (c) MAE, (d) MSE for RR.

An unexpected realization of the work was showing us random slopes, linear mixed effects models were better at representing human respiration across individuals than random intercepts models. Inter-individual variation in responses to stimuli from the indoor environment is getting greater acceptance, especially as related to thermal comfort (Schweiker et al., 2018). The current findings lead us to believe a similar approach is needed in indoor air quality study. Occupants not only do they have different thresholds, they also respond in different ways to changes in the air that they breathe.

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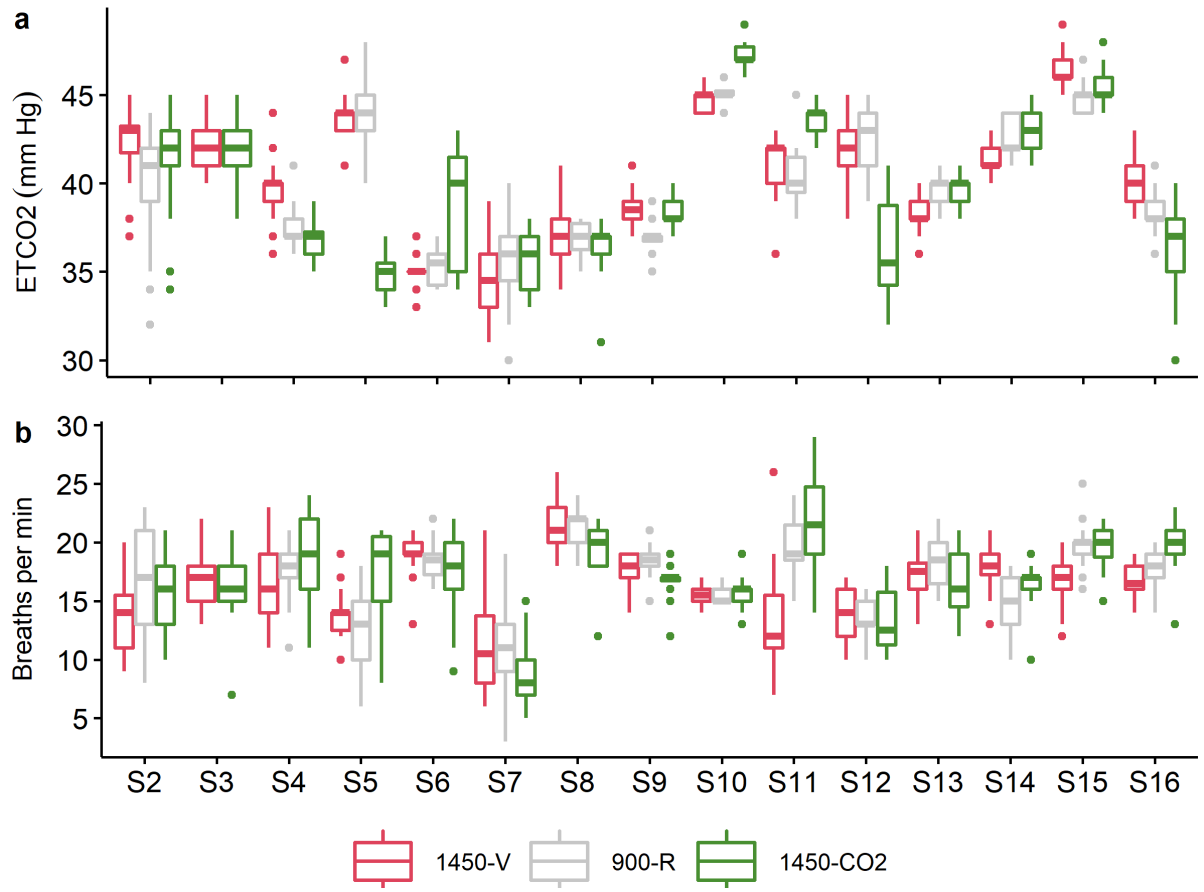

Figure S3. ETCO2 (a) and RR (b) values during the sessions, for all 15 participants, across all three exposures.

Figure S3 is used to illustrate the difference in nature and magnitude of variation for ETCO2 and RR, across individuals. Such variation likely explains why random slopes models are more suitable.

Spirometry results

Table S3. Mixed effects models comparisons output for PEF

	PEF model		
Fixed effects			
	Estimate	Std. Error	t value
(Intercept)	328	21.4	15.32
1450-V	-26	13.8	-1.87
1450-CO2	11	13.8	0.80

Table S3 shows that for the 900-R condition the average PEF value was 328 litres per min (Lpm) while for the 1450-CO2, there was on average a small rise of 11 Lpm over this value while for

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1450-V, there was on average a reduction of about 26 Lpm. As shown in Table S3, only the change at the 1450-V condition was significant (P=0.041).

Subjective feedback

Affects - comparison across three exposures

High arousal: $\chi^2(2)=3.8$, $p = 0.15$; High arousal negative: $\chi^2(2)=1.3$, $p = 0.51$;

Low arousal: $\chi^2(2)=2.0$, $p = 0.37$; Low arousal negative: $\chi^2(2)=1.7$, $p = 0.43$;

Low arousal positive: $\chi^2(2)=1.4$, $p = 0.49$; Positive: $\chi^2(2)=1.6$, $p = 0.45$;

Negative: $\chi^2(2)=1.3$, $p = 0.53$

Subjective feedbacks at end of session - comparison across three exposures

Thermal sensation: $\chi^2(2)=7.4$, $p = 0.025$; Thermal acceptability: ($\chi^2(2)=1.6$, $p = 0.44$;

Thermal preference: $\chi^2(2)=0.02$, $p = 0.99$; Air movement acceptability: $\chi^2(2)=2.3$, $p = 0.32$;

Humidity acceptability: $\chi^2(2)=0.6$, $p = 0.74$; Air quality acceptability: $\chi^2(2)=0.1$, $p = 0.93$;

Ventilation preference: $\chi^2(2)=1.7$, $p = 0.43$; Air movement preference: $\chi^2(2)=0.4$, $p = 0.80$;

Air freshness: $\chi^2(2)=0.9$, $p = 0.64$; Odor: $\chi^2(2)=0.0$, $p = 0.99$; Eye irritation: $\chi^2(2)=0.7$, $p = 0.72$;

Nose/Throat irritation: $\chi^2(2)=1.2$, $p = 0.54$; Difficulty breathing: $\chi^2(2)=2.0$, $p = 0.36$;

Skin irritation: $\chi^2(2)=5.1$, $p = 0.08$; Headache: $\chi^2(2)=4.7$, $p = 0.10$;

Dizziness: $\chi^2(2)=2.4$, $p = 0.30$; Fatigue: $\chi^2(2)=6.2$, $p = 0.04$;

Sleepiness: $\chi^2(2)=1.8$, $p = 0.41$; Difficulty concentrating: $\chi^2(2)=4.3$, $p = 0.12$

Table S4. Mixed effects models comparisons output for TSV and Fatigue

TSV model				**Fatigue Model**		
Fixed effects				Fixed effects		
	Estimate	Std. Error	t value	Estimate	Std. Error	t value
(Intercept)	-0.2	0.25	-0.80	1.4	0.15	9.45
1450-V	-0.6	0.22	-2.90	-0.3	0.17	-2.08
1450-CO2	-0.4	0.22	-1.70	0.0	0.17	0.29

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