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Direct human health risks of increased atmospheric carbon dioxide

Tyler A. Jacobson[1], Jasdeep S. Kler[2], Michael T. Hernke[3,4]*, Rudolf K. Braun[5], Keith C. Meyer[6] and William E. Funk[1]

Growing evidence suggests that environmentally relevant elevations in CO_2 (<5,000 ppm) may pose direct risks for human health. Increasing atmospheric CO_2 concentrations could make adverse exposures more frequent and prolonged through increases in indoor air concentrations and increased time spent indoors. We review preliminary evidence concerning the potential health risks of chronic exposure to environmentally relevant elevations in ambient CO_2, including inflammation, reductions in higher-level cognitive abilities, bone demineralization, kidney calcification, oxidative stress and endothelial dysfunction. This early evidence indicates potential health risks at CO_2 exposures as low as 1,000 ppm—a threshold that is already exceeded in many indoor environments with increased room occupancy and reduced building ventilation rates, and equivalent to some estimates for urban outdoor air concentrations before 2100. Continuous exposure to increased atmospheric CO_2 could be an overlooked stressor of the modern and/or future environment. Further research is needed to quantify the major sources of CO_2 exposure, to identify mitigation strategies to avoid adverse health effects and protect vulnerable populations, and to fully understand the potential health effects of chronic or intermittent exposure to indoor air with higher CO_2 concentrations.

Recent data show an increasing trend in serum bicarbonate, indicative of CO_2 stored in the body, among the general US population[1]. This increase—from 23.7 mmol l^{-1} in 2000 to 25.2 mmol l^{-1} in 2012—may reflect increased environmental exposure to CO_2 (refs. [1,2]). Climate change is recognized as a substantial threat to human health[3,4]. However, few studies have focused on the direct human health effects of increasing exposure to CO_2. The authors of a 2011 Institute of Medicine report acknowledged that studies investigating health risks of chronic or intermittent exposures to elevated CO_2 (below 5,000 ppm) are lacking for the young, the elderly, and the infirm[5]. Atmospheric CO_2 concentrations were stable at ~250 ppm throughout human evolution[6], and humans may therefore not be adapted to chronic or intermittent exposures to elevated CO_2. According to projections from the IPCC (Representative Concentration Pathways; RCPs), atmospheric CO_2 concentrations may increase from approximately 400 to 670 ppm (under RCP 6.0) or 936 ppm (under RCP 8.5) by the end of the century[7].

Mounting evidence suggests that human exposure to CO_2 is higher than previously realized, and that multiple factors are increasing this exposure. Health effects from CO_2 exposure are also being observed at concentrations lower than expected. The potential for these two trends to intersect is the purpose of this Review, providing two aims:

- To summarize the factors increasing human exposure to CO_2, and the frequency, duration and magnitude of possible adverse exposure.
- To present preliminary evidence on the direct human health risks of chronic or intermittent environmentally relevant (<5,000 ppm) exposures (Table 1), and the implications for indoor air quality, atmospheric carbon emissions and the design of adaptation and mitigation strategies to avoid potential adverse health effects.

We synthesize information from disparate fields such as physiology, immunology, cognitive psychology, environmental health and building engineering. Although there are few independent replicates of these findings, we highlight key patterns and gaps, and recommend promising avenues of future research. For our second aim, we systematically searched PubMed, the Web of Science and PsychINFO for studies that met predetermined inclusion criteria (Fig. 1). We screened the abstracts of all identified studies and read the full-text articles if appropriate. More articles were identified by reviewing the reference lists of relevant studies (see more details in the Supplementary Information). Key metrics were extracted from studies that met the inclusion criteria and are highlighted in the qualitative synthesis (Tables 2 and 3). To meet our inclusion criteria, studies were required to: (1) examine direct human or mammalian-model health effects of artificially raised ambient CO_2 at realistic environmental exposures (<5,000 ppm); (2) isolate the effects of CO_2 through statistical or methodological controls; or (3) employ animal models that used metabolically generated CO_2 if the authors implied that CO_2 had direct health effects.

Increased human exposure to CO_2

This section surveys the major sources of human exposure to CO_2 and the factors likely to increase it. Following studies that demonstrate direct effects of CO_2 on human cognitive performance and productivity, Gall et al. defined the exposure level of possible concern (ELPC1) as mean personal exposures that exceed 1,000 ppm for durations greater than 2.5 h (ref. [8]). Here, we consider these exposure levels as health-relevant under the precautionary principle[9].

[1]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. [2]School of Public Health, University of Michigan, Ann Arbor, MI, USA. [3]Department of Operations & Information Management, Wisconsin School of Business, University of Wisconsin–Madison, Madison, WI, USA. [4]The Nelson Institute for Environmental Studies, University of Wisconsin–Madison, Madison, WI, USA. [5]Department of Pediatrics, University of Wisconsin School of Medicine & Public Health, Madison, WI, USA. [6]Department of Medicine, University of Wisconsin School of Medicine & Public Health, Madison, WI, USA. *e-mail: mthernke@wisc.edu

Table 1 | Overview of potential health effects

	CO_2 concentration (ppm)	Duration	Selected key references
Adverse health outcomes associated with acute CO_2 exposure			
CO_2 retention	1,000–5,000	<4 h	Zhang et al.[75]; Zhang et al.[73]; Vehvilainen et al.[77]; Shiraram et al.[76]
Inflammation	2,000–4,000	2 h	Thom et al.[80,81]; Schneberger et al.[82]
Cognitive effects	1,000–2,700	1–6 h	Kajtar and Herczeg[85]; Satish et al.[86]; Allen et al.[87,88]; Zhang et al.[75]; Zhang et al.[73,74]; Rodeheffer et al.[91]; Snow et al.[90]
Adverse health outcomes associated with chronic CO_2 exposure			
Chronic, low-grade systemic inflammation	~3,000	13 d	Zappulla[2,69]; Beheshti et al.[101]
Bone demineralization and kidney calcification	~2,000–3,000	60–90 d	Schaefer et al.[102,103]
Chronic, low-grade (sub-clinical) respiratory acidosis	Unknown	Decades	Carnauba et al.[109]; Robertson[61,106]
Behavioural changes and physiological stress	700–3,000	13–15 d	Beheshti et al.[101]; Wade et al.[104]; Martrette et al.[111]; Kiray et al.[112]
Hedonic feeding behaviours	Unknown	Ecological	Hersoug et al.[113]; Zheutlin et al.[1]
Oxidative stress and endothelial dysfunction	3,000–5,000	13 d to 6 months	Beheshti et al.[101]; Thom et al.[80,81]; Zwart et al.[119]

Exposure levels, including magnitude and duration, for which health effects may manifest. The selected key references are most relevant to the health end-point.

Current indoor exposure. Increases in serum bicarbonate levels among the general US population[1] could be driven by increased exposure to indoor CO_2. In industrialized countries, people spend 80–90% of their time indoors, while vulnerable populations (including the elderly and the infirm) often spend entire days indoors[10–12]. Indoor air quality is thus critical to public health.

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) Standard 62.1-2013 recommends that building ventilation rates are sufficient to keep indoor CO_2 concentrations <700 ppm above outdoor concentrations for occupant satisfaction and comfort[13]. The standard considers CO_2 to be a proxy for other indoor air pollutants, such as human bioeffluents (body odours), and not itself an agent of adverse health effects[13–15]. As CO_2 is a product of human metabolism and respired into ambient air, building occupant density is the most significant source of indoor CO_2 elevations[15,16]. Average indoor CO_2 concentrations in offices, schools and homes typically range from 600 to 1,000 ppm (refs. [15,17–22]), but can exceed 2,000 ppm with increased room occupancies and reduced building ventilation rates[18,19,23,24]. Building ventilation rates may be reduced to conserve energy, slow climate change and avoid conveying outdoor air pollutants indoors, thereby increasing indoor CO_2 concentrations[5,10,16].

Children spend a substantial amount of time in schools; the only other indoor environment where they spend more time being the home[25]. Fisk reviewed 28 studies investigating CO_2 concentrations in classrooms and found that all reported median peak CO_2 values above 1,000 ppm, with many above 2,000 ppm, suggesting widespread inadequate ventilation in schools[19]. The home and bedroom environments can also be significant sources of CO_2 exposure. People spend nearly one-third of their life sleeping[26], and in industrialized societies, more than 60% of their time in their homes[8,12]. Bedrooms can exceed 2,500 ppm when the doors are closed for privacy, the windows closed for energy conservation and the building ventilation reduced[27]. When ventilation rates are normal, but the windows and bedroom doors are closed, CO_2 concentrations exceed 1,000 ppm about 50% of the time[28]. Lower CO_2 concentrations in bedrooms have been associated with both subjective and objective improvements in sleep quality[27,28].

Indoor CO_2 concentrations in tropical climates are often higher because of reduced outside building ventilation to lower the demand for cooling[8]. Gall et al. quantified personal exposures to CO_2 among university students and young professionals in Singapore, and found that ELPC1 events occurred about once every 2 d and were most frequent in the home[8]. The type of bedroom ventilation was a major determinant of personal CO_2 exposure. Nearly all participants, regardless of ventilation type, spent 1.2 h d^{-1} exposed to CO_2 concentrations greater than 1,100 ppm, whereas participants with air-conditioned bedrooms spent 1.2 h d^{-1} exposed to CO_2 concentrations greater than 2,200 ppm (ref. [8]). ELPC2 events (defined as mean personal exposure exceeding 2,500 ppm for >2.5 h) occurred only in the group with air-conditioned bedroom ventilation, about once every 8 d (ref. [8]).

Air conditioning influences personal CO_2 exposures because CO_2 is a dense gas and tends to concentrate at lower elevations. Most air-conditioning units ventilate air closer to the ceiling, introducing CO_2 into rooms more quickly than removing it[29]. Another source of exposure is sedentary desk work under normal office conditions, which results in relatively static air and less occupant movement[30]. These conditions can result in higher CO_2 concentrations around the nose and mouth, causing occupants to rebreathe their own exhaled CO_2 (refs. [30,31]). Personal CO_2 bubbles can average 1,200 ppm (compared to 650 ppm in the surrounding indoor air) under normal ventilation conditions in an office-like environment[30]. Thus, a full characterization of personal CO_2 exposure entails the measurement of concentrations around the inhalation zone, which can be significantly higher[30,31].

Brief exposures to elevated CO_2 are also routine in transit[8,32]. Among participants in air-conditioned public transportation in Singapore, median exposure levels of 1,300 ppm and spikes above 4,000 ppm for shorter intervals have been reported[8]. Measurements and mathematical modelling both demonstrate CO_2 build-up in vehicles[33,34]. With two occupants and recirculating ventilation, CO_2 concentrations can increase to 2,000 ppm for average commutes (26.1 min) and exceed 3,000 ppm during long commutes (61.3 min)[33]. Longer exposures to elevated CO_2 also occur on aeroplane flights, which average concentrations of approximately 1,350 ppm and can exceed 2,000 ppm during boarding time[35].

Future outdoor exposure. Rising concentrations of atmospheric CO_2 increase personal exposures directly through the respiration of outdoor air. This is especially relevant in urban environments and areas that have higher levels of CO_2 due to meteorological effects. The sum of these two factors could increase outdoor concentrations of CO_2 to health-relevant levels within this century.

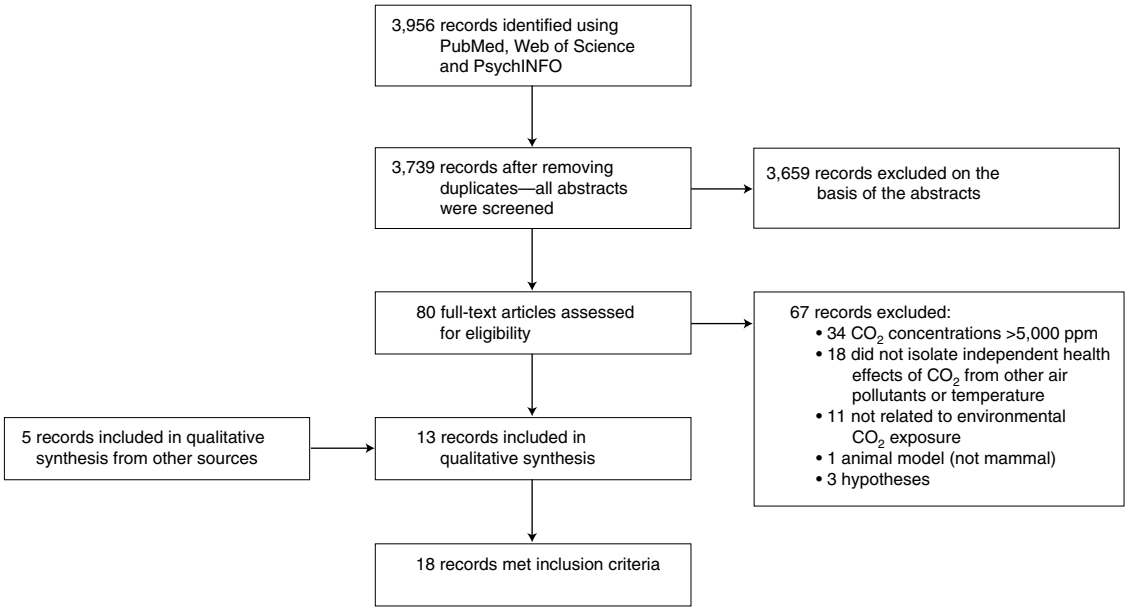

Fig. 1 | Flow diagram for the identification of appropriate studies from the literature. Records from other sources were identified by reviewing the reference lists of relevant studies.

Cities contribute substantially to anthropogenic CO_2 emissions[36–39], which accumulate to form what are known as CO_2 domes over many urban centres[36,40–42]. Urban populations constituted 55% of the global population in 2018 and are expected to grow to 68% by 2050[43]. Fluxes of CO_2 from dense city centres can be two- to five-times larger than surrounding suburban residential areas[37]. Studies that investigated urban–rural transects have reported urban CO_2 domes with atmospheric concentrations reaching 500 and 600 ppm, depending on factors including the time of day, traffic conditions, seasonality, the density of buildings and wind speeds[38,39,42,44–53].

Geographic and meteorological factors can enhance urban CO_2 domes. For example, the Phoenix urban CO_2 dome is characterized by still atmospheric conditions and can reach 650 ppm (ref. [40]). Atmospheric temperature inversion effects can also trap air pollution (including anthropogenic CO_2 emissions) within city centres[54–57]. Densely populated cities with high-rise buildings and narrow streets can trap atmospheric CO_2 because reduced airflow generates lower wind speeds, resulting in less air dispersion[58,59]. Outdoor concentrations of CO_2 could reach health-relevant levels for cities in low-lying areas in basins, such as Mexico City and Athens, where CO_2 accumulates[60,61]. If atmospheric CO_2 continues to increase at 3 ppm yr^{-1}, urban areas could experience concentrations between 500 and 700 ppm CO_2 by 2050[62]. Under RCP 8.5, atmospheric CO_2 in large cities could surpass 1,000 ppm by 2100 for parts of the year[63].

Future indoor exposure. As outside air is used to dilute indoor air, outdoor concentrations of CO_2 set a 'floor' for indoor concentrations that cannot be breached without the use of chemical adsorbents or sinks[14,19,23]. Continued atmospheric CO_2 increases will require more demanding mitigation strategies to prevent a concomitant rise in indoor concentrations—especially in cities[52,62,63]. Increasing building ventilation rates to offset rising atmospheric CO_2 may have untoward consequences, intensifying anthropogenic CO_2 emissions owing to greater energy requirements[52,63] and introducing outdoor air pollutants indoors, including air particulate matter and ozone[5,16,64,65]. Moreover, increasing building ventilation may be less effective than alternative strategies. For example, in tropical climates, increasing building ventilation increases cooling **demand, which increases both energy requirements and the amount of CO_2 indoors through greater use of air conditioning.** Under RCP 8.5, building ventilation rates would need to double to offset half of the increase in atmospheric CO_2 by 2100 (ref. [63]), assuming that outdoor concentrations remain below a target indoor concentration of 1,000 ppm. Such a partial offsetting strategy under RCP 8.5 would result in average indoor concentrations ~300 ppm above current levels[63].

Other factors are likely to drive increasing exposure to CO_2. Trends in building designs, including increasing airtightness to save energy, can reduce indoor air quality[66] and increase CO_2 concentrations[8,22,67]. Installing more ductless air-conditioning units in response to global climate change will likely increase indoor CO_2 concentrations[8,67,68]. Human exposure to CO_2 may also increase with climate-change-induced heat stress[4], resulting in greater time spent indoors and more intensive use of air conditioning[68–71]. As people spend more time indoors—especially in urban environments because of heat island effects[58,70] and in equatorial low- and middle-income countries (LMICs)[4,72]—higher occupant densities could increase indoor CO_2 concentrations along with exposure duration[16,17,24,69]. The greatest urban growth rates are projected for LMICs in Asia and Africa[43]. Increasing urbanization and associated rises in urban CO_2 emissions in LMICs in Asia and Africa, combined with other factors described here, could raise CO_2 exposure beyond thresholds for healthful environments.

Although quantifying the contribution of these factors to increasing exposure to CO_2 is beyond our scope, a substantial portion of the global population is exposed to elevated CO_2 levels of possible concern. The frequency and durations of potential adverse exposures could increase because of the many factors described here, including increasing atmospheric CO_2, which raises the potential for exposure events.

Retention of CO_2

Two studies isolated the effects of elevated CO_2 concentrations on human CO_2 retention. Zhang et al.[73,74] reported that end-tidal CO_2 ($ETCO_2$) increased by ~0.4 mm Hg and 1.1 mm Hg when CO_2 exposure increased from 500 to 1,000 and 3,000 ppm for 4 h,

Table 2 | Human studies that met our inclusion criteria

Studies	Experimental design	CO_2 concentrations considered (ppm)	Total exposure duration (h)	CO_2 concentration range at which effects are observed (ppm)	Outcome variable	Effect present?	Main findings	Sample size and type	Difficulty of task	Physiological data
Kajtar and Herczeg (ref. [85])[a]	A	1,500; 2,500; 600; 5,000	2.3	n.a.	Proofreading task	No	No significant differences in proofreading performance	10 healthy young adults	Simple	Blood pressure, heart rate, skin temperature
Kajtar and Herczeg (ref. [85])[b]	A	1,500; 3,000; 600; 4,000	2.3–3.5	3,000–4,000	Proofreading task	Yes*	Accuracy declined at 4,000 compared to 600 ppm after 2.3 h	10 healthy young adults	Moderate	Blood pressure, heart rate, skin temperature
Satish et al.[86]	B	600; 1,000; 2,500	2.5	1,000–2,500	SMS	Yes*	Significant dose-dependent declines in SMS performance	22 healthy young adults	Difficult	None
Allen et al.[87]	B	550; 945; 1,400	~7.5	945–1,400	SMS	Yes*	SMS performance was 15% lower for 945 ppm and 50% lower for 1,400 ppm relative to 550 ppm	24 professional-grade employees	Difficult	MacNaughton et al.[93]
Zhang et al.[75]	B	500 or 5,000	2.5	5,000	Tsai–Partington; text typing; addition	No	No difference in cognitive performance; $ETCO_2$ and salivary amylase increased at 5,000 ppm	10 healthy young adults	Simple and moderate	Heart rate, $ETCO_2$, pulse oximetry, salivary stress biomarkers
Zhang et al.[73,74]	B	500; 1,000; 3,000	4.25	1,000–3,000	Office work, neurobehavioural	Yes	Non-significant decreases in cognitive performance	25 healthy young adults	Simple and moderate	Zhang et al.[73]
Allen et al.[88]	B	700; 1,500; 2,500	3	1,500–2,500	Aeroplane flight manoeuvres	Yes*	Odds of passing flight manoeuvres declined at 1,500 and 2,500 ppm; performance decrements were more pronounced with increasing manoeuvre difficulty and exposure duration	30 commercial aeroplane pilots	Both simple and difficult manoeuvres	Cao et al.[89]
Rodeheffer et al.[91]	C	600; 2,500; 15,000	2.1	2,500	SMS	Yes, at 2,500 ppm	No significant differences between exposure groups; however, point estimates declined from 600 to 2,500 ppm	36 submariners (12 per condition)	Difficult	None
Snow et al.[92]	C	800 or 2,700	0.17–0.3 (post-ventilation)	2,700	EEG indicative of drowsiness	Yes	EEG under elevated CO_2 more indicative of drowsiness	23 experimental/ 13 control; university students and staff	n.a.	EEG
Snow et al.[90]	B	800 or 2,700	0.89–1.4	2,700	Cognitive battery (CNS vital signs); EEG	Yes	Absence of expected learning effects; EEG more indicative of drowsiness in participants who slept less in the previous night	31 university students and staff	Simple and moderate	EEG, heart rate, skin temperature, respiratory rate

All studies measured the effects of exposure to artificially raised (pure) CO_2. [a]The first series of experiments of ref. [85]. [b]The second series of experiments of ref. [85]. Experimental designs: A, within-subject, series exposure; B, within-subject, counterbalanced; C, between-subject. n.a., not applicable. Total exposure duration refers to the total amount of time participants were exposed to an experimental condition. For series exposure, study participants were exposed to different experimental conditions consecutively and in the same specified order; proofreading tasks started immediately. The SMS takes 1.5 h; therefore, approximate exposure duration before testing can be determined by subtracting this amount from the total exposure duration. The concentration range at which effects are observed refers to the exposure levels where cognitive or neurophysiological changes were recorded. The level of difficulty is relative to the SMS; the SMS was considered the most difficult test of cognitive performance. *Statistically significant ($P < 0.05$).

Table 3 | Animal studies that met our inclusion criteria

Studies	Animal model	CO_2 concentrations considered (ppm)	Exposure duration	CO_2 source	Outcome variables	Main findings	*N*
Schaefer et al.[103]	Guinea pigs	5,000	8 weeks	P	Blood pH; kidney calcium; plasma calcium; ultrastructural lung changes	Elevated kidney and calcium in exposed group; after 8 weeks of recovery, calcium in exposed guinea pigs returned to normal levels	6 experimental; 4 control
Schaefer et al.[102]	Guinea pigs	2,000–3,000 (preliminary work; details missing)	60–90 d	P	Blood pH; kidney calcium; plasma calcium	Kidney calcification and bone demineralization processes	Not specified
Wade et al.[104]	Rats	3,000; 7,000; 20,000	30 d	P	Body composition, renal function, eating and feeding behaviours	Chronic exposure to 3,000 ppm increased total body sodium; reduced adrenal mass; increased lethargic behaviours	10 experimental; 10 control (each condition)
Kiray et al.[112]	Postnatal rats	500; 1,000; 3,000	38 d	M	Effect on hippocampus, prefrontal cortex and amygdala; IGF-1	Higher CO_2 exposure was associated with cognitive impairment; stress response; neuropathological changes; decreased IGF-1 in serum, hippocampus and prefrontal cortex; increased oxidative stress	8 rats per group (24 total)
Martrette et al.[111]	Young female rats	Exposed: 700; Control: 450	Intermittent: 6 h/24 h for 15 d	P	Behaviour, corticosterone (stress), muscular structures	Higher CO_2 exposure was associated with lethargy; increased plasma corticosterone; altered upper-airway muscle composition	12 experimental; 12 control
Schneberger et al.[82]	Mice	400; 5,000; 7,500	6 h	M	Pro-inflammatory markers in the lung	Co-exposure to elevated CO_2 with organic hog barn dust dose-dependently augmented inflammatory responses	4 to 8 mice per group
Thom et al.[81]	Human and murine neutrophils (ex vivo)	400; 1,000; 2,000; 4,000; 10,000; 20,000	2 h	P	MV production per human or murine neutrophil; IL-1β content of MVs	1,000 to 4,000 ppm caused human and murine neutrophils to increase MV production with higher content of IL-1β	4 to 7 (human cells) and 4 to 20 (mouse cells)
Thom et al.[80]	Mice	400; 1,000; 2,000; 4,000; 10,000	2 h	P	Circulating MVs; neutrophil and platelet activation; IL-1β content of MVs	2,000 and 4,000 ppm increased circulating MVs, increased IL-1β content of MVs, and caused widespread vascular damage	4 to 10 mice per group
Beheshti et al.[101]	3 mouse, 1 rat studies	~300; 700; 3,000	~13 d	P	Global transcriptomic patterns	Higher CO_2 exposure was associated with tissue-specific, transcriptomic changes in metabolism and immunity; stimulation of possible tumorigenic pathways in muscle and breast tissues	4 datasets

We included studies that used artificially raised CO_2 as well as studies that used metabolically generated CO_2 (by controlling mechanical ventilation, for example). For studies that used metabolically generated CO_2, the authors discuss potential direct health effects of exposure to environmentally relevant elevations in CO_2. CO_2 sources: P, pure CO_2; M, metabolically generated CO_2. *N*, sample size. IGF-1, insulin-like growth factor-1, which is important for early brain development.

respectively. When CO_2 exposure was increased from 500 to 5,000 ppm for 2.4 h, $ETCO_2$ increased by ~1.5 mm Hg (ref. [75]). Similar exposures to CO_2 with bioeffluents dose-dependently impair gas exchange in the lungs leading to greater CO_2 retention[73,76,77]. Studies of extended missions on the International Space Station (ISS) suggest significant CO_2 retention in healthy astronauts with prolonged exposures to ~5,000 ppm (refs. [31,78,79]). Such observations suggest that some aspects of spaceflight, such as microgravity and/or months-long inspiration of elevated CO_2, may lead to a diminished capacity to expel CO_2 (refs. [31,78]). Thus, CO_2 retention from environmentally relevant CO_2 increases is measurable and may be exacerbated by the duration of exposure (Table 4). It is therefore imperative to study the direct health effects of prolonged exposures at these lower levels.

Acute CO_2 exposure and health

Acute exposure to high levels of atmospheric CO_2 can have adverse health outcomes in terms of inflammation and cognitive effects.

Inflammation. Inflammation could be a pathway that links elevated CO_2 exposure with adverse health outcomes. Exposure to 2,000 or 4,000 ppm CO_2 induced inflammatory responses in neutrophils ex vivo (human and murine) and in vivo (mice) that were characterized by activation of the nucleotide-binding domain-like receptor 3

Table 4 | Human CO_2 retention from environmental exposure

	Human CO_2 retention (mm Hg)	Measurement	Exposure magnitude (ppm)	Exposure duration	Key references
Environmental CO_2 exposure (pure)	~0.4–1.5	$ETCO_2$	1,000–5,000	Less than 4 h	Zhang et al.[73,75]
Environmental CO_2 exposure with human bioeffluents	~1.3–4	$ETCO_2$ and transcutaneous	1,000–5,000	Less than 4 h	Shiraram et al.[76] Vehvilainen et al.[77] Zhang et al.[73]
Environmental CO_2 exposure with microgravity and months-long inspiration of elevated atmospheric CO_2	~6.1	$ETCO_2$	~5,000 (range: 3,000–7,000)	~6 months (spaceflight)	Hughson et al.[78]

CO_2 retention refers to the increase in $ETCO_2$ or in transcutaneous monitored CO_2, which estimates changes in arterial CO_2 pressure. In the first condition, CO_2 exposure was artificially raised to the desired concentrations. In the second condition, CO_2 exposure was controlled by ventilation and therefore additional CO_2 was generated by the occupants and accompanied by human bioeffluents. In the third condition, CO_2 was also metabolically generated during long-duration spaceflight under conditions of microgravity; significantly greater CO_2 retention is observed and could be a result of microgravity, persistent exposure to elevated concentrations of atmospheric CO_2, increased magnitude of exposure, and/or the presence of other air contaminants.

(NLRP3) inflammasome and elevated interleukin (IL)-1β production[80,81]. In vivo, neutrophils were stimulated to release microvesicles (MVs) containing high concentrations of IL-1β that caused vascular damage in muscle, brain and distal colon tissue, which persisted for 13 h after a 2 h exposure[80]. Activation of the NLRP3 inflammasome was exceptionally rapid, which exacerbates the risks associated with elevated CO_2 exposures[80,81]. The dose–response relationship, however, was biphasic and was not observed at 10,000 ppm (refs. [80,81]). Exposure to 1,000 ppm induced inflammatory responses ex vivo[81] but not in vivo[80]. In addition, mice exposed to 5,000 ppm CO_2 show possible increased inflammation in bronchial epithelium[82], and exposure to 3,000 ppm might induce mild inflammation of the nasal cavity in humans[73]. Co-exposure to organic hog barn dust and 5,000 ppm CO_2 in mice enhances lung inflammation in a dose-specific manner[82]. Exposure to CO_2 at environmentally relevant levels could therefore augment inflammatory responses to other air contaminants by altering innate immunity[82].

Cognitive effects. Elevated concentrations of CO_2 have been strongly associated with headache incidences aboard the ISS, symptoms of Sick Building Syndrome in office buildings, and increased student absenteeism and decreased cognitive performance among elementary students[18,19,79,83]. Two recent reviews concluded that environmentally relevant elevations in CO_2 may directly affect higher-level cognitive performance, including decision-making and problem resolution[63,84]. We summarize the results of studies reporting direct effects of CO_2 on cognition and potential mechanisms to explain these effects in Table 2.

Kajtar and Herczeg[85] reported reductions in performance in proofreading tasks when comparing 3,000 and 4,000 to 600 ppm CO_2; these reductions were only visible when the difficulty of the task and exposure duration were increased. Following these findings, Satish et al.[86] demonstrated a significant dose-dependent decline in decision-making performance for exposure to 1,000 and 2,500 ppm compared with 600 ppm CO_2 using the Strategic Management Simulation (SMS) software. In a follow-up study, Allen et al.[87] demonstrated that both volatile organic compounds and CO_2 concentrations were independently and negatively associated with higher-level cognitive functions in the SMS. Participants were exposed to 550, 945 and 1,400 ppm during normal 8 h workdays throughout the week in a randomized, double-blind controlled office environment[87]. Cognitive scores were 15% lower in 945 ppm and 50% lower in 1,400 ppm relative to 550 ppm CO_2. On average, participant scores decreased by 21% per 400 ppm increase[87]. In another study, Allen et al.[88] reported lower passing rates among pilots performing flight simulation manoeuvres with elevated CO_2 (2,500 and 1,500 ppm – relative to 700 ppm) for 3-hour exposures (see also ref. [89]). This lower performance was more pronounced with increasing manoeuvre difficulty and exposure duration, and the authors suggest a 60 min lag period for the onset of CO_2-mediated effects[88]. Partially corroborating these findings, Snow et al.[90] exposed participants to 830 and 2,700 ppm for less than 1 h and reported that higher CO_2 exposure eliminated expected learning effects in two cognitive tasks: executive function and cognitive flexibility.

Three studies have reported non-significant results. Zhang et al.[74] found no significant reductions in cognitive performance in simple and moderately difficult tasks for 255 min exposures up to 3,000 ppm. Allen et al.[87] attribute the discrepancy to task difficulty and point out that, although not statistically significant, elevated CO_2 was associated with a lower cognitive score. A follow-up by Zhang et al.[75] found increases in $ETCO_2$ with no decrements in cognitive performance when comparing 150-min exposures to 500 or 5,000 ppm CO_2. Rodeheffer et al.[91] used a between-subject design with groups receiving a 45-min exposure to 600, 2,500 or 15,000 ppm CO_2 before taking the SMS, and on the basis of the lack of statistical significance, reported no differences in SMS scores between groups. However, comparing point estimates, performance declined in all nine SMS categories for the 2,500 ppm group compared to the 600 ppm group[91]; the decline was greater than 7% for six of the nine SMS metrics and the largest decline was 36%. SMS performance did not decline further in the group exposed to 15,000 ppm CO_2, which might suggest a U-shaped dose–response curve, consistent with biphasic inflammatory responses[80,81]. Rodeheffer et al. speculate that the non-significant findings could be explained by submariners having developed physiological adaptations to CO_2 increases because of their routine exposures to elevated CO_2 in submarines[91].

The mechanisms underlying potential reductions in higher-level cognitive performance in healthy young adults need further elucidation. Snow et al.[92] reported that the electroencephalograms (EEGs) of groups exposed to 2,700 ppm for 10 min more closely resembled drowsiness than those exposed to 830 ppm CO_2. However, using a within-subject design with a larger sample size and longer exposure duration (35 min), CO_2-induced drowsiness was observed only in participants who had slept less in the previous night[90]. Exposure to elevated CO_2 has been independently associated with increases in heart rate—which is suggestive of CO_2-induced autonomic system changes[73,85,89,90,93]. Zhang et al.[73] proposed that elevated $ETCO_2$ and vasodilation lead to acute health symptoms such as headaches and somnolence, which could explain the reduced cognitive performance[73]. Moreover, aberrant activation of the NLRP3 inflammasome and IL-1β-mediated inflammation have been linked to an increased predisposition for depressive behaviours, with inflammatory mediators acting on target neurotransmitters and neurocircuitry[94].

The blood–brain barrier is also highly permeable to CO_2, which could influence the cerebrospinal fluid environment[95].

Bloch-Salisbury et al.[96] investigated normal elevations in arterial CO_2 (from a resting average of 39 mm Hg to an average high of 47 mm Hg) on cognitive function and EEG spectral changes in healthy young adults. Despite significant slowing of the EEG power spectra, the study reported non-significant results on cognitive performance. However, the cognitive tasks were simple to moderate in difficulty. The effects of varying levels of chronic hypercapnia on cortical function have received little attention[96–98]. Recent evidence suggests that chronic hypercapnia in goats independently contributes to reductions in cognitive function[99]. The depletion of serotonin, alterations in cerebral blood flow and sleep disruption are potential mechanisms to explain these effects, which may be relevant in environmental CO_2 exposure[99].

Chronic CO_2 exposure and health

Chronic exposure to high levels of atmospheric CO_2 can have a diverse range of health effects, related to inflammation, changes in the composition of bones and kidney, respiratory acidosis, behavioural and physiological changes, and oxidative stress.

Chronic, low-grade systemic inflammation. One hypothesis links elevated levels of CO_2 in the body (which are attributable to both increasing environmental exposure to CO_2 and excess food intake) to chronic, low-grade systemic inflammation, as seen in the metabolic syndrome[2,69]. Elevated CO_2 in circulating blood may deoxygenate haemoglobin, causing mild hypoxaemia, and trigger the formation of methaemoglobin and peroxynitrite that can lead to subsequent oxidative damage within red blood cells. The response to such damage includes the activation of macrophages, which release pro-inflammatory cytokines that strongly correlate with co-morbidities including cardiovascular diseases[2,100]. Beheshti et al. suggest that environmentally relevant chronic CO_2 exposure could also increase aldosterone and induce hepatic changes in gene expression in rodents, indicating the inhibition of hepatic metabolism and promotion of glucose intolerance[101].

Bone demineralization and kidney calcification. Preliminary data on chronic CO_2 exposures between 2,000 and 3,000 ppm provide evidence of kidney calcification and bone demineralization processes in guinea pigs[102]. These effects appear to be reversible; however, generational studies may be required to determine whether there is an exposure duration at which effects become irreversible[102]. The question therefore remains whether persistent exposure to environmentally relevant increases in CO_2 could result in adaptive diseases and strain physiological systems[102,103], as the direct effects of prolonged, lower-level exposures on the acid–base balance are not fully established in non-burrowing mammals. Burrowing mammals, including rodents, may adapt more rapidly to acid–base fluctuations as they evolved intermittently exposed to environments with CO_2 concentrations of approximately 14,000 ppm (refs. [104,105]).

Chronic, low-grade respiratory acidosis. A few articles have hypothesized that over a lifetime of exposure, increasing atmospheric CO_2 may harm human health via alterations in acid–base homeostasis[61,106,107]. Exposure to elevated CO_2 increases the body's acid load, and higher levels cause respiratory acidosis[108]. Although an imperfect analogy, an increased acid load caused by diet can induce a chronic, low-grade (sub-clinical) metabolic acidosis. Here, the effects on blood pH are within normal range (7.35 to 7.45) but remain towards the lower end. Recent evidence suggests that when sustained over decades, this condition may increase the risk for several non-communicable diseases, including chronic kidney disease, type 2 diabetes mellitus, non-alcoholic fatty liver disease, sarcopenia and osteoporosis[109,110].

Behavioural changes and physiological stress. Rodents exposed to 700 or 3,000 ppm for 13 d show increased signs of chronic, low-grade stress relative to controls[101]. Differences in CO_2 exposure between enclosure modules could explain these signs, which include systemic immune dysregulation and decreases in metabolism[101]. Rats exposed to 3,000 ppm for 30 d had significantly reduced adrenal mass (consistent with chronic, low-grade stress) and decreases in daily food intake (consistent with lethargy)[104]. Young female rats intermittently exposed to 700 ppm CO_2 for 15 d exhibit lethargic behaviours and have elevated circulating plasma corticosterone, suggesting a stress response[111]. Chronic exposure to 1,000 or 3,000 ppm metabolically generated CO_2 adversely affected early brain development, induced a stress response and elevated anxiety behaviours in adolescent rats[112].

Hedonic feeding behaviours. Increasing inspired CO_2 may be linked to obesity and weight gain by the following mechanism: an increased acidic load (that is, decreased plasma pH) lowers the pH of cerebrospinal fluid, stimulating orexinergic neurons in the hypothalamus and increasing appetitive behaviours[113]. Hersoug et al. estimate that orexinergic neuronal firing has increased by 1% as a result of greater CO_2 exposures from pre-industrial times, not considering the respiration of indoor air[113]. Only one study tested this hypothesis and used an ecological model to investigate the associations between CO_2 emissions and changes in the prevalence of diabetes and obesity[1]. The study found a non-significant positive association between CO_2 emissions and changes in obesity prevalence after adjusting for sociodemographic factors, urbanicity, spatial autocorrelation and air particulate matter[1]. It is worth noting that hypercapnia has recently been proposed to be obesogenic, although through a direct mechanism promoting adipogenesis[114].

Oxidative stress and endothelial dysfunction. A recent global analysis of transcription-level differences in rodents housed in CO_2 concentrations of ~300, 700 or 3,000 ppm for 13 d found the stimulation of possible tumour-promoting pathways in muscle and breast tissues with higher CO_2 exposure[101]. Thus, chronic exposure to environmentally relevant CO_2 elevations could induce a mild hypercapnia, acidosis and/or hypoxia, thereby causing tissue-specific insults via oxidative stress and/or inflammation[101].

An imbalance in reactive oxygen species causes oxidative stress, and increasing amounts of reactive oxygen species may lead to carcinogenic effects, cellular death and accelerated aging processes. The CO_2–bicarbonate buffer system, when pushed above physiological levels, can stimulate redox pathways that cause oxidative damage via free radical formation independently of acid–base imbalance[115,116]. This phenomenon may contribute to the oxidative damage resulting from conditions associated with chronic or intermittent hypercapnia[115]. Whether CO_2 inhibits or propagates free radical formation depends on the physiologic environment. In hypercapnia, CO_2 may protect against peroxynitrite toxicity in vivo by stabilizing the iron–transferrin complex and therefore preventing iron ions from propagating free radicals[117]. However, Ezraty et al. demonstrated that exposure of *Escherichia coli* to up to 1,000 ppm CO_2 exacerbates H_2O_2 (that is, reactive oxygen species) toxicity in vivo[116]. Elevated levels of circulating MVs containing high levels of IL-1β, resulting from elevated CO_2 exposure, can also induce endothelial damage in mice[80].

Overall, oxidative stress may induce endothelial dysfunction via decoupling of the nitric oxide (NO) system. The concentrations of CO_2 on the ISS are approximately 5,000 ppm, and astronauts can spend six months in spaceflight[95]. Given the role of CO_2 in vasodilation via the NO system and impairment of the cerebrovascular NO-dependent dilatory mechanisms after long-duration spaceflight[118], it is plausible that elevated CO_2 in blood and tissues (as a result of prolonged elevation of inspired CO_2)[78] contributes to endothelial dysfunction via oxidative stress and/or reductions in NO

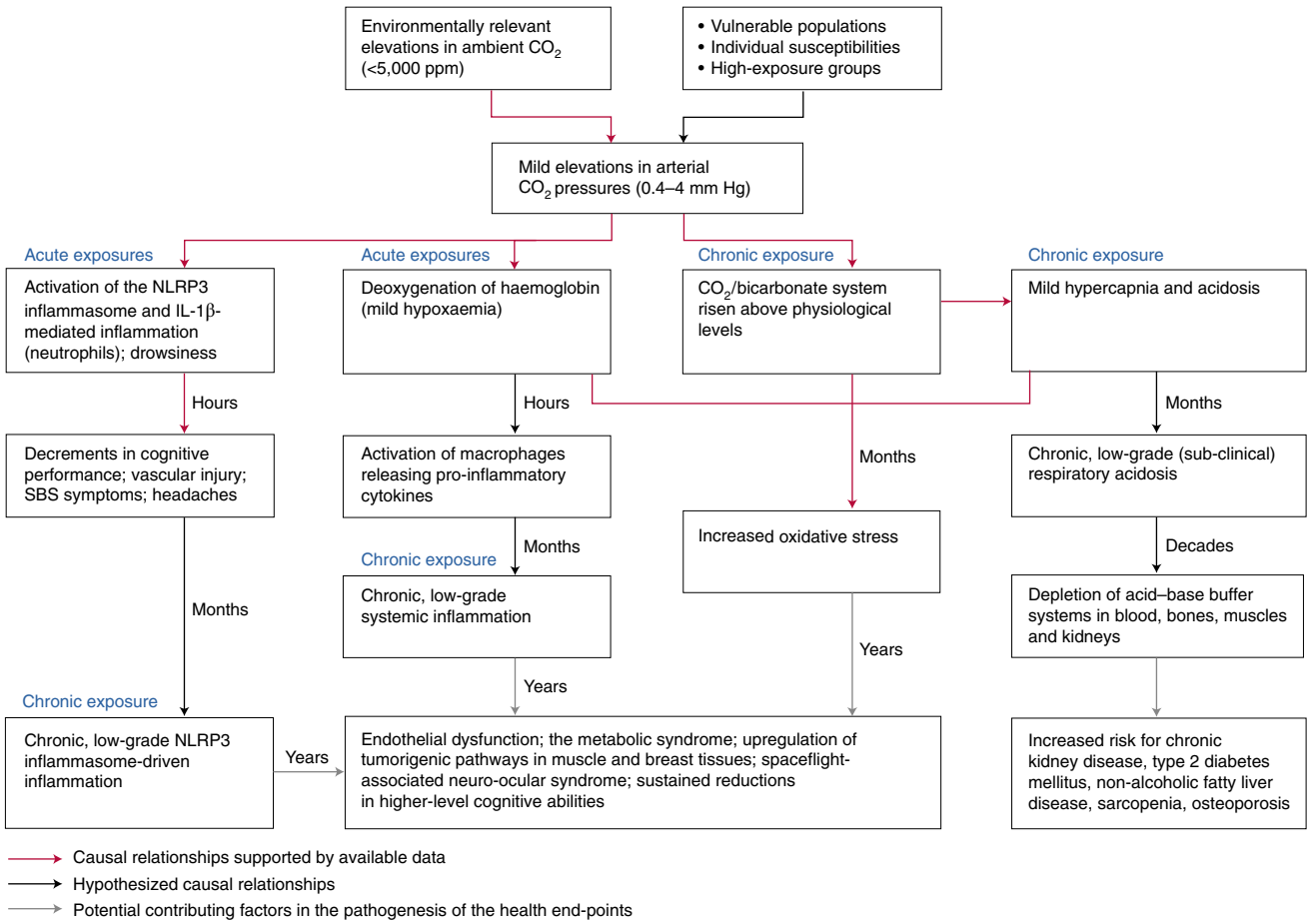

Fig. 2 | Summary of potential mechanisms by which CO_2 might affect human health. Vulnerable populations and susceptible individuals could experience greater CO_2 retention resulting from environmental CO_2 exposures, while high-exposure groups could experience greater CO_2 retention due to the greater magnitude and duration of exposures. Thom et al.[80] are currently investigating whether chronic exposure to 2,000–4,000 ppm CO_2 induces chronic, low-grade NLRP3 inflammasome-driven inflammatory responses in vivo.

bioavailability[2,80,69]. Oxidative stress and decreases in NO bioavailability have been hypothesized to contribute to spaceflight-associated neuro-ocular syndrome; however, the relative contributions of elevated ambient CO_2, microgravity, other environmental stressors and genetic predispositions are under investigation[78,79,118–121].

Vulnerable populations

The direct health effects of environmental CO_2 increases may be particularly problematic for infants and children, who breathe more air relative to their body weights and are exposed during a critical period of growth and development[122]. Other vulnerable populations may include patients with pulmonary or neuromuscular diseases that cause the body to retain CO_2 (hypercapnia) due to impaired ventilation[123]. Individuals with neurodegenerative or neurovascular diseases show an impaired capacity to increase cerebral blood flow in response to increases in arterial CO_2 (ref. [124]); their neurovascular architecture may therefore be susceptible to sustained CO_2 retention. Moreover, the body's ability to maintain blood pH declines with increasing age, and elderly individuals—who are prone to decreased buffering capacity and often have diets with high net acid loads—have been theorized to benefit the most from alkali therapies[110]. Osteoporosis may also make individuals more susceptible to the long-term consequences of slight bone demineralization processes[123]. Holy et al. demonstrated an increased risk for chronic osteopenia after prolonged exposures to CO_2 for populations with vitamin D deficiencies[125]. Hypersensitivity to CO_2 has also been linked to psychiatric problems—panic disorder or separation anxiety disorder, for example—which may be due to biological traits that increase sensitivity to acidic brain pH and/or a heightened alarm system for suffocation[126]. Hypertensive individuals may also be at increased risk[123,127–129], and there is probably large interindividual variability in predisposition for CO_2 retention, even among healthy individuals[31].

Discussion

Emerging evidence supports the possibility that CO_2 (at concentrations <5,000 ppm) poses direct risks to human health. These risks include inflammation, reduced higher-level cognitive abilities, bone demineralization, kidney calcification, oxidative stress and endothelial dysfunction (Fig. 2). Environmental exposure to CO_2 should be viewed from the perspective of vulnerable populations, including infants, elderly, and the infirm, and high-exposure groups, such as populations residing in urban CO_2 domes and in tropical climates. We found plausible mechanisms for some of the potential risks, including some that might affect multiple health end-points. Further studies are needed to confirm these findings and elucidate the mechanisms underlying these potential health effects.

Our Review supports an urgent call for two types of studies: (1) controlled chamber-like experiments with subjects exposed to environmentally relevant CO_2 levels to identify direct health effects of acute exposures; and (2) large, cohort-based longitudinal studies to evaluate the impacts of long-term chronic CO_2 exposures. Cohort studies should include groups residing in urban CO_2 domes,

as well as groups of lower socioeconomic status, who experience inequities in living conditions[22,24] and are subjected to elevated CO_2 exposures. It will also be important to enrol vulnerable populations within high-exposure groups who bear the greatest risk. In addition to characterizing biological responses to acute exposures, future research should link the integration of exposures over longer periods to potential adverse health outcomes. Chronic exposure to expected increases in CO_2, if not mitigated, can lead to significant reductions in cognitive performance. Reductions in cognitive performance must have an underlying mechanism, such as inflammation and/or vasodilation, which may have health consequences with persistent exposure. Furthermore, CO_2 accumulation can progressively displace oxygen in the air, inducing a mild chronic hypoxaemia that also has untoward health effects[101].

New and emerging exposomic approaches can evaluate the links between exposures and potential adverse health outcomes. Combining wearable CO_2 sensors[130] and omics technologies (such as metabolomics, proteomics, transcriptomics and epigenetics) can characterize human exposure and biological responses to CO_2 associated with adverse health outcomes[131,132] while controlling for other air pollutants[87,93]. These technologies will yield better insights into potential downstream human health effects and/or adaptations resulting from chronic and episodic exposures to realistic elevations in CO_2. Future studies should also characterize concentrations at the inhalation zone and how different environments can influence these concentrations[30,31]. The studies by Satish et al.[86] and Allen et al.[87,88], which have the strongest experimental designs and are the basis for the ELPCs[8], must be replicated to provide convincing evidence that CO_2 adversely affects higher-level cognitive abilities. Future studies should also measure the direct effects of CO_2 on sleep and next-day cognitive performance[27,28], and how sleep deprivation can increase susceptibility to CO_2-mediated cognitive/neurological effects[90].

The development and implementation of green buildings can mitigate direct health effects of CO_2 by keeping indoor concentrations at healthy levels[21,87,93]. The primary guiding principle for the design and operation of future buildings is beginning to shift from 'sustainable and intelligent' to 'healthy design'[133–137]. Pursuing energy efficiency by itself can lead to elevated indoor CO_2 concentrations, whereas green buildings can optimize sustainable building designs and operations without compromising indoor air quality[20,66,68]. Green buildings, however, ventilate indoor air with outdoor air. Therefore, the development of inexpensive CO_2 adsorbents may be necessary to avoid adverse health effects if (1) atmospheric concentrations of CO_2 continue to increase under RCP 6.0 or RCP 8.5, and (2) research confirms that prolonged exposures as low as 1,000 ppm CO_2 affect human health and well-being.

These technologies may raise environmental justice considerations, as society determines who has access to them, and which buildings merit the investments required to meet green-certified standards. Regional frameworks for addressing air pollution may need to be amended to include the possible direct effects of CO_2 on human health in establishing targets for reducing carbon emissions. Identifying clear causal links between increased CO_2 exposure and human health, especially indoors, could urge the international community to regulate CO_2 emissions more vigorously in the name of public health.

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Author contributions

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Competing interests

The authors declare no competing interests.

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Correspondence should be addressed to M.T.H.

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