

Direct human health risks of increased atmospheric carbon dioxide

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Growing evidence suggests that environmentally relevant elevations in CO₂ (<5,000 ppm) may pose direct risks for human health. Increasing atmospheric CO₂ 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 CO₂, 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 CO₂ 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 CO₂ could be an overlooked stressor of the modern and/or future environment. Further research is needed to quantify the major sources of CO₂ 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 CO₂ concentrations.

Recent data show an increasing trend in serum bicarbonate, indicative of CO₂ stored in the body, among the general US population¹. This increase—from 23.7 mmol l⁻¹ in 2000 to 25.2 mmol l⁻¹ in 2012—may reflect increased environmental exposure to CO₂ (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 CO₂. The authors of a 2011 Institute of Medicine report acknowledged that studies investigating health risks of chronic or intermittent exposures to elevated CO₂ (below 5,000 ppm) are lacking for the young, the elderly, and the infirm⁵. Atmospheric CO₂ concentrations were stable at ~250 ppm throughout human evolution⁶, and humans may therefore not be adapted to chronic or intermittent exposures to elevated CO₂. According to projections from the IPCC (Representative Concentration Pathways; RCPs), atmospheric CO₂ 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 century⁷.

Mounting evidence suggests that human exposure to CO₂ is higher than previously realized, and that multiple factors are increasing this exposure. Health effects from CO₂ 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 CO₂, 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 CO₂ at realistic environmental exposures (<5,000 ppm); (2) isolate the effects of CO₂ through statistical or methodological controls; or (3) employ animal models that used metabolically generated CO₂ if the authors implied that CO₂ had direct health effects.

Increased human exposure to CO₂

This section surveys the major sources of human exposure to CO₂ and the factors likely to increase it. Following studies that demonstrate direct effects of CO₂ 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 principle⁹.

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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 ⁸⁶ ; Satish et al. ⁸⁶ ; Allen et al. ^{82,86} ; Zhang et al. ⁷⁵ ; Zhang et al. ^{73,74} ; Rodeheffer et al. ⁷⁹ ; Snow et al. ⁸⁰
Adverse health outcomes associated with chronic CO ₂ exposure			
Chronic, low-grade systemic inflammation	>3,000	13 d	Zappulla ^{2,68} ; 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. ¹⁰² ; Wade et al. ¹⁰⁴ ; Martrette et al. ¹⁰⁵ ; Kiray et al. ¹⁰²
Hedonic feeding behaviours	Unknown	Ecological	Hersoug et al. ¹⁰³ ; Zheutlin et al. ¹
Oxidative stress and endothelial dysfunction	3,000–5,000	13 d to 6 months	Beheshti et al. ¹⁰² ; Thom et al. ^{80,81} ; Zwart et al. ¹⁰⁹

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 population¹ could be driven by increased exposure to indoor CO₂. 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 CO₂ concentrations <700 ppm above outdoor concentrations for occupant satisfaction and comfort¹³. The standard considers CO₂ 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 CO₂ is a product of human metabolism and respired into ambient air, building occupant density is the most significant source of indoor CO₂ elevations^{15,16}. Average indoor CO₂ 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 CO₂ 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 home²⁵. Fisk reviewed 28 studies investigating CO₂ concentrations in classrooms and found that all reported median peak CO₂ values above 1,000 ppm, with many above 2,000 ppm, suggesting widespread inadequate ventilation in schools¹⁹. The home and bedroom environments can also be significant sources of CO₂ exposure. People spend nearly one-third of their life sleeping²⁶, and in industrialized societies, more than 60% of their time in their homes^{1,12}. Bedrooms can exceed 2,500 ppm when the doors are closed for privacy, the windows closed for energy conservation and the building ventilation reduced²⁷. When ventilation rates are normal, but the windows and bedroom doors are closed, CO₂ concentrations exceed 1,000 ppm about 50% of the time²⁸. Lower CO₂ concentrations in bedrooms have been associated with both subjective and objective improvements in sleep quality^{27,28}.

Indoor CO₂ concentrations in tropical climates are often higher because of reduced outside building ventilation to lower the demand for cooling⁴. Gall et al. quantified personal exposures to CO₂ 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 home⁸. The type of bedroom ventilation was a major determinant of personal CO₂ exposure. Nearly all participants, regardless of ventilation type, spent 1.2 h d⁻¹ exposed to CO₂ concentrations greater than 1,100 ppm, whereas participants with air-conditioned bedrooms spent 1.2 h d⁻¹ exposed to CO₂ concentrations greater than 2,200 ppm (ref. ⁹). 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. ⁹).

Air conditioning influences personal CO₂ exposures because CO₂ is a dense gas and tends to concentrate at lower elevations. Most air-conditioning units ventilate air closer to the ceiling, introducing CO₂ into rooms more quickly than removing it²⁹. Another source of exposure is sedentary desk work under normal office conditions, which results in relatively static air and less occupant movement³⁰. These conditions can result in higher CO₂ concentrations around the nose and mouth, causing occupants to rebreathe their own exhaled CO₂ (refs. ^{30,31}). Personal CO₂ bubbles can average 1,200 ppm (compared to 650 ppm in the surrounding indoor air) under normal ventilation conditions in an office-like environment³⁰. Thus, a full characterization of personal CO₂ exposure entails the measurement of concentrations around the inhalation zone, which can be significantly higher^{30,31}.

Brief exposures to elevated CO₂ are also routine in transit³². 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 reported⁸. Measurements and mathematical modelling both demonstrate CO₂ build-up in vehicles^{33,34}. With two occupants and recirculating ventilation, CO₂ 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 CO₂ also occur on aeroplane flights, which average concentrations of approximately 1,350 ppm and can exceed 2,000 ppm during boarding time³⁵.

Future outdoor exposure. Rising concentrations of atmospheric CO₂ increase personal exposures directly through the respiration of outdoor air. This is especially relevant in urban environments and areas that have higher levels of CO₂ due to meteorological effects. The sum of these two factors could increase outdoor concentrations of CO₂ to health-relevant levels within this century.

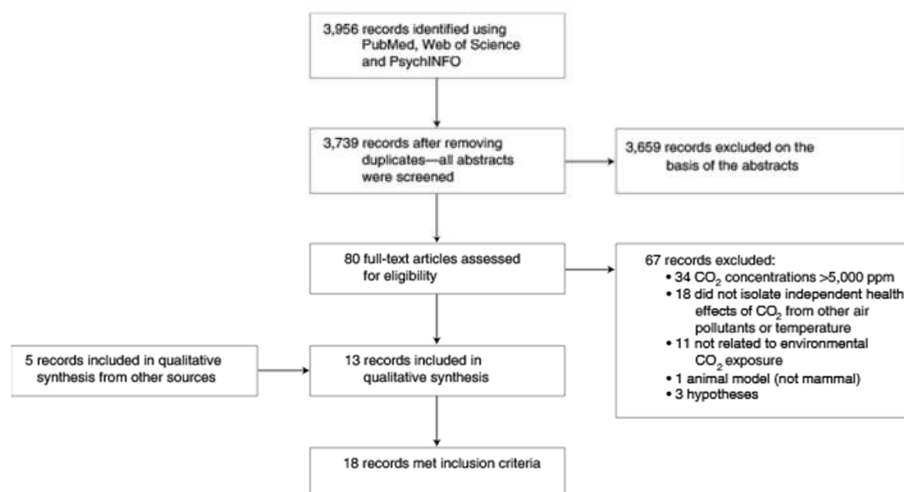


Fig. 1 | Flow diagram for the identification of appropriate studies from the literature. Records from other sources were identified by reviewing the reference lists of relevant studies.

Cities contribute substantially to anthropogenic CO₂ emissions^{36–39}, which accumulate to form what are known as CO₂ 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 2050⁴³. Fluxes of CO₂ from dense city centres can be two- to five-times larger than surrounding suburban residential areas³⁷. Studies that investigated urban–rural transects have reported urban CO₂ 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 CO₂ domes. For example, the Phoenix urban CO₂ 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 CO₂ emissions) within city centres^{54–57}. Densely populated cities with high-rise buildings and narrow streets can trap atmospheric CO₂ because reduced airflow generates lower wind speeds, resulting in less air dispersion^{58,59}. Outdoor concentrations of CO₂ could reach health-relevant levels for cities in low-lying areas in basins, such as Mexico City and Athens, where CO₂ accumulates^{60,61}. If atmospheric CO₂ continues to increase at 3 ppm yr^{–1}, urban areas could experience concentrations between 500 and 700 ppm CO₂ by 2050⁶². Under RCP 8.5, atmospheric CO₂ in large cities could surpass 1,000 ppm by 2100 for parts of the year⁶³.

Future indoor exposure. As outside air is used to dilute indoor air, outdoor concentrations of CO₂ set a ‘floor’ for indoor concentrations that cannot be breached without the use of chemical adsorbents or sinks^{14,19,23}. Continued atmospheric CO₂ 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 CO₂ may have untoward consequences, intensifying anthropogenic CO₂ emissions owing to greater energy requirements^{52,63} and introducing outdoor air pollutants indoors, including air particulate matter and ozone^{36,64,65}. 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 CO₂ 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 CO₂ 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 levels⁶³.

Other factors are likely to drive increasing exposure to CO₂. Trends in building designs, including increasing airtightness to save energy, can reduce indoor air quality⁶⁶ and increase CO₂ concentrations^{8,22,67}. Installing more ductless air-conditioning units in response to global climate change will likely increase indoor CO₂ concentrations^{8,67,68}. Human exposure to CO₂ may also increase with climate-change-induced heat stress⁴, 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 CO₂ concentrations along with exposure duration^{16,17,24,69}. The greatest urban growth rates are projected for LMICs in Asia and Africa⁴³. Increasing urbanization and associated rises in urban CO₂ emissions in LMICs in Asia and Africa, combined with other factors described here, could raise CO₂ exposure beyond thresholds for healthful environments.

Although quantifying the contribution of these factors to increasing exposure to CO₂ is beyond our scope, a substantial portion of the global population is exposed to elevated CO₂ levels of possible concern. The frequency and durations of potential adverse exposures could increase because of the many factors described here, including increasing atmospheric CO₂, which raises the potential for exposure events.

Retention of CO₂

Two studies isolated the effects of elevated CO₂ concentrations on human CO₂ retention. Zhang et al.^{73,74} reported that end-tidal CO₂ (ETCO₂) increased by ~0.4 mm Hg and 1.1 mm Hg when CO₂ 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
Kajzar and Herczeg (ref. ¹⁵)	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
Kajzar and Herczeg (ref. ¹⁵)	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. ¹⁶	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. ¹⁷	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. ¹⁸
Zhang et al. ¹⁹	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. ¹⁹	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. ¹⁹
Allen et al. ¹⁰	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. ²⁰
Rodeheffer et al. ²¹	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. ²²	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. ²²	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) CO₂. *The first series of experiments of ref. ¹⁰. The second series of experiments of ref. ¹⁰. 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. ¹⁰²	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. ¹⁰¹	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. ¹⁰²	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-1 β content of MVs	1,000 to 4,000 ppm caused human and murine neutrophils to increase MV production with higher content of IL-1 β	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-1 β content of MVs	2,000 and 4,000 ppm increased circulating MVs, increased IL-1 β 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 CO₂ as well as studies that used metabolically generated CO₂ (by controlling mechanical ventilation, for example). For studies that used metabolically generated CO₂, the authors discuss potential direct health effects of exposure to environmentally relevant elevations in CO₂. CO₂ sources: P, pure CO₂; M, metabolically generated CO₂. N, sample size. IGF-1, insulin-like growth factor-1, which is important for early brain development.

respectively. When CO₂ exposure was increased from 500 to 5,000 ppm for 2.4 h, ETCO₂ increased by ~1.5 mm Hg (ref. ⁷⁵). Similar exposures to CO₂ with bioeffluents dose-dependently impair gas exchange in the lungs leading to greater CO₂ retention^{73,76,77}. Studies of extended missions on the International Space Station (ISS) suggest significant CO₂ 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 CO₂, may lead to a diminished capacity to expel CO₂ (refs. ^{31,78}). Thus, CO₂ retention from environmentally relevant CO₂ 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 CO₂ exposure and health

Acute exposure to high levels of atmospheric CO₂ can have adverse health outcomes in terms of inflammation and cognitive effects.

Inflammation. Inflammation could be a pathway that links elevated CO₂ exposure with adverse health outcomes. Exposure to 2,000 or 4,000 ppm CO₂ 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 CO₂ 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

CO₂ retention refers to the increase in ETCO₂ or in transcutaneous monitored CO₂, which estimates changes in arterial CO₂ pressure. In the first condition, CO₂ exposure was artificially raised to the desired concentrations. In the second condition, CO₂ exposure was controlled by ventilation and therefore additional CO₂ was generated by the occupants and accompanied by human bioeffluents. In the third condition, CO₂ was also metabolically generated during long-duration spaceflight under conditions of microgravity; significantly greater CO₂ retention is observed and could be a result of microgravity, persistent exposure to elevated concentrations of atmospheric CO₂, increased magnitude of exposure, and/or the presence of other air contaminants.

(NLRP3) inflammasome and elevated interleukin (IL)-1 β production^{80,81}. In vivo, neutrophils were stimulated to release microvesicles (MVs) containing high concentrations of IL-1 β that caused vascular damage in muscle, brain and distal colon tissue, which persisted for 13 h after a 2 h exposure⁸⁰. Activation of the NLRP3 inflammasome was exceptionally rapid, which exacerbates the risks associated with elevated CO₂ 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 CO₂ show possible increased inflammation in bronchial epithelium⁸², and exposure to 3,000 ppm might induce mild inflammation of the nasal cavity in humans⁷³. Co-exposure to organic hog barn dust and 5,000 ppm CO₂ in mice enhances lung inflammation in a dose-specific manner⁸². Exposure to CO₂ at environmentally relevant levels could therefore augment inflammatory responses to other air contaminants by altering innate immunity⁸².

Cognitive effects. Elevated concentrations of CO₂ 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 CO₂ 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 CO₂ on cognition and potential mechanisms to explain these effects in Table 2.

Kajtar and Herczeg⁸⁵ reported reductions in performance in proofreading tasks when comparing 3,000 and 4,000 to 600 ppm CO₂; 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 CO₂ using the Strategic Management Simulation (SMS) software. In a follow-up study, Allen et al.⁸⁷ demonstrated that both volatile organic compounds and CO₂ 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 environment⁸⁷. Cognitive scores were 15% lower in 945 ppm and 50% lower in 1,400 ppm relative to 550 ppm CO₂. On average, participant scores decreased by 21% per 400 ppm increase⁸⁷. In another study, Allen et al.⁸⁸ reported lower passing rates among pilots performing flight simulation manoeuvres with elevated CO₂ (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 CO₂-mediated effects⁸⁸. 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 CO₂ 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 CO₂ was associated with a lower cognitive score. A follow-up by Zhang et al.⁷³ found increases in ETCO₂ with no decrements in cognitive performance when comparing 150-min exposures to 500 or 5,000 ppm CO₂. Rodeheffer et al.⁹¹ used a between-subject design with groups receiving a 45-min exposure to 600, 2,500 or 15,000 ppm CO₂ 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 group⁹¹; 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 CO₂, 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 CO₂ increases because of their routine exposures to elevated CO₂ in submarines⁹¹.

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 CO₂. However, using a within-subject design with a larger sample size and longer exposure duration (35 min), CO₂-induced drowsiness was observed only in participants who had slept less in the previous night⁹³. Exposure to elevated CO₂ has been independently associated with increases in heart rate—which is suggestive of CO₂-induced autonomic system changes^{73,85,89,90,93}. Zhang et al.⁷³ proposed that elevated ETCO₂ and vasodilation lead to acute health symptoms such as headaches and somnolence, which could explain the reduced cognitive performance⁷³. Moreover, aberrant activation of the NLRP3 inflammasome and IL-1 β -mediated inflammation have been linked to an increased predisposition for depressive behaviours, with inflammatory mediators acting on target neurotransmitters and neurocircuitry⁹⁴.

The blood–brain barrier is also highly permeable to CO₂, which could influence the cerebrospinal fluid environment⁹⁵.

Bloch-Salisbury et al.⁹⁶ investigated normal elevations in arterial CO₂ (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 function⁹⁹. 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 CO₂ exposure⁹⁹.

Chronic CO₂ exposure and health

Chronic exposure to high levels of atmospheric CO₂ 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 CO₂ in the body (which are attributable to both increasing environmental exposure to CO₂ and excess food intake) to chronic, low-grade systemic inflammation, as seen in the metabolic syndrome^{2,49}. Elevated CO₂ 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 CO₂ exposure could also increase aldosterone and induce hepatic changes in gene expression in rodents, indicating the inhibition of hepatic metabolism and promotion of glucose intolerance¹⁰¹.

Bone demineralization and kidney calcification. Preliminary data on chronic CO₂ exposures between 2,000 and 3,000 ppm provide evidence of kidney calcification and bone demineralization processes in guinea pigs¹⁰². These effects appear to be reversible; however, generational studies may be required to determine whether there is an exposure duration at which effects become irreversible¹⁰². The question therefore remains whether persistent exposure to environmentally relevant increases in CO₂ 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 CO₂ 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 CO₂ may harm human health via alterations in acid–base homeostasis^{61,106,107}. Exposure to elevated CO₂ increases the body's acid load, and higher levels cause respiratory acidosis¹⁰⁸. 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 controls¹⁰¹. Differences in CO₂ exposure between enclosure modules could explain these signs, which include systemic immune dysregulation and decreases in metabolism¹⁰¹. 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 CO₂ for 15 d exhibit lethargic behaviours and have elevated circulating plasma corticosterone, suggesting a stress response¹¹¹. Chronic exposure to 1,000 or 3,000 ppm metabolically generated CO₂ adversely affected early brain development, induced a stress response and elevated anxiety behaviours in adolescent rats¹¹².

Hedonic feeding behaviours. Increasing inspired CO₂ 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 behaviours¹¹³. Hersoug et al. estimate that orexinergic neuronal firing has increased by 1% as a result of greater CO₂ exposures from pre-industrial times, not considering the respiration of indoor air¹¹³. Only one study tested this hypothesis and used an ecological model to investigate the associations between CO₂ emissions and changes in the prevalence of diabetes and obesity¹. The study found a non-significant positive association between CO₂ emissions and changes in obesity prevalence after adjusting for sociodemographic factors, urbanicity, spatial autocorrelation and air particulate matter¹. It is worth noting that hypercapnia has recently been proposed to be obesogenic, although through a direct mechanism promoting adipogenesis¹¹⁴.

Oxidative stress and endothelial dysfunction. A recent global analysis of transcription-level differences in rodents housed in CO₂ 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 CO₂ exposure¹⁰¹. Thus, chronic exposure to environmentally relevant CO₂ elevations could induce a mild hypercapnia, acidosis and/or hypoxia, thereby causing tissue-specific insults via oxidative stress and/or inflammation¹⁰¹.

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 CO₂–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 hypercapnia¹¹⁵. Whether CO₂ inhibits or propagates free radical formation depends on the physiologic environment. In hypercapnia, CO₂ may protect against peroxynitrite toxicity in vivo by stabilizing the iron–transferrin complex and therefore preventing iron ions from propagating free radicals¹¹⁷. However, Ezraty et al. demonstrated that exposure of *Escherichia coli* to up to 1,000 ppm CO₂ exacerbates H₂O₂ (that is, reactive oxygen species) toxicity in vivo¹¹⁸. Elevated levels of circulating MVs containing high levels of IL-1β, resulting from elevated CO₂ exposure, can also induce endothelial damage in mice⁹⁰.

Overall, oxidative stress may induce endothelial dysfunction via decoupling of the nitric oxide (NO) system. The concentrations of CO₂ on the ISS are approximately 5,000 ppm, and astronauts can spend six months in spaceflight⁹⁵. Given the role of CO₂ in vasodilation via the NO system and impairment of the cerebrovascular NO-dependent dilatory mechanisms after long-duration spaceflight¹¹⁹, it is plausible that elevated CO₂ in blood and tissues (as a result of prolonged elevation of inspired CO₂)⁷⁸ contributes to endothelial dysfunction via oxidative stress and/or reductions in NO

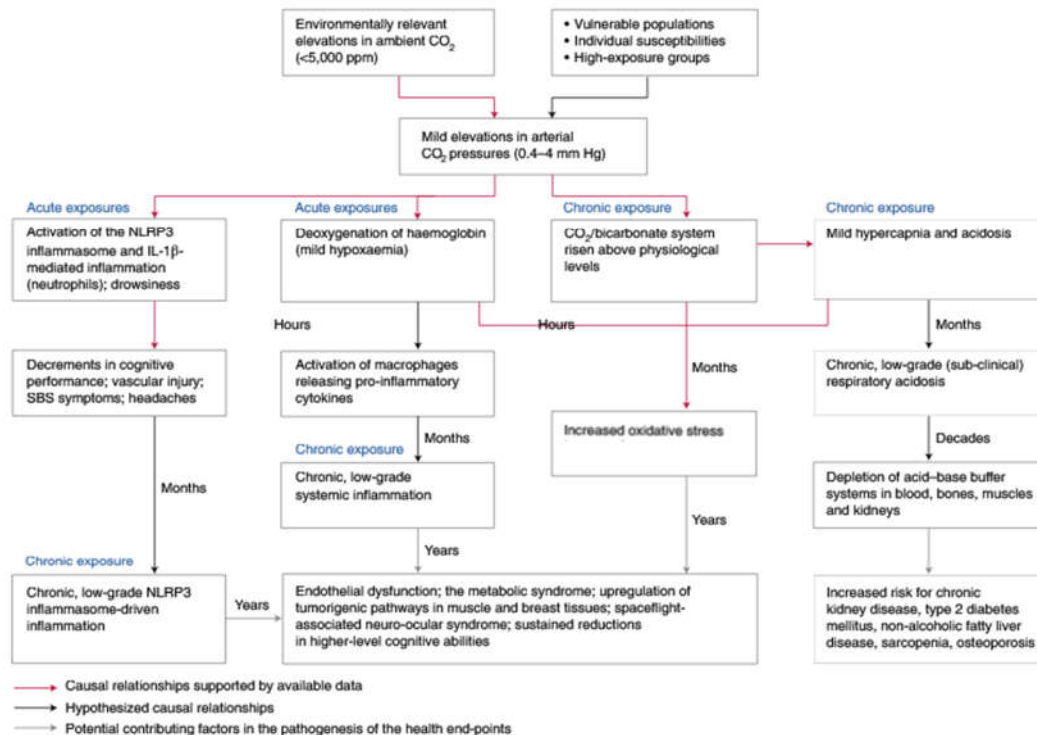


Fig. 2 | Summary of potential mechanisms by which CO₂ might affect human health. Vulnerable populations and susceptible individuals could experience greater CO₂ retention resulting from environmental CO₂ exposures, while high-exposure groups could experience greater CO₂ retention due to the greater magnitude and duration of exposures. Thom et al.⁴⁰ are currently investigating whether chronic exposure to 2,000–4,000 ppm CO₂ 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 CO₂, microgravity, other environmental stressors and genetic predispositions are under investigation^{78,79,118–121}.

Vulnerable populations

The direct health effects of environmental CO₂ 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 development¹²². Other vulnerable populations may include patients with pulmonary or neuromuscular diseases that cause the body to retain CO₂ (hypercapnia) due to impaired ventilation¹²³. Individuals with neurodegenerative or neurovascular diseases show an impaired capacity to increase cerebral blood flow in response to increases in arterial CO₂ (ref. 124); their neurovascular architecture may therefore be susceptible to sustained CO₂ 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 therapies¹⁰. Osteoporosis may also make individuals more susceptible to the long-term consequences of slight bone demineralization processes¹²⁵. Holy et al. demonstrated an increased risk for chronic osteopenia after prolonged exposures to CO₂ for populations with vitamin D deficiencies¹²⁶. Hypersensitivity to CO₂ 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 suffocation¹²⁸. Hypertensive individuals may also be at increased risk^{123,127–129}, and there is probably large interindividual variability in predisposition for CO₂ retention, even among healthy individuals³¹.

Discussion

Emerging evidence supports the possibility that CO₂ (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 CO₂ 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 CO₂ 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 CO₂ levels to identify direct health effects of acute exposures; and (2) large, cohort-based longitudinal studies to evaluate the impacts of long-term chronic CO₂ exposures. Cohort studies should include groups residing in urban CO₂ domes,

as well as groups of lower socioeconomic status, who experience inequities in living conditions^{22,24} and are subjected to elevated CO₂ 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 CO₂, 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, CO₂ accumulation can progressively displace oxygen in the air, inducing a mild chronic hypoxaemia that also has untoward health effects¹⁰¹.

New and emerging exposomic approaches can evaluate the links between exposures and potential adverse health outcomes. Combining wearable CO₂ sensors¹³⁰ and omics technologies (such as metabolomics, proteomics, transcriptomics and epigenetics) can characterize human exposure and biological responses to CO₂ associated with adverse health outcomes^{131,132} while controlling for other air pollutants^{87,89}. 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 CO₂. 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 ELPCs⁸, must be replicated to provide convincing evidence that CO₂ adversely affects higher-level cognitive abilities. Future studies should also measure the direct effects of CO₂ on sleep and next-day cognitive performance^{27,28}, and how sleep deprivation can increase susceptibility to CO₂-mediated cognitive/neurological effects⁹⁰.

The development and implementation of green buildings can mitigate direct health effects of CO₂ by keeping indoor concentrations at healthy levels^{133,137}. 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 CO₂ concentrations, whereas green buildings can optimize sustainable building designs and operations without compromising indoor air quality^{20,46,48}. Green buildings, however, ventilate indoor air with outdoor air. Therefore, the development of inexpensive CO₂ adsorbents may be necessary to avoid adverse health effects if (1) atmospheric concentrations of CO₂ continue to increase under RCP 6.0 or RCP 8.5, and (2) research confirms that prolonged exposures as low as 1,000 ppm CO₂ 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 CO₂ on human health in establishing targets for reducing carbon emissions. Identifying clear causal links between increased CO₂ exposure and human health, especially indoors, could urge the international community to regulate CO₂ 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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