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CO_2 and Lung Function: An *in Vivo* Exploration of Potential Climate Change Implications

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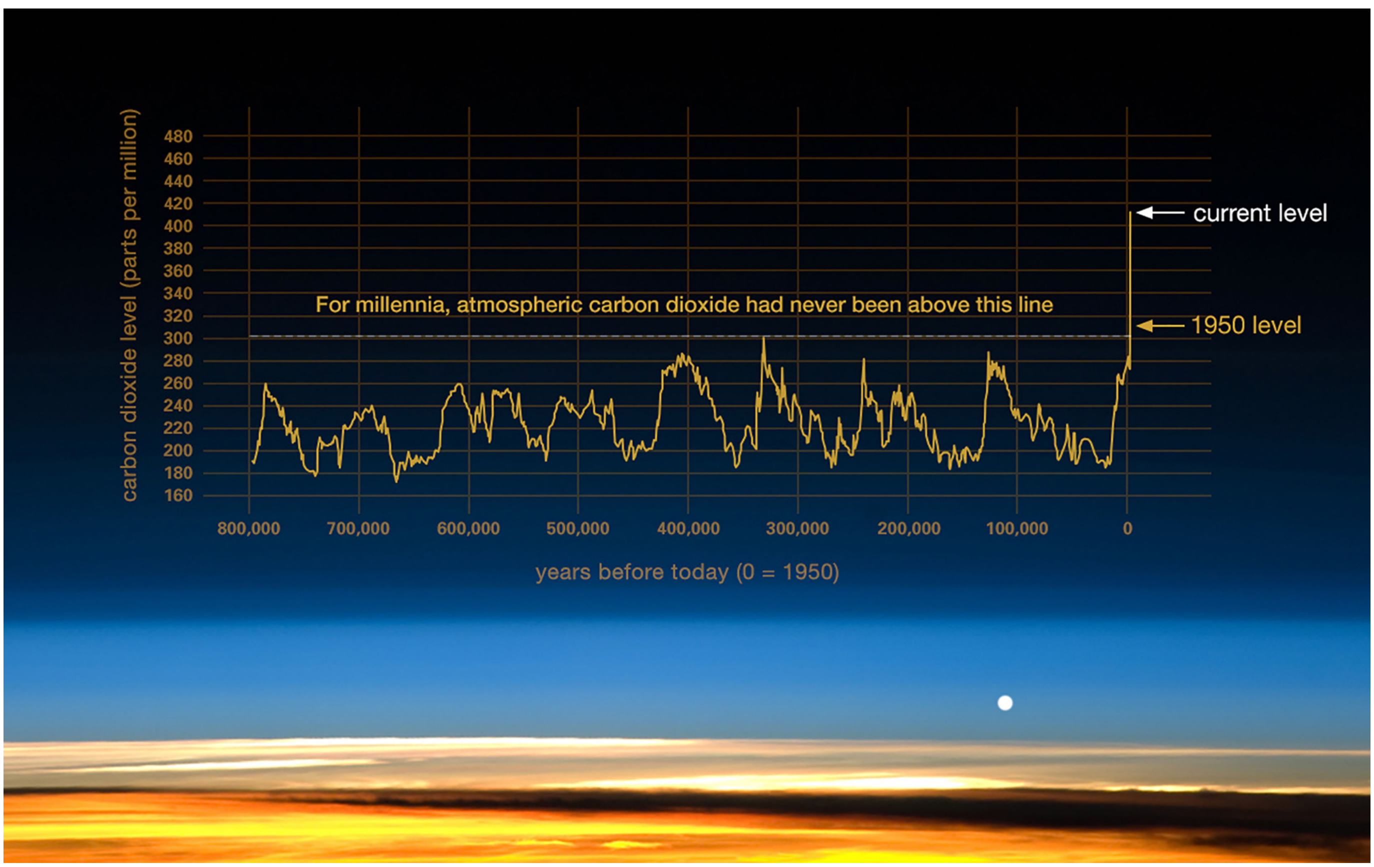
Atmospheric carbon dioxide (CO_2) hit a milestone in 2015, when global average concentrations reached 400 ppm for the first time in recorded history.[1] By 2100, the global average could more than double if emissions remain unabated, according to the RCP8.5 ("business as usual") scenario used by the Intergovernmental Panel on Climate Change in its assessments.[2] Although much attention has been paid to the effect of CO_2 as a climate forcing agent, multiple reports suggest this greenhouse gas also may have direct health effects.[3] A recent report in *Environmental Health Perspectives* used a mouse model to assess the pulmonary effects of chronic exposure to ambient CO_2 at concentrations comparable to those projected by climate modeling.[4]

A 2019 review in *Nature Sustainability* summarized evidence on the effects on lung function of very high (>1,000 ppm), acute CO_2 exposures.[3] In contrast, current report is the first known study to directly assess the physiological impact of long-term exposure to CO_2 concentrations that are realistically possible in the near future, says first author Alexander Larcombe, an associate professor at the Telethon Kids Institute and Wal-yan Respiratory Research Center in Nedlands, Australia.

In the new study, investigators exposed adult female mice and their offspring to either control (approximately 465 ppm) or elevated (approximately 890 ppm) concentrations of CO_2. Dams began exposure with a 1-week acclimation period before mating, and offspring were exposed from preconception to adulthood. At postnatal week 12, the investigators assessed the offspring's respiratory function and lung structure. To compare the effects of exposure during lung development versus exposure during adulthood, they also examined the dams' lung function.

Their results indicate that, among female offspring, exposures to high ambient CO_2 caused modest measurable changes in lung function and structure compared with exposure to control CO_2 levels. The fact that deficits were seen only in offspring suggests the differences were developmental rather than adaptational.

Lung development impairment is well documented to occur in a low-oxygen environment (hypoxia);[5] however, the exposure model used in this study did not mimic hypoxic conditions, where oxygen levels are significantly lower while CO_2 levels remain unchanged. In the lung, gas exchange occurs in tiny air sacs called alveoli, and perturbations in ambient CO_2 levels would be



Humans have been exposed to atmospheric CO_2 concentrations averaging roughly 230 ppm since the time of our earliest ancestor.[9,10] However, intensified human activity and associated CO_2 emissions have led to increases of 2–3 ppm per year for the past 50 years. In its most recent update as of this writing, Hawaii's Mauna Loa Observatory reported a seasonally adjusted CO_2 concentration of 414.88 ppm for the month of December 2020.[11] Image: National Aeronautics and Space Administration. Based on data from Lüthi et al. (2008).[12]

expected to result in increased lung area through alveolarization,[6] which in the mouse develops almost exclusively after birth.[7] Consistent with this notion, male mice exhibited higher numbers of alveoli; conversely, females showed decreased alveolarization. Other markers of lung function suggested that high CO_2 exposure affected female mice exclusively.

The authors proposed respiratory acidosis, a change in blood chemistry that results from CO_2 exposure, as a possible basis for impaired lung function in female mice. However, they explored no foundation for the sex-specific effects.

The findings reported by the authors might not rule out an effect on male mice given the relatively small sample size and inherent animal-to-animal variability, cautions Darryl Zeldin, head of the Environmental Cardiopulmonary Disease Group and scientific director of the National Institute of Environmental Health Sciences. Zeldin was not involved in the study.

An additional caveat to the study is the choice of animal model. As burrowing animals, mice are more tolerant to elevated CO_2 than animals that stay aboveground.[8] Larcombe suggests that future studies should address whether similar outcomes occur in larger, nonburrowing mammals, which would help to give further insight into potential implications for human health.

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