Articles



Effect of increased concentrations of atmospheric carbon dioxide on the global threat of zinc deficiency: a modelling study



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Summary

Background Increasing concentrations of atmospheric carbon dioxide (CO₂) lower the content of zinc and other nutrients in important food crops. Zinc deficiency is currently responsible for large burdens of disease globally, and the populations who are at highest risk of zinc deficiency also receive most of their dietary zinc from crops. By modelling dietary intake of bioavailable zinc for the populations of 188 countries under both an ambient CO, and elevated CO, scenario, we sought to estimate the effect of anthropogenic CO, emissions on the global risk of zinc deficiency.

Methods We estimated per capita per day bioavailable intake of zinc for the populations of 188 countries at ambient CO, concentrations (375-384 ppm) using food balance sheet data for 2003-07 from the Food and Agriculture Organization. We then used previously published data from free air CO, enrichment and open-top chamber experiments to model zinc intake at elevated CO, concentrations (550 ppm, which is the concentration expected by 2050). Estimates developed by the International Zinc Nutrition Consultative Group were used for country-specific theoretical mean daily per-capita physiological requirements for zinc. Finally, we used these data on zinc bioavailability and population-weighted estimated average zinc requirements to estimate the risk of inadequate zinc intake among the populations of the different nations under the two scenarios (ambient and elevated CO₂). The difference between the population at risk at elevated and ambient CO₂ concentrations (ie, population at new risk of zinc deficiency) was our measure of impact.

Findings The total number of people estimated to be placed at new risk of zinc deficiency by 2050 was 138 million (95% CI 120-156). The people likely to be most affected live in Africa and South Asia, with nearly 48 million (32-63) residing in India alone. Global maps of increased risk show significant heterogeneity.

Interpretation Our results indicate that one heretofore unquantified human health effect associated with anthropogenic CO, emissions will be a significant increase in the human population at risk of zinc deficiency. Our country-specific findings can be used to help guide interventions aimed at reducing this vulnerability.

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Introduction

Adequate zinc intake is a cornerstone of global maternal and child health, and roughly 17% of the global population was estimated to be at risk of zinc deficiency in 2011.^{1,2} Zinc deficiency increases the risk of premature delivery and reduces growth and weight gain in infants and young children.3 Adequate zinc intake is also important in proper immune function.4 Preventive zinc supplementation in zinc-deficient populations decreases morbidity from childhood diarrhoea, acute lower respiratory infections, and all-cause mortality.5-8 The global burden of disease attributed to zinc deficiency is high, with greater than 100000 deaths per year from diarrhoea and pneumonia in children younger than 5 years attributable to zinc deficiency.9

Food crops such as wheat, rice, barley, soya, and field peas, which serve as an important source of dietary zinc for billions of people around the world, have recently been shown to contain lower concentrations of zinc and other nutrients when grown under open field conditions at a concentration of carbon dioxide (hereafter referred to as [CO₂]) the world is expected to experience by 2050 (roughly 550 ppm).10,11

To understand the global health implications of these changes, we aimed to model the per-capita availability of dietary zinc and phytate (a phosphate storage molecule that inhibits absorption of zinc in the diet) worldwide under both ambient and elevated [CO₂] scenarios. For each country, under each scenario, we aimed to calculate the proportion of the population at risk of inadequate zinc intake. By comparing the results for each scenario, we aimed to estimate the proportion of each national population that would be placed at new risk of inadequate zinc intake as a result of rising [CO₂] in the atmosphere, and to identify geographical regions where populations are particularly vulnerable to the nutritional impacts of

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Research in context

Evidence before this study

Before this study, there was strong evidence that zinc deficiency was a significant global health problem affecting at least 17% of the global population and responsible for large burdens of disease around the world. More recently, strong evidence has emerged from free air carbon dioxide enrichment (FACE) experiments that the edible portions of food crops grown at elevated atmospheric carbon dioxide concentrations $[CO_2]$ have lower zinc, iron, and protein contents than identical cultivars of the same crops grown under identical growing conditions at ambient $[CO_2]$. These same experiments showed that phytate concentrations were lower in wheat cultivars grown at elevated $[CO_3]$ but phytate content in other food crops was unaffected.

Added value of this study

This is the first study to combine data on nutrient changes in food crops expected at higher levels of atmospheric CO, with

increasing [CO₂] as a result of their diets and their overall zinc and phytate intake.

Methods

Effect of elevated [CO₂] on zinc and phytate concentrations

To estimate the size of the effect of elevated [CO₂] on zinc and phytate concentrations, we used a previously published meta-analysis of data pooled by crop, from free air carbon dioxide enrichment (FACE) and open-top chamber experiments in which crops were grown at ambient and elevated [CO₂] and the edible portion of the food crop was tested for zinc, phytate, or both.¹⁰ Phytate concentrations were only found to change significantly in wheat (p<0·05) in response to elevated [CO₂] so only wheat phytate concentrations were adjusted in our scenarios. Estimates of the effect of elevated [CO₂] on nutrient content were used to adjust per-capita nutrient intake from each food commodity as described below.

Country-specific, per-capita zinc and phytate intake

We analysed national food balance sheet data from 2003-07, which are available from the Food and Agriculture Organization, 12 to estimate country-specific, per-capita zinc and phytate intake under both ambient (375-384 ppm during this time period)13 and elevated (roughly 550 ppm) [CO2] scenarios. The food balance sheets provide estimated country-specific data for 210 countries or areas on the average daily per-capita consumption of 95 "standardised" food commodities (kcal per capita per day). Of these 210 countries or areas, we could obtain demographic data for 188 countries, which became the subjects of our analysis. The remaining 22 territories and states, mostly small island entities, were excluded from further analyses because we restricted the analyses to national populations. Plantsource food commodities reported in the food balance

estimates of dietary intake of most of the world's population in order to model the effect of rising $[CO_2]$ on the global risk of zinc deficiency. The study indicates that, in addition to disrupting the global climate system, anthropogenic CO_2 emissions are also threatening millions of people with increased risk of zinc deficiency. The study also indicates that the distribution of the populations at risk of increased zinc deficiency is heterogeneous and concentrated in Africa and South Asia

Implications of all the available evidence

From a policy perspective, these findings suggest that interventions including biofortification of staple food crops, supplementation, and fortification should be targeted at those populations identified as most vulnerable. In addition, these findings provide additional support for the urgent need to mitigate global CO₂ emissions.

sheets were initially categorised as C, legumes, C, tubers, C₃ other plants, or C₄ grasses. If crop-specific data on the effects of elevated [CO2] on changes in the zinc and phytate contents were available from FACE or open-top chamber experiments, commodities were subsequently assigned to these "primary" groups: maize, peas, rice, sorghum, soya, wheat, barley, and potatoes. When cropspecific data were not available, commodities were assigned to one of three "composite" groups, which were composed of the weighted means of crop-specific data from the FACE or open-top chamber experiments (C3 plants: wheat and barley, with and without rice; C₃ legumes: soya and peas; C₄ grasses: corn and sorghum). Tubers other than potatoes were assumed to be closest to potatoes and the values for potatoes were used for those crops. Because rice is grown under very different (immersion) conditions than other C3 plants, it was not clear whether it should be included in our composite estimates of the mean effect of elevated [CO₂] on C₃ plants. To address this uncertainty, we generated two different models for adjusting zinc and phytate contents of the food balance sheet food commoditiesone which included rice in the C3 plant composite estimates and one which did not. The assignment of each food commodity is listed in the appendix (p 1).

The food balance sheet country-specific data on food availability (kcal per capita per day) were used to calculate the per-capita zinc and phytate contents of the daily food supply (mg per capita per day), prior to accounting for the effects of elevated [CO₂]. The estimated zinc and phytate content (mg/100 kcal) for each food commodity at ambient [CO₂] was obtained from a composite nutrient composition database created specifically for the analysis of the zinc and phytate content of national food supplies as reported. Mean estimated zinc and phytate content (mg/100 kcal) for each food commodity was calculated, adjusting for the effects of food processing methods (eg,

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decortication, milling, fermentation, and nixtamalisation), according to previous regional assumptions. ^{2,14} The mean per-capita zinc and phytate intakes for each country were calculated as the sum of the zinc and phytate contribution from each food commodity. To model physiological zinc intake at elevated [CO₂], we used Monte Carlo simulations to account for uncertainties. In the simulation, 1000 random draws were made from the established range of altered nutrient concentrations for each food crop or commodity to generate confidence intervals (CI) which reflect the precision of the estimates free of distributional assumptions.

Population at risk of zinc deficiency

We estimated the prevalence of inadequate zinc intake under each scenario by comparing the estimated absorbable zinc content of the national food supply, as above, with the population's estimated physiological requirements for absorbed zinc. Detailed methodological and model assumptions, as well as results based on original data, have been described previously. ^{2,14,15} We took risk of inadequate zinc intake based on food balance sheet analysis as a proxy for risk of zinc deficiency, and, for clarity, we use the term "risk of zinc deficiency" instead of "risk of inadequate zinc intake" in our results and discussion.

The fractional absorption of zinc and the absorbable zinc content of the daily food supply for each country under both ambient and elevated [CO₃] scenarios were predicted using a saturation response model of zinc absorption as a function of dietary zinc and phytate (the Miller equation).16 The age and sex distribution of country populations estimated by the 2010 revision of the World Population Prospects¹⁷ were used to calculate the country-specific theoretical mean daily per-capita physiological requirement for zinc, as developed by the International Zinc Nutrition Consultative Group.1 We used these estimates of physiological zinc requirements because they are based on a large number of studies among both men and women and including studies in both developed and developing countries; they are intended to be generalisable internationally. However, because there is a lack of consensus on physiological requirements for zinc, we generated an additional model using the effect estimate of elevated [CO₃] on nutrient levels from the best-estimate model, but with country-specific theoretical mean daily per-capita physiological requirements for zinc based on the Food and Nutrition Board of the US Institute of Medicine recommendations.18

For each scenario, we calculated the estimated proportion of the mean physiological requirement for zinc available in the national food supply by dividing the estimated absorbable zinc content of the national food supply by the calculated national physiological requirement. We then applied an estimated average requirement cut-point-based method to estimate the proportion of

national populations at risk of inadequate zinc intake, assuming a normal population distribution with a 25% interindividual variation, as has been done in previous analyses of global risk of zinc deficiency. Variation in dietary zinc requirements takes into account both variation in requirements for absorbed zinc (ie, variations in metabolism and rate of zinc turnover) as well as variation in the fractional absorption of zinc. We took the difference between the population at risk at elevated [CO₂] and the population at risk under ambient [CO₂] as our measure of impact.

Statistical analysis

Regional classifications are based on the reporting regions of the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study²¹ with the exception that we broke out India and China separately because of their large population sizes. Regional and global data were weighted by national population sizes. All statistical analyses were completed using SAS System for Windows release 9.3 (SAS Institute, Cary, NC, USA) and the R statistical package V 3.0. Data are presented as means (95% CI), unless otherwise noted.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data and final responsibility for the decision to submit for publication.

Results

In a previously published meta-analysis, we found that, when grown under open field conditions at a [CO₂] the world is expected to experience by 2050 (roughly 550 ppm), wheat (-9·1%), rice (-3·1%), barley (-13·6%), soya (-5·0%), and field peas (-6·8%) have significantly reduced zinc content. At 550 ppm CO₂, estimated percapita zinc intake varied from a low of 8 mg/day in sub-Saharan Africa to 13 mg/day in China, whereas estimated phytate intake was lowest in southern and tropical Latin America and more than twice as high in Central Asia, North Africa, and the Middle East (table).

The choice of estimates of the physiological requirements for zinc intake has very large implications for the proportion of the global population at risk of zinc deficiency at ambient [CO₂] (17% using the International Zinc Nutrition Consultative Group model, table; and 66% using the US Institute of Medicine Food and Nutrition Board model, appendix p 2). However, the estimated effect of elevated [CO₂] on global risk of zinc deficiency using these two models varied much less. The total number of people estimated to be placed at new risk of zinc deficiency by 2050 was 138 million (95% CI 120–156) with the International Zinc Nutrition Consultative Group model (table) and 180 million (164–196) with the US Institute of Medicine model

| | High- income | Southern and tropical Latin America | Central and Andean Latin America and Caribbean | Central and eastern Europe | Central Asia, north Africa, and Middle East | Sub- Saharan Africa | South Asia* | India | East and southeast Asia and Pacific† | China | Global |
|---|-----------------|--|---|----------------------------------|--|---------------------------|-------------|-------------|---|-------------|---------------|
| Number of countries | 30 | 5 | 27 | 20 | 28 | 48 | 5 | 1 | 21 | 3 | 188 |
| Population (millions) | 937-2 | 249-4 | 301-4 | 330-1 | 481-4 | 757-8 | 355-0 | 1140.5 | 606-8 | 1337-7 | 6497.5 |
| Energy intake (kcal/day) | 3423-9 | 3031.4 | 2835-7 | 3285.8 | 3089-2 | 2350-5 | 2233.7 | 2295.2 | 2585.2 | 2905-0 | 2776-2 |
| Zinc intake (mg/day) | 12·8 | 11·9 | 10·3 | 11·2 | 13·1 | 8·0 | 9·0 | 9·3 | 8.6 | 13·2 | 10·9 |
| | (12·7-12·9) | (11·8–12·0) | (10·2–10·4) | (11·1-11·3) | (13·0-13·2) | (7·9–8·1) | (8·9–9·1) | (9·1–9·5) | (8.5–8.7) | (13·0-13·4) | (10·8–11·1) |
| Phytate intake (mg/day) | 1162·2 | 1162·0 | 1881·7 | 1183·0 | 2702·7 | 1777·3 | 1981·2 | 2286·4 | 1436·0 | 1440·0 | 1707·3 |
| | (1158·8- | (1157·4– | (1880·1- | (1176·1– | (2680·3– | (1776·3- | (1953·4– | (2248·5- | (1434·6- | (1427·0- | (1699·8- |
| | 1165·6) | 1166·6) | 1883·3) | 1189·9) | 2725·1) | 1778·3) | 2009·0) | 2324·3) | 1437·4) | 1453·0) | 1714·8) |
| Absorbable zinc intake | 3·27 | 3·17 | 2·47 | 3·04 | 2·48 | 2·10 | 2·18 | 2·11 | 2·41 | 3·12 | 2·65 |
| (mg/day) | (3·26–3·28) | (3·16-3·18) | (2·45–2·49) | (3·03–3·05) | (2·47–2·49) | (2·09–2·11) | (2·17–2·19) | (2·09–2·13) | (2·40–2·42) | (3·10-3·14) | (2·64–2·66) |
| Proportion of mean physiological requirement of zinc available‡ | 158·6% | 162·2% | 129·9% | 146·2% | 129·4% | 118·9% | 118·2% | 110·3% | 124·4% | 153·2% | 135% |
| | (158·3– | (161·5- | (129·0- | (145·7- | (129·1– | (118·1- | (117·6- | (109·2- | (123·7- | (152·4- | (134·7- |
| | 158·9) | 162·9) | 130·8) | 146·8) | 129·7) | 119·8) | 118·8) | 111·4) | 125·1) | 154·0) | 135·3) |
| Proportion of population with inadequate zinc intake | 8·1% | 6·9% | 19% | 10·6% | 19·6% | 29·5% | 27·3% | 35·4% | 24·6% | 8·4% | 19·5% |
| | (8·0-8·2) | (6·7-7·1) | (18·4–19·6) | (10·4-10·8) | (19·4–19·8) | (28·6–30·4) | (26·6–28·0) | (34·0–36·8) | (23·8–25·4) | (8·2–8·6) | (19·2–19·8) |
| Absolute % increase in population with inadequate zinc intake | 0.6% | 0·5% | 2·0% | 1·0% | 2·5% | 3·9% | 2·9% | 4·2% | 2·4% | 0.6% | 2·1% |
| | (0.5–0.7) | (0·3–0·6) | (1·4-2·6) | (0·8–1·2) | (2·3-2·7) | (3·0-4·8) | (2·2-3·6) | (2·8–5·6) | (1·6–3·2) | (0.4–0.8) | (1·8–2·3) |
| Relative % increase in population with inadequate zinc intake | 6.9% | 6·5% | 11·1% | 10·2% | 14·6% | 14·9% | 12·2% | 13·4% | 10·4% | 7·3% | 10·6% |
| | (6.0-7.8) | (4·1-8·9) | (7·8–14·4) | (8·2–12·2) | (13·2–16·0) | (11·6–18·2) | (9·8–14·6) | (9·0-17·8) | (7·8-13·0) | (4·6–10·0) | (9·5–11·7) |
| Population newly at risk of inadequate zinc intake (millions) | 5·4 | 1·1 | 5·9 | 3·3 | 12·2 | 29·7 | 10·4 | 47·8 | 14·8 | 7·8 | 138·4 |
| | (4·5-6·2) | (0·7-1·6) | (4·2-7·7) | (2·8-3·9) | (11·1–13·2) | (22·6–36·8) | (8·0–12·8) | (32·1–63·5) | (10·1–19·5) | (5·1–10·5) | (120·0–156·8) |

Data are n or mean (95% CI). Data are weighted by national population sizes and are for 188 countries. Regional classifications are based on the reporting regions of the Global Burden of Diseases, Injuries, and Risk Factors 2010 Study, and are grouped according to geographical location and dietary patterns. *Not including India. †Not including China. ‡Estimated proportion of the mean physiological requirement for zinc available in the national food supply at 550 ppm CO₂.

Table: Altered risk of zinc deficiency under elevated [CO₂] (550 ppm) scenario, calculated regionally

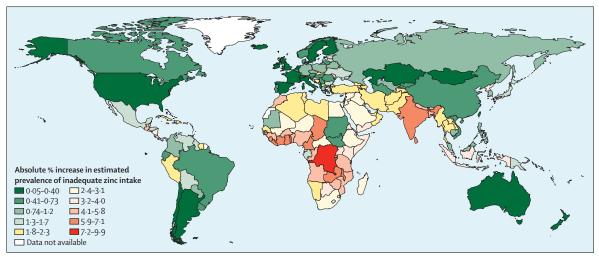
(appendix p 2). Both models estimated the absolute increase in the proportion of the global population at risk under elevated $[CO_2]$ as 2–3%. We found that populations in Africa and parts of Asia are likely to be most affected (figure 1), with increased risk in sub-Saharan Africa, South Asia, and India of 3.9% (3.0-4.8), 2.9% (2.2-3.6), and 4.2% (2.8-5.6), respectively (table). We found the population of India particularly vulnerable to the impact of elevated $[CO_2]$ on crop nutrients, with nearly 48 million additional people estimated to be newly at risk of zinc deficiency by 2050.

The decision of whether or not to include rice in the composite index for C₃ grains did not have a large effect on our results. The "best-estimate" model was considered to be that which did not include rice in the C₃ weighted mean. However, with rice included in the composite index, we estimated 133 million (115–150) people at new risk of zinc deficiency globally (appendix p 3) compared with 138 million (120–156) when rice is not included in the composite index. The inclusion or exclusion of rice from the composite index or the choice of which physiological requirements to use did not alter appreciably the order of countries most affected by rising [CO₂] (appendix pp 4–5).

Discussion

The global [CO₂] in the atmosphere is expected to reach 550 ppm in the next 40–60 years, even if further actions are taken to decrease emissions.¹¹ These concentrations of CO₂ have been shown to reduce the nutritional value of important food crops,¹⁰ and here we show that such nutrient reductions threaten an additional 138 million people concentrated in Africa and south Asia with the risk of zinc deficiency. Zinc deficiency has been consistently shown to be associated with compromised immune function and increased susceptibility to morbidity and mortality from infectious diseases.^{6,22}

Our analysis does not include the changes in the global diet that will almost certainly take place over the next few decades while global $[CO_2]$ rises to 550 ppm. We have tried to isolate the CO_2 effect by simply modelling a world in which food availability is the same as in 2010, but the nutrient contents of those foods have changed in response to elevated $[CO_2]$. Anticipating how the global diet is likely to change over the coming decades is difficult. Economic growth might allow populations to consume more calories or receive a higher proportion of their calories from animal source foods. However, it is also estimated that agricultural production globally will have to roughly double by 2050 in order to keep up with



 $\textit{Figure 1:} Absolute \ percentage \ increase \ in \ risk \ of \ zinc \ deficiency \ in \ response \ to \ elevated \ atmospheric \ [\text{CO}_2]$

increased demand,²³ and the combination of water scarcity, arable land degradation, and climate change represent very significant obstacles to such increases in production.²⁴ Because of this complexity, we believe the simplest approach is to model diets that are unchanged with respect to calories and composition, an achievement that many would consider optimistic in the face of rapidly changing environmental conditions.

We have also made no attempt to account for population growth in our analysis. The human population is expected to rise to between 9 and 10 billion by 2050,25 but we have used 2010 estimates of population size for our analysis. This means that our estimates of individuals likely to be placed at risk of zinc deficiency are almost certainly a considerable underestimate. A simple scaling of population growth to the effect we have measured would lead us to conclude that, in fact, 187 million people (using 9.5 billion as an estimate of the 2050 global population) are likely to become newly zinc deficient as a result of increased [CO₂]. And the fact that most of this population growth is expected to occur in the regions that are disproportionately affected by the nutritional consequences of rising [CO2] suggests that even this number is likely to be an underestimate. However, to maintain the most transparent analysis possible with the fewest assumptions, we have not attempted to project these demographic changes but believe that our results are a conservative estimate.

One assumption we do make for this study is that effects of elevated [CO₂] on crop nutrients that have been quantified in developed country settings for a subset of crops and cultivars consumed globally can be generalised to estimate nutrient intakes around the world. Of course, to be certain of the nutritional effects of elevated [CO₂] on the global population we would need to conduct FACE experiments for every consumed cultivar of every food crop in every country—an undertaking that is not feasible. But we are reassured that having found a very

similar pattern of effects across 41 different cultivars of six different food crops grown on three continents in seven locations over 10 years under vastly different growing conditions, ¹⁰ that these nutrient changes are a robust finding and are likely to be similar across the different growing conditions around the world. This assumption was also recently supported by a broad meta-analysis showing similar changes in the nutrient content of a diverse number of plants across many plant tissues and many locations. ²⁶

An additional conservative assumption embedded in this analysis is that food availability in populations around the world is in proportion to physiological requirements. Children younger than 5 years and women (especially during pregnancy) are likely to be at increased risk of zinc deficiency owing to increased nutrient requirements. The assumed optimal distribution of foods is unlikely to be met in most settings, but in the absence of global data on food distributions an assumption must be made, and this assumption is the most conservative approach. Less optimal food distributions would lead to increased effects of elevated [CO₂] on risk of zinc deficiency.

Finally, we have assumed that there is no change in the zinc content of animal source foods. There is clear evidence that most plants, not just food crops, have lower concentrations of zinc when grown at elevated [CO₃]. Meta-analyses of plants that include many different tissues from a variety of grasses, trees, and shrubs show consistent reductions in zinc content,26 making it likely that animal forage would have reduced zinc content in a world experiencing higher atmospheric [CO₃]. However, there are no data available on how these changes in the nutrient content of forage might alter the concentrations of zinc in animal source foods such as meat, milk, or eggs. Until such data are available, we can only assume no change in nutrient concentrations, but this, too, is likely to lead to underestimates of the impact of rising [CO₃] on risk of zinc deficiency.

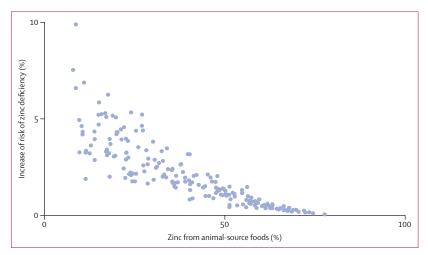


Figure 2: Correlation between proportion of dietary zinc received from animal-source foods and risk of new zinc deficiency in response to elevated [CO.]

Data are derived from analysis of food balance sheets. Percentage of dietary zinc availability from animal-source foods was calculated by dividing amount of per-capita daily bioavailable zinc from animal-source foods by total per-capita daily bioavailable zinc estimates. The percentage increase in risk of zinc deficiency was calculated as described in the Methods section of this manuscript. Zinc content in animal-source foods is assumed to remain unchanged.

The effect we have identified highlights an issue of social justice. Wealthier people are associated with higher CO₂ emissions,²⁷ whereas the people who are most vulnerable to the nutritional effects of rising [CO₂] are those who receive the smallest proportion of their dietary zinc from animal source foods (figure 2). These tend to be the poorest people within a country or region. The wealthy world's CO₂ emissions are putting the poor in harm's way.

By modelling national data for 188 countries, we identify populations who are at highest risk of increased zinc deficiency as a consequence of rising [CO₂]. These populations could be the target of interventions designed to address this risk. Such interventions might include zinc supplementation, fortification of staple foods with additional zinc, the application of zinc-containing fertilisers to crops, and the development and introduction of biofortified crop strains such as rice and wheat. Earlier work has also shown that, at least for rice, different cultivars of a crop show different levels of sensitivity to the [CO₂] effect on zinc content which could provide an opportunity for breeding crop cultivars with lower nutritional sensitivity to rising [CO₂].¹⁰

Anthropogenic change to Earth's natural systems will affect human health in multiple ways through pathways that are often quite complex.²⁸ Here we describe one such pathway that would have been challenging to anticipate in advance of the experimental data. We suspect that there will be others as human transformation of natural systems becomes increasingly profound and pervasive.

Contributors

SSM designed the study. KRW and IK led the data analysis. AZ and JS provided statistical support. All authors contributed to data interpretation and the writing of the article.

Declaration of interests

We declare no competing interests.

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