Hidden shift of the ionome of plants exposed to elevated CO_2 depletes minerals at the base of human nutrition

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Competing interest:

The author declares that no competing interests exist.

Abstract

Mineral malnutrition stemming from undiversified plant-based diets is a top global challenge. In C_3 plants (e.g. rice, wheat), elevated concentrations of atmospheric carbon dioxide (eCO_2) reduce protein and nitrogen concentrations, and can increase the total nonstructural carbohydrates (TNC; mainly starch, sugars). However, contradictory findings have obscured the effect of eCO_2 on the ionome – the mineral and trace-element composition – of plants. Consequently, CO_2-induced shifts in plant quality have been ignored in the estimation of the impact of global change on humans. This study shows that eCO_2 reduces the overall mineral concentrations (-8%, 95% confidence interval: -9.1 to -6.9, $p<0.00001$) and increases TNC:minerals > carbon:minerals in C_3 plants. The meta-analysis of 7,761 observations, including 2,264 observations at state of the art FACE centers, covers 130 species/cultivars. The attained statistical power reveals that the shift is systemic and global. Its potential to exacerbate the prevalence of 'hidden hunger' and obesity is discussed.

INTRODUCTION

Mankind's ultimate source of carbohydrates is atmospheric carbon dioxide (CO_2) converted by photosynthesis to sugars. The bulk of the terrestrial conversion of CO_2-to-carbohydrates is done by C_3 plants, which account for over three quarters of global primary production and for over 90% of Earth's plant species (Still et al. 2003). (*If not stated otherwise, hereafter, terms 'plant(s)' and 'crop(s)' refer to* C_3 *species*). When exposed to CO_2 concentrations twice the preindustrial level of ~280ppm, plants increase the synthesis of carbohydrates by 19-46% (Leakey et al. 2009). Currently, CO_2 concentrations are reaching 400 ppm – the highest level since the dawn of agriculture and likely to be the highest since the rise of modern humans (Siegenthaler et al. 2005). Within a single human lifespan, CO_2 levels are projected to reach 421-936ppm (IPCC 2013). Will rising CO_2 concentrations – one of the most certain and pervasive aspects of global climate change – alter the quality of crops and wild plants? Will the CO_2-induced stimulation of carbohydrate synthesis increase the carbohydrates-to-minerals ratio in crops? Can such shifts in crop quality affect human nutrition and health?

Elevated CO_2 effects on plant *quantity* (productivity and total biomass) have been extensively studied and show higher agricultural yields for crops, including wheat, rice, barley, and potato. But eCO_2 effects on plant *quality*, and possible cascading effects on human nutrition, have been largely ignored in the estimation of the impact of eCO_2 on humans. Notably, IPCC (2007, 2013) and AAAC Climate Science Panel (2014) include direct CO_2 effects (e.g. ocean acidification) in their climate change assessments but do not mention any CO_2 effects on crop or wild plant quality. However, it is unwarranted to assume that plants will balance the increased carbohydrate synthesis with other adjustments to their physiology to maintain the nutritional quality for their consumers in a state of unperturbed homeostasis. The stoichiometry – the relative ratios of chemical elements – in plants is plastic and, to a considerable degree, reflects their environment (Sterner & Elser 2002). However, detecting CO_2-induced shifts in plant quality is challenging for several reasons. First, plant quality involves multiple nutritional currencies, e.g. macronutrients (carbohydrates, protein and fat) and micronutrients (minerals, vitamins and phytonutrients). Assessing relative changes within and among multiple currencies requires significantly more effort and funding than measuring only plant quantity (e.g. yield). Second, plant quality, including the plant ionome – all the minerals and trace-elements found in a plant (Lahner et al. 2003; Salt et al.

2008) – is inherently variable; and measurement imprecisions further amplify the variability. For example, Stefan et al. (1997) report the accuracy test for 39 facilities that analyzed samples of the same plant tissues: the inter-laboratory variance was 6.5% for N, but twice as large for phosphorus (P) and calcium (Ca), and reached 130% for sodium (Na). Therefore, CO_2-induced changes in the plant ionome (the signal) can be easily lost amid highly variable data (the noise), especially when such data are limited and sample sizes are small. However, it is important to bear in mind that a low signal-to-noise ratio does *not* imply that the signal is practically insignificant, especially if it is global and sustained – a point revisited in the Discussion.

Elusive CO_2 effect on the plant ionome: contradictory findings

The first empirical evidence of lower mineral content in plants exposed to eCO_2 appeared over a quarter century ago (e.g. Porter & Grodzinski 1984; Peet et al. 1986; O'Neill et al. 1987). Physiological mechanisms responsible for the overall decline of mineral content in plants grown in eCO_2 have been proposed: the increased carbohydrate production combined with other eCO_2 effects such as reduced transpiration (Loladze 2002; McGrath & Lobell 2013). However, most of the experimental evidence showing mineral declines came from artificial facilities, mainly closed chambers and glasshouses, and the majority of the results were statistically nonsignificant. This led some research groups to challenge altogether the notion of lower mineral content in plants exposed to eCO_2 in field conditions. Such conditions are most accurately represented in Free-Air Carbon dioxide Enrichment (FACE) centers, which have been established in at least eleven countries.

In the grains of rice harvested at four FACE paddies in Japan, Lieffering et al. (2004) found no decline in any of the minerals but lower N content. The result disagreed with Seneweera & Conroy (1997), who were the first to report lower iron (Fe) and zinc (Zn) in grains of rice grown at eCO_2 and warned that altered rice quality can negatively affect developing countries. Lieffering et al. (2004), however, argued that the result of Seneweera & Conroy (1997) could be an artifact of growing rice in pots, which restrict rooting volumes. Furthermore, Lieffering et al. (2004) hypothesized that in FACE studies, which provide unrestricted rooting volumes, plants would increase uptake of all minerals to balance the increased carbohydrate production. This hypothesis, however, found no support in the FACE studies of Pang et al. (2005) and Yang et al. (2007) (carried out in China and latitudinally not very far from the study in Japan), who found that eCO_2 significantly altered the content of several minerals in rice grains.

The contradictory results coming from these studies on rice seem perplexing, especially in light of the very robust effect that eCO_2 has on N in plants. Elevated CO_2 reduces N concentrations by 10-18% systemically throughout all plant tissues: leaves, stems, roots, tubers, reproductive and edible parts, including seeds and grains (Cotrufo et al. 1998; Jablonski et al. 2002; Taub et al. 2008). If the increased carbohydrate production dilutes the nutrient content in plants, why does the dichotomy seem to exist between the responses of N and minerals to eCO_2? In addition to the carbohydrate dilution and reduced transpiration, eCO_2 can further lower N concentrations in plants by: 1) reducing concentrations of Rubisco – one of the most abundant proteins on Earth that comprises a sizable N-pool in plants (Drake et al. 1997), and 2) inhibiting nitrate assimilation (Bloom et al. 2010). Hence, it is reasonable to expect the effect of eCO_2 on N to be larger and, thus, easier to discern than its effect on most minerals. The stronger signal for N combined with the plentiful and less noisy data on N can help explain why by the end of last century the effect of eCO_2 on N had been already elucidated (Cotrufo et al. 1998), but its effect on minerals has remained elusive.

The obscure nature of the effect of eCO_2 on minerals becomes particularly apparent in the largest to date meta-analysis on the issue by Duval et al. (2011), who fragmented data from 56 eCO_2 studies into 67 cases. In 51 of the cases, the effect of eCO_2 on minerals was statistically nonsignificant, i.e. the 95% Confidence Interval (CI) for the effect size overlapped with 0. The remaining 16 cases were statistically significant but showed no pattern: e.g. Fe increased in grasses but decreased in trees, Zn increased in roots but decreased in stems, while in grains only sulfur (S) decreased. Duval et al. (2011) concluded: "A major finding of this synthesis is the lack of effect of CO_2 on crop grains nutrient concentration." This would imply laying to rest the hypothesis that eCO_2 consistently alters the plant ionome and would render mitigation efforts to combat declining crop mineral concentrations in the rising CO_2 world unnecessary. However, a close examination of the results of Duval et al. (2011) reveals that every statistically significant *increase* in mineral concentrations was obtained by bootstrapping a sample of size 2, 4 or 5 – a recipe for generating invalid 95% CIs. Ioannidis (2005) showed that false research findings, stemming from small sample sizes and associated low statistical power, are a persistent problem in biomedical sciences.

'Power failure' and the plant ionome

Calling the problem as 'power failure,' Button et al. (2013) emphasized that the probability of a research finding to reflect a true effect drops drastically if the statistical power is reduced from 0.80 (considered as appropriate) to low levels, e.g. < 0.30. Since the power of a statistical test drops nonlinearly with the effect size, a sample size that is sufficient for detecting a 15% effect, e.g. a decline in N content, can be inadequate for detecting a 5% effect, e.g. a decline in a mineral content. Considering that the standard deviation of mineral concentrations in a plant tissue can reach 25% (Duquesnay et al. 1998; Lahner et al. 2003), the 5% effect size standardized as Cohen's d is $d=5/25=0.2$. A t-test applied for $d=0.2$ to a sample size of 3-5 – a typical size used in eCO_2 studies – yields the power of 0.06-0.10 (Faul et al. 2007). (Unfortunately, *MetaWin* (Rosenberg et al. 2000), a statistical package routinely used in meta-analytic and other CO_2 studies in ecology, provides neither *a priori* nor *post-hoc* power estimates.) Such a small power not only raises the probability of obtaining a false negative to 90-94% but also increases the likelihood that a statistically significant result does not reflect a true effect (Button et al. 2013).

Answering questions with adequate power

As of this writing, researchers on four continents have generated data sufficient for answering with an adequate statistical power the following questions:

1) Does eCO_2 shift the plant ionome? If yes, what are the direction and magnitude of shifts for individual chemical elements? How does the effect of eCO_2 on N compares to its effect on minerals?

2) Do FACE studies differ principally from non-FACE studies in their effect on the plant ionome?

3) Do the plant ionomes in temperate and subtropical/tropical regions differ in their response to eCO_2?

4) Do the ionomes of photosynthetic tissues and edible parts differ in their response to eCO_2? How does eCO_2 affect the ionomes of various plant groups (woody/herbaceous, wild/crops, C_3/C_4) and grains of the world's top C_3 cereals – wheat, rice, and barley?

RESULTS

For brevity, hereafter 'minerals' refer to all elements except C, hydrogen (H), oxygen (O) and N. All results are for C_3 plants except when noted otherwise.

Power analysis

Plotting the effect sizes (with 95% CIs) for the 25 minerals against their respective statistical power reveals a clear pattern (Fig 1). In the very low power (< 0.20) region, the noise completely hides the CO_2-induced shift of the plant ionome. In the low power region (<0.40), the shift still remains obscure. However, as the statistical power increases, so does the likelihood that a statistically significant result reflects true effect and, consequently, the direction and the magnitude of the CO_2 effect on minerals become increasingly visible in the higher power regions of the plot.

To increase the likelihood of reporting true effects, *only results with the statistical power >.40 are reported* in this section. However, Table S1 lists all the results together with their p-values irrespective of the statistical power (e.g. results for chromium (Cr) or the bean ionome are not shown here due to low power, but are listed in Table S1).

CO_2 effect on individual elements

Across all the data, eCO_2 reduced concentrations of P, potassium (K), Ca, S, magnesium (Mg), Fe, Zn, and copper (Cu) by 6.5-10% ($p<0.0001$) as shown on Fig 2. Across all the 25 minerals, the mean change was (-8%, -9.1 to -6.9, $p<0.00001$). Only manganese (Mn) showed no significant change (Figs 2, 4, 5). It is not clear whether the oxygen-evolving complex (OEC) demands for Mn separate this mineral from the pattern of declines exhibited by other minerals. Among all the measured elements, only C increased (6%, 2.6 to 10.4, $p<0.01$). The sharp difference between the responses of C and minerals to eCO_2 is expected if a higher carbohydrate content drives the change in the plant ionome: for most plant tissues the dilution by carbohydrates lowers the content of minerals while having little effect on C (Loladze 2002). (This also suggests that the increase in C concentrations found here could be a result of a higher content of lipids or lignin – the two sizable plant compounds that are very C-rich (~60-75% C).)

The patterns of change within edible and foliar tissues are similar: N, P, Ca, Mg, Zn, and Cu declined significantly in both tissues (Figs 3, 4). Aside from Mn, only K showed no significant decline in the edible tissues (on Fig 1, it is visible as one of the only two black 95% CI in the 'High Power' region). In the foliar tissues, Mg declined the most (-12.3%, -16 to -8.7), which is congruent with the hypothesis of McGrath & Lobel (2013) that Mg should exhibit a larger decline in photosynthetic tissues because "chlorophyll requires a large fraction of total plant Mg, and chlorophyll concentration is reduced by growth in elevated CO_2." However, the 95% CIs for Mg and for most other minerals overlap. A richer data set would shed more light on the issue of Mg in photosynthetic tissues.

As expected, among all elements N declined the most (-15%, -17.8 to -13.1, $p<0.00001$) (Fig 2) matching very closely previous findings (Figs 3-6): the 17-19% decline in leaves found by Cotrufo et al. (1998) and the 14% decline in seeds found by Jablonski et al. (2002). Since the contents of N and protein correlate strongly in plant tissues, the lower N in edible tissues (Fig 4) corroborates the protein declines in crops found by Taub et al. (2008).

FACE vs. non-FACE studies

With respect to the types of experiments, the CO_2 effect on the plant ionome is surprisingly robust: in both the FACE and the non-FACE studies eCO_2 significantly reduced N, P, K, Ca, S, Mg, and Zn (Figs 5, 6). The high cost of CO_2 required for running free-air experiments led to a much lower average level of eCO_2 in the FACE studies (560ppm) cf. 732ppm in the non-FACE studies. It is plausible that the lower levels of CO_2 in the FACE studies contributed to a smaller overall mineral decline (-6.1%, -7.8 to -4.4) cf. (-8.7%, -10.1 to -7.4) for the non-FACE studies. In both the FACE and the non-FACE studies, the overall mineral concentrations declined significantly in herbaceous plants and crops, foliar and edible tissues, including wheat and rice (Figs 5, 6).

Geographical analysis

The CO_2 effect on the plant ionome appears to be pervasive throughout latitudes (Fig 7, 8). With the exception of three small centers (in Bangladesh, Japan, and UK), the mean mineral concentrations declined in every FACE and open top chamber (OTC) center on four continents. The mineral decline in the tropics and subtropics (-7.2%, -10.4 to -4.0, $p<0.0001$) is comparable to the decline in the temperate region (-6.4%, -7.9 to 5.0, $p<0.00001$). A finer regional fragmentation currently is not possible due to lack of data for Africa, South America, Russia and Canada. For many existing centers the data are limited and yield a low statistical power.

Germany leads the world in data generation with the largest number of *mean* observations of mineral concentrations (285), followed by the USA (218) (Fig 8). Though Australia generated only 30 *mean* observations, it stands out in the exceptional precision of some of its studies: the wheat experiments of Fernando et al. (2014) employed an unprecedented for FACE studies 48 replicates (for this reason, the study is easily identifiable on Fig 9).

CO_2 effect on various plant groups and tissues

Since eCO_2 does not stimulate carbohydrate production in C_4 plants to a degree that it does in C_3 plants, one would expect a milder CO_2 effect on minerals for C_4 plants. Indeed, no significant effect was found on the ionome of C_4 plants (Fig 8). Note, however, that the very limited data on this plant group are insufficient for deducing the absence of the effect; rather, it is likely that the effect size < 5% for C_4 plants.

The CO_2 effect on the plant ionome shows its systemic character through the analysis of various plant groups and tissues (Figs 3, 4, 8). Elevated CO_2 reduced the overall mineral concentrations in crops (-7.2%, -8.6 to -5.6); wild (-9.7%, -11.6 to -7.8), herbaceous (-7.5%, -8.7 to -5.6) and woody (-9.6%, -12.1 to -7.6) plants; foliar (-9.2%, -10.8 to -7.6) and edible (-6.4%, -7.8 to -5.1) tissues, including grains (-7.2%, -8.6 to -5.6). The cereal specific declines in *grains* are as follows: wheat (-7.6%, -9.3 to -5.9), rice (-7.2%, -11.3 to -3.1) and barley (-6.9%, -10.5 to -3.2) (Fig 8). This is notable because wheat and rice provide over 40% of calories to humans.

DISCUSSION

The analysis of all the data shows that eCO_2 shifts the plant ionome toward lower mineral content; the mean change across all the 25 measured minerals is (-8%, -9.1 to -6.9) (Fig 2). This shift, however, is hidden from low-powered statistical tests (Fig 1). Attaining adequate meta-analytic power reveals that the shift is:

1) Empirically robust – evident in both artificial (chambers, greenhouses) and field (FACE) conditions (Figs 5 and 6);

2) Geographically pervasive – found in temperate and subtropical/tropical regions (Figs 7 and 8).

3) Systemic – affecting herbaceous and woody plants, crops and wild plants, photosynthetic and edible tissues, including wheat, rice, and barley grains (Figs 3, 4, 8).

Elevated CO_2 alters plant C:N:P:S stoichiometry

Not only does eCO_2 reduce the plant mineral content, but it also alters plant stoichiometry. Specifically, the effect of eCO_2 on N is nearly twice as large as its mean effect on minerals. The differential effect of eCO_2 on N (15%), P (9%) and S (9%) translates into a ~7% reduction in the plant N:P and N:S. In contrast to the lower N and mineral content, eCO_2 increased C content by 6% (Figs 2, 3, 5). It follows then that eCO_2 increases C:P and C:S by 16%, and C:N by 25% confirming the previous findings of 19–27% higher C:N in plants grown in eCO_2 (Poorter et al. 1997; Stiling & Cornelissen 2007; Robinson et al. 2012).

Data scarcity

The current dataset (available at Dryad depository) suffices to show the overall shift in the plant ionome. However, it would require much richer datasets to quantify differences among the shifts of various minerals and to assess shifts in the ionomes of individual species. Unfortunately, funding hurdles for analyzing fresh and archived samples at FACE centers have significantly delayed progress in this area. Only two CO_2 studies report selenium (Se) content (Högy et al. 2013; Högy et al. 2009), and none report data on tin (Sn), lithium (Li) and most other trace-elements. For many of the world's popular crops, pertinent data are non-existent or very limited, including (in the descending order of calories provided to the world's population, FAO 2013): maize (the top C_4 crop), soybeans (including oil), cassava, millet, beans, sweet potatoes, bananas, nuts, apples, yams, plantains, peas, grapes, rye, and oats.

The current data scarcity, however, should not detract our attention from what is likely to be the overarching physiological driver behind the shift in the plant ionome – the CO_2-induced increase in carbohydrate production and the resulting dilution by carbohydrates. Let us take a closer look at this nutritionally important issue.

TNC:protein and TNC:minerals respond strongly to elevated CO_2

Carbohydrates in plants can be divided into two types: total structural carbohydrates (TSC; e.g. cellulose or fiber) that human body cannot digest, and total non-structural carbohydrates (TNC), most of which – including starch and sugars (fructose, glucose, sucrose, and maltose) – is readily digestible and absorbed in the human gut. Hence, for humans, TNC carries the most of caloric and metabolic load of carbohydrates. Out of the two types of carbohydrates, eCO_2 affects stronger the latter, boosting TNC concentration by 10-45% (Stiling & Cornelissen 2007; Robinson et al. 2012). Furthermore, eCO_2 tends to lower protein in plant tissues (Taub et al. 2008). Hence, we can reason that eCO_2 should exacerbate the inverse relationship found between TNC and protein (Poorter & Villar 1997). Considering that TNC and protein are two out of the three primary macronutrients (with fats/lipids being the third), it becomes imperative to quantify changes in

TNC:protein when estimating the impact of altered plant quality on human nutrition in the rising CO_2 world.

Regrettably, TNC:protein is rarely reported by CO_2 studies; instead C:N is used as a yardstick for accessing changes in the plant quality. However, C:N poorly correlates with TNC:protein because protein is more C-rich than carbohydrates are (C content in protein is 52–55% cf. 40-45% in carbohydrates). Thus, a *higher* carbohydrate:protein results in a *lower* C content. This means that CO_2-induced changes in the nutritionally and metabolically important ratios – TNC:protein and TNC:minerals – can substantially exceed the respective changes in C:N. We can calculate changes in TNC:protein using reported changes in TNC and protein (see 'Formula for calculating percentage changes in TNC:protein and TNC:minerals' in Materials and methods). Table 1 compares CO_2-induced changes in C:N with respective changes in TNC:protein. It shows that eCO_2 can elevate TNC:protein up to five-fold higher than it does C:N.

How shifts in TNC:protein affect human nutrition is still unknown. New evidence, however, challenges "the notion that a calorie is a calorie from a metabolic perspective" by showing that changes in dietary carbohydrate:protein:fat ratios affect metabolism and weight gain in humans (Ebbeling et al. 2012). The new evidence supports an emerging view that while obesity is quantified as an imbalance between energy inputs and expenditures (Hall et al. 2011), it could also be a form of malnutrition (Wells 2013), where increased carbohydrate:protein (Simpson & Raubenheimer 2005) and excessive carbohydrate consumption (Taubes 2013) could be possible culprits.

Absolute CO_2 effect on TNC. Spoonful of sugars for everyone?

The baseline TNC content in plant tissues varies widely. In grains and tubers, it is very high, 50-85% of dry mass (DM). Therefore, in these tissues a percentage increase in TNC is arithmetically limited (e.g. a 60% increase is impossible). However, even a modest percentage increase in TNC-rich tissues can be nutritionally meaningful in absolute terms. For example, the FACE study of Porteaus et al. (2009) reports a 7-8% increase in starch concentrations in wheat grains, which translates to ~4g of additional starch per 100g DM. In contrast to grains and tubers, the baseline TNC level in photosynthetic tissues is small (usually < 25%), which makes large TNC increases possible. For example, Teng et al. (2006) reports that eCO_2 increased TNC by 76% in leaves of *Arabidopsis thaliana*. What is interesting here is that in absolute terms (per 100g DM) the ~5g TNC increase in *Arabidopsis thaliana* is comparable to the ~4g TNC increase in wheat grains.

More generally, CO_2 studies show that – irrespective of the baseline TNC content – eCO_2 tends to boost TNC by a few grams (1-8g) per 100g DM of plant tissue (Poorter et al. 1997; Keutgen & Chen 2001; Katny et al. 2005; Erbs et al. 2010; Azam et al. 2013). Note that such an infusion of carbohydrates into plant tissues, all else being equal, dilutes the content of all other nutrients by 1-7.4%. Let us compare the dilution with its pragmatic and easily graspable analog – adding a spoonful of sugar-and-starch mixture. Table 2 shows that the CO_2 effect on TNC:protein and TNC:minerals is stoichiometrically similar to the effect of adding a spoonful of carbohydrates to every 100g DM of plant tissue.

Clearly, adding a spoonful of sugar sporadically to one's diet is not a cause for concern. However, the inescapable pervasiveness of globally rising atmospheric CO_2 concentrations raises new questions: What are health consequences, if any, of diluting every 100g DM of raw plant products with a spoonful of starch-and-sugar mixture? What are the consequences if the dilution is not sporadic but unavoidable and lifelong? These questions are better left for nutritionists, but it is worth noting that WHO (2014) conditionally recommends that intake of free sugars not exceed 5% of total energy, which is equivalent to 5-8 teaspoons of sugar for a typical 2000-3000kcal/day diet.

Below, I shift focus on a direct consequence of the CO_2-induced increase in carbohydrate production – the mineral decline in plant tissues, and explore its potential effect on human nutrition.

Plant minerals and 'hidden hunger'

'Hidden hunger' stems from poorly diversified plant-based diets meeting caloric but not nutritional needs. It is currently the world's most widespread nutritional disorder (Kennedy et al. 2003; Welch & Graham 2005). It lowers the GDP of the most afflicted countries by 2-5% and is partly responsible for their Third World status (WHO 2002; Stein 2009). A paradoxical aspect of 'hidden hunger' is that the minuscule amount of minerals, which a human body requires, could be provided easily and inexpensively – at least in theory – to all people in need by fortifying foods with minerals. However, in practice, such required mineral levels do not reach large parts of the world's community. The case of iodine is illustrative: while iodized table salt nearly wiped out iodine deficiency in the industrialized world, a billion people still have no regular access to it, making iodine deficiency the leading cause of preventable brain damage, cretinism, and lower IQ in children (Welch & Graham 1999; WHO 2002). Hence, the reality of logistic, economic, and cultural hurdles for fortification leaves *the natural and bioavailable mineral content in food, and in plants in particular, to be the major, and sometimes the only, consistent mineral supply for a large part of mankind* (White & Broadley 2009; Bouis & Welch 2010). This supply, unfortunately, is suboptimal for human nutrition with some of the consequences outlined below.

Every third person in the world is at risk of inadequate Zn intake with its deficiency substantially contributing to stunting, compromised immunity, and child mortality (Brown et al. 2001; UNICEF 2009). Iron deficiency affects at least two billion people and is the leading cause of anemia that increases maternal mortality (WHO 2002; UNICEF 2009). Millions are Ca, Mg and Se deficient (Stein 2009; White & Broadley 2009), including some population segments of developed countries (Rayman 2007; Khokhar et al. 2012). Ironically, a person can be obese *and* mineral undernourished – the so called 'hunger-obesity paradox' (Scheier 2005), e.g. the many homeless in the US that rely on "cheap and energy-dense but low-nutrient" foods (Koh et al. 2012). With every third adult in the world being overweight or obese (Keats & Wiggins 2014), WHO ranks both mineral undernutrition and obesity among the top twenty global health risks (WHO 2002; Hill et al. 2003; Stein 2009). While the role of mineral deficiency in obesity is still unclear, intriguing links have been found between the lower blood serum concentrations of Ca, Cr, Fe, Mg, Mn, Se, Zn and increased body mass index (BMI), with most of the findings appearing in the last decade (Singh et al. 1998; Martin et al. 2006; Arnaud et al. 2007; García et al. 2009; Payahoo et al. 2013; Yerlikaya et al. 2013).

How can the CO_2-induced depletion of minerals in crops affect humans? I emphasize that the impact of CO_2-induced shifts in the quality of crops on human health is far from settled. The purpose of what follows is not to make definitive claims but to stimulate research into this important but unresolved issue.

Stoichiometric thought experiment

A randomized controlled trial for a human diet based exclusively (directly or indirectly) on plants grown in eCO_2 is unlikely and ethically questionable; and even if feasible, the trial might take years to generate results. In lieu of relevant data, we can employ a thought experiment. While such 'experiments' are usually reserved for physical sciences, any living system, notwithstanding its complexity, adheres to simple but irrefutable elemental mass balance, which can help us to elucidate plausible scenarios.

For simplicity, let us focus on one question: how can a 5% reduction in the plant mineral content affect human nutrition? Thus, we ignore other potential or likely CO_2 effects: e.g. higher agricultural yields; altered concentrations of lipids, vitamins, and polyphenols; substantially higher TNC:protein and TNC:minerals; differential C_3 and C_4 plant responses; changes in the phytate content that affects mineral bioavailability (Manoj-Kumar 2011); and multiplicative health effects of the concomitant declines of many minerals in the same tissue.

Suppose that starting tomorrow and without our knowledge, the baseline mineral content of all plants on Earth drops by 5%. A self-evident but easily overlooked mass-balance law tells us that neither thermal nor mechanical processing of raw plants enriches them with minerals (i.e. transmutations are impossible). Thus, the mineral decline in raw crops will follow into plant-based foods (except for a few food items that are fortified with certain minerals in some countries).

We can safely assume that the individuals, whose dietary intake of each essential mineral has exceeded the recommended dietary intake (RDI) by > 5%, will be unaffected by the depletion. This leaves us with the majority of the human population, whose diet is either at risk of deficiency or already deficient in a least one mineral (WHO 2002; Kennedy et al. 2003; Stein 2009). Though a human body can synthesize complex compounds (e.g. vitamins K and D, nonessential amino acids), the mass balance low implies that *no organism can synthesize any amount of any mineral*. Therefore, to compensate for the mineral deficit, an organism has to increase mineral intake (or, otherwise, endure the consequences of the deficit). Taking supplements or intentionally shifting one's diet toward mineral-rich foods, e.g. animal products, can eliminate the deficit. Such dietary changes, however, presuppose behavioral adjustments on the part of the individuals who are aware of their mineral deficiency and have both the means and motivation to address it. A simpler way to compensate for the mineral deficit is to *increase food intake,* whether consciously or not. (The notion of compensatory feeding is not entirely alien – herbivores do increase consumption by 14-16% when consuming plants grown in eCO_2; Stiling & Cornelissen 2007; Robinson et al. 2012).

For a calorie deficient person, eating 5% more (to be exact 5.26%, because $1.0526*(1-.05) \approx 1$) is likely to be beneficial. But for a calorie sufficient *but* mineral deficient person, eating 5% more could be detrimental. The dynamic mathematical model of human metabolism, which links weight changes to dietary and behavioral changes (Hall et al. 2011), can help to quantify the effect of a prolonged 5% increase in food intake. When parameterized with anthropometric data for an average moderately active American female [age 38, height 163cm, weight 76kg, BMI 28.6, energy intake 2431kcal/day (10171kJ)] (CIA 2013; Fryar et al. 2012), the model outputs a weight gain of 4.8kg over a three-year period, provided all other aspects of behavior and diet remain unchanged. For a male, the respective weight gain is 5.8kg. The results are congruent with Hill et al. (2003), who argued that a 4–5% difference in total daily energy intake, a mere 100 kcal/day, could be responsible for most weight gain in the population.

The above 'experiment' suggests that a systemic and sustained 5% mineral depletion in plants can be nutritionally significant. While the rise in the atmospheric CO_2 concentration is expected to be nearly uniform around the globe, its impact on crop quality might unequally affect the human population: from no detrimental effects for the well-nourished to exacerbation of 'hidden hunger' or potential weight gain for the calorie-sufficient but mineral-undernourished.

Has rising CO_2 already altered the plant ionome?

The rise in CO_2 levels over the last 18-30 years has already been implicated in the two effects that can influence the plant ionome: higher C assimilation and plant growth (Donohue et al. 2013), and lower transpiration (Keenan et al. 2013). Considering that over the last 250 years, the atmospheric CO_2 concentration has increased by 120ppm — an increase that is not far from the mean 184ppm enrichment in the FACE studies — it is plausible that plant quality has changed. Indeed, declines in mineral concentrations have been found in wild plants and in crop fruits, vegetables, and grains over 22-250 years (Penuelas & Matamala 1993; Duquesnay et al. 1998; Davis et al. 2004; Ekholm et al. 2007; Fan et al. 2008; Jonard et al. 2009). While the mineral declines in crops can be an unintended consequence of the Green Revolution that produced high-yield cultivars with altered mineral content (Davis et al. 2004; Fan et al. 2008), the reason for the mineral declines in wild plants cannot be attributed to it.

Can eCO_2 directly affect human health? Hersoug et al. (2012) proposed that rising CO_2 promotes weight gains and obesity in the human population directly (via breathing) by reducing the pH of blood and, consequently, increasing appetite and energy intake. Weight gain has been observed in wild mammals, lab animals, and humans over the last several decades (Klimentidis et al. 2011). However, it is not clear what role, if any, the rising CO_2 could have played either directly (breathing) or indirectly (altered plant quality). And disentangling the rising CO_2 effect from other plausible factors currently does not seem feasible due to scarce data. This brings us to the broader issue of detecting – amid high local noise – signals that are small in their magnitude but global in their scope.

Hidden shifts of global change

While some scientific areas (e.g. genomics, bioinformatics) have experienced a data deluge, many areas of global change, including the issue of shifting plant quality, have been hindered by chronic data scarcity. Fortunately, researchers worldwide have been steadily generating data on the effects of eCO_2 on the chemical composition of plants. It is their collective efforts that have made it possible to reveal the CO_2-induced shift in the plant ionome.

Human activities profoundly alter the biogeochemical cycle not only of C but also of N, P, and S – four elements central to all known life forms. It is plausible that other subtle global shifts in the physiology and functioning of organisms lurk amid the highly noisy data. The small magnitude of such shifts makes them hard to detect and easy to dismiss. But by virtue of being global and sustained, the shifts can be biologically potent.

Revealing hidden shifts requires plentiful data to attain sufficient statistical power. (For example, Rohde et al (2013) analyzed 14 million *mean* monthly local temperature records to uncover the 1.5 °C rise in the global average temperature since 1753 – undoubtedly an important but a very small change relative to the variations of tens of degrees in local temperature.) New data on the effects of eCO_2 on plant quality (e.g. minerals, TNC: protein, TNC:minerals, lipids, bioavailability of nutrients) can be generated very cost-efficiently by analyzing fresh and archived plant samples from FACE centers worldwide (directors of many centers are keen to share such samples, I.L. personal communication, 2006). With regard to minerals, the application of the high-throughput techniques of ionomics (Salt et al. 2008) can generate rich phenotypic data that can be linked with functional genomics. Such analyses will shed more light on changes in plant quality in the rising CO_2 world. Anticipating and assessing such changes will help not only in mitigating their effects but also in steering efforts to breed nutritionally richer crops for the improvement of human health worldwide.

MATERIALS AND METHODS

Search for data

I searched Google Scholar, Google, PubMed, the ISI Web of Science, AGRICOLA, and Scopus to find relevant articles with sensible combinations of two or more of the following search-words: elevated, rising, CO_2, carbon dioxide, ppm, FACE, effects, content, concentration, %, mg, dry matter, micronutrients, plant(s), crop(s), tree(s), C_3, C_4, foliar, leaves, grains, fruits, minerals, chemical elements, and names/symbols of various chemical elements (e.g. zinc/Zn). I found additional studies from references in the articles identified in the initial searches.

Study suitability and data selection criteria

Among all plant tissues for which mineral concentrations are reported in the literature, the most abundant data are on foliar tissues (leaves, needles, shoots), and - for herbaceous plants- on above ground parts. Hence, focusing on the foliar tissues and above ground parts allows one to maximize the number of *independent* observations of the effect of eCO_2 on each mineral. Although the data on edible parts of crops are scarcer, a dataset on crop edible tissues was compiled due to their direct relevance for human nutrition.

The following objective and uniform criteria were applied for deciding which studies to include into the dataset: 1) a study grew plants at two or more CO_2 levels, 2) a study directly measured the content of one or more minerals in foliar or edible plant tissues at low (ambient) and high (elevated) CO_2 levels, and 3) a study reported either absolute concentrations at each treatment or relative change/lack thereof in the concentrations for each mineral between treatments. Studies that indirectly deduced mineral concentrations, reported data on N but not on any mineral, exposed only a part (e.g. a branch) of the plant, used super-elevated or uncontrolled CO_2 levels were not included. Table 3 lists all the studies together with their respective species/cultivars and CO_2 enrichment levels (the dataset with all the details is deposited at Dryad). When a study reported the low CO_2 level as 'ambient' with no specific numerical values, then I used the Keeling curve to approximate the ambient CO_2 level for the year the study was carried out.

The following data-inclusion rules were applied to the studies with multiple co-dependent datasets for the foliar dataset: 1) the lowest and the highest CO_2 levels for studies with multiple CO_2 levels, 2) the control and single-factor CO_2 for studies with environmental co-factors (e.g. observations from combined eCO_2 and ozone experiments were excluded), 3) the highest nutrient regime when the control could not be identified in a study with multiple nutrient co-factors, 4) the last point, i.e. the longest exposure to ambient/eCO_2 for studies with time series, 5) the most mature needles/leaves for studies reporting foliar tissues of various ages. If, in rare instances, a publication reported three or more separate datasets for the same species or cultivar, the data were averaged prior to the inclusion into the foliar dataset. For the edible tissue dataset, the study inclusion rules were the same as for the foliar dataset with the following exception: due to relative scarcity of data for edible tissues, the data with co-factors were included in the dataset (e.g. observations from combined eCO_2 and ozone experiments were included). The "Additional info" column in the dataset specifies exactly what datasets were extracted from each study with multiple data sets.

The above publication-inclusion and data-inclusion rules allow treating each study as independent in the dataset. At no instance, potentially co-dependent observations (e.g. multiple observations of the same plant throughout a growing season or observations of various parts of the same plant) were included in either the foliar or the edible dataset as separate studies. I used GraphClick v.3.0 and PixelStick v.2.5 to digitize data presented in a graphical form, e.g. bar charts.

The foliar dataset reflects 4,733 observations of 25 chemical elements covering 110 species and cultivars. The edible tissues dataset reflects 3,028 observations of 23 elements covering 41 species and cultivars. The FACE studies reflect 2,264 observations of 24 elements covering 25 species and cultivars. The two datasets cover 125 C_3 and five C_4 species/cultivars.

Effect size measure

While the amount of statistical details provided in each study varies considerably, the following data were extractable from each study: 1) the relative change (or lack thereof) in the mean concentration between the low and the high CO_2 treatments: (E-A)/A, where A and E are the mean concentrations of an element at the low and the high CO_2 treatments respectively, 2) the sample size or the number of replicates (*n*).

Since a decrease in the concentration of a mineral is limited to 100%, but an increase in its concentration is theoretically unlimited, a standard technique was applied to reduce biases towards increases. Specifically, the natural log of the response ratio, i.e. $ln(E/A)$, was used as the effect size metric (e.g. Hedges et al. 1999; Jablonski et al. 2002; Taub et al. 2008). The response ratio, $r = E/A$, was calculated from the relative change as follows: $r = 1+(E-A)/A$. After performing statistical analyses, I converted all the results back from the log form to report them as ordinary percent changes.

Making results replicable

Published meta-analytic and biostatistical results need to be replicable and the process of replication needs to be made as easy as possible and clearly traceable to the original sources (Peng 2009). In this regard, I have made the following efforts to ease the replication (from the original sources) of each and every result presented here:

1) While copyright restrictions do not permit posting the original published data sources online, I will share, upon request, all the data sources in PDF form, where all the pertinent data are clearly marked for easy identification, thus removing any potential ambiguity about what data were extracted from each study.

2) The entire dataset for the foliar and the edible tissues is available at Dryad digital depository, www.datadryad.org, under DOI: 10.5061/dryad.6356f. The dataset is available as an Excel file (formatted for easy viewing) and as a "CSV" file; the latter is made-ready for analysis with open-source (R Core Team 2014) and commercial statistical packages (e.g. SPSS).

3) An executable R code is available at the above-mentioned depository to generate individual results. Assistance for replicating any result and figure presented in this study will be provided to any interested party.

Statistical Analysis

I performed all the analyses using R (R Core Team 2014), SPSS v. 21 (IBM, Armonk, NY, USA) and G*Power 3 (Faul et al. 2007). Meta-analytic studies often weight effect sizes by the reciprocal of their variance, which tends to give a greater weight to studies with greater precision. However, many eCO_2 studies do not report measures of variation in the data (standard error, standard deviation, or variance). In lieu of the measures of variance, studies can be weighted by the number of replicates (*n*) or, alternatively, each study can be assigned equal weight, i.e. unweighted method (Jablonski et al. 2002). I used both methods (weighted and unweighted) to calculate the means of effect sizes with 95% CIs and compared the results of both methods. Nearly in all instances, the difference between the weighted and the unweighted means was small and < the standard error of the unweighted mean. For example, across all the FACE studies, the overall mineral change was (-6.1%, -7.8 to -4.4) when unweighted cf. the (-6.5%, -8.0 to -5.1) when weighted. For the reason of close similarity between weighted and unweighted approaches, I used the simpler out of the two methods, i.e. the unweighted one, when reporting the results.

Since the distribution of effect sizes is not necessarily normal, I applied both parametric (*t*-test) and nonparametric (bootstrapping with 10,000 replacements) tests for calculating the 95% CI for the mean effect size and the statistical power. The latter was calculated for: 1) an absolute effect size of 5%, and 2) the probability of Type I error, $\alpha = 0.05$. If the variance of a small sample << the true population variance, then this leads to substantial overestimations of Cohen's *d* and the statistical power. To be conservative when estimating power for small samples (m<20), I used the *larger* of the sample variance or 0.047, which is the variance for the entire mineral dataset.

The results from the parametric and nonparametric tests were very close. For example, for Zn in edible tissues (sample size = 65), *t*-test yields (-11.4%, -14.0 to -8.7) and 0.91 power cf. (-11.4%, -13.9 to -8.7) and 0.92 power for the bootstrapping procedure. A close similarity between the results of *t*-test and nonparametric test is expected when sample size (*m*, the number of independent observations for each mineral) is > 30, which often was the case in this study. For reporting purposes, I used the 95% CI, power, and p-values generated by the nonparametric method, i.e. the bootstrapping procedure.

Testing for publication bias

To test for publication bias or 'the file drawer effect' in the dataset, I plotted effect sizes against corresponding sample sizes/replicates, *n*, to provide a simple visual evaluation of the distribution of effect sizes (Fig 9). The resulting cloud of points is funnel-shaped, narrowing toward larger sample sizes, and overall is symmetrical along the mean effect size. This indicates the absence of any significant publication bias (Egger et al. 1997).

Fragmenting the dataset into categories

Meta-analytic CO_2 studies often partition their datasets into various categories (e.g. plant group, plant tissue, fertilization or water regime). This is done to estimate effect sizes for each category. Such data fragmentation, however, is warranted only if the statistical power of the resulting test for each category is adequate. Otherwise, low power can lead to nonsignificant outcomes and Type II errors. As tempting as it can be to partition the current dataset into many categories and cases (e.g. Zn in fruits, Fe in tuber, Cu in annuals, multiple CO_2 levels), only by fragmenting the data into sufficiently large categories an adequate statistical power can be retained. Such categories include: foliar tissues, edible tissues, woody plants (trees and shrubs), herbaceous plants, FACE studies, non-FACE studies, crops, wild plants (all non-crops, including ornamental plants), C_3 plants, C_4 plants, rice, wheat, barley, and potato. Furthermore, I fragmented the data for C_3 plants, the foliar and the edible tissues, the non-FACE and the FACE studies into individual chemical elements and into individual common plant names (e.g. all rice cultivars grouped under 'rice'). For regional analysis, only OTC and FACE studies were used because they reflect local environment much more accurately than studies using complete-enclosures (e.g. closed chamber, glasshouse). If an OTC or FACE study did not report precise geographic coordinates, then the latitude and longitude of the nearby research facility or city was used (all coordinates in the dataset are in decimal units). Figs 1-7 include results with the statistical power >.40 for each element, country, region, plant tissue or category. Generally, power > 0.80 is considered acceptable (Cohen 1988). Unfortunately, such a level was achievable only for elements for which the data are most abundant and for the ionomes of some plant groups and species. Note that the power was calculated for a 5% effect size, while the true effect size is likely to be larger (~8%); therefore, the true power is likely to be higher than the calculated power for most results. All the results, irrespective of the statistical power, can be found in Table S1. Furthermore, Fig 1 shows the mean effect sizes (with their 95% CI) plotted against their respective statistical powers for all the minerals and all the plant groups/tissues.

Formula for calculating percentage changes in TNC:protein and TNC:minerals

If the concentration of substance X in a plant increases by $x\%$ *and concomitantly the concentration of substance Y decreases by* $y\%$ *in the plant, then the X-to-Y ratio of the plant (X:Y) increases by:*

$$\frac{x+y}{100-y}\cdot 100\% \qquad (1)$$

Proof: Let us denote the initial concentrations of substances *X* and *Y* in a plant as x_A and y_A, respectively. Suppose the *X* and *Y* content in the plant *changed* by $x\%$ and $-y\%$, respectively. Then the new *X* content in the plant, x_E, is

$$x_E = x_A \cdot (100 + x)\%$$

and the new *Y* content in the plant, y_E, is

$$y_E = y_A \cdot (100 - y)\%$$

The original *X:Y* = x_A / y_A, while the new *X:Y* = x_E / y_E. Since the percentage change in the *X:Y* equals to:

$$\frac{new-orginal}{original}\cdot 100\%,$$

substituting x_A/y_A and x_E/y_E for the original and the new, respectively, yields:

$$\frac{x_E/y_E - x_A/y_A}{x_A/y_A} = \frac{x_E/y_E}{x_A/y_A} - 1 = \frac{x_E \cdot y_A}{x_A \cdot y_E} - 1 = \frac{x_A(100+x)\% \cdot y_A}{x_A \cdot y_A(100-y)\%} - 1 = \frac{100+x}{100-y} - 1 = \frac{x+y}{100-y}.$$

An advantage of formula (1) is that it holds true irrespective of whether the decrease in *Y* is driven by some reason applicable only to Y or by the increase in *X*, i.e. dilution by X.

Acknowledgments

The author thanks George Kordzakhia, Nik Loladze and Marina Van for discussions, David Salt and four anonymous referees for comments, and Dmitri Logvinenko for providing access to library resources. The author acknowledges NSF rejections to support this research (proposals Nos. 0548181, 0644300, 0746795).

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Figure 1. Statistical power and the effect of CO_2 on the plant ionome.
The effect of elevated atmospheric CO_2 concentrations (eCO_2) on the mean concentration of minerals in plants plotted (with the respective 95% confidence intervals (CI)) against the power of statistical analysis. The figure reflects data on 25 minerals in edible and foliar tissues of 125 C_3 plant species and cultivars. The very low and the low power regions hide the direction and magnitude of the CO_2 effect (the probability is low that a statistically significant result reflects a true effect). As the statistical power increases, the true effect becomes progressively clearer: the systemic shift of the plant ionome.

Figure 2. The effect of CO_2 on individual chemical elements in plants. Change (%) in the mean concentration of chemical elements in plants grown in eCO_2 relative to those grown at ambient levels. Unless noted otherwise, all results in this and subsequent figures are for C_3 plants. Average ambient and elevated CO_2 levels across all the studies are 368ppm and 689ppm respectively. The results reflect the data from four continents on plants (foliar and edible tissues, FACE and non-FACE studies). Error bars represent the standard error of the mean (calculated using the number of mean observations for each element). The number of mean and total (with all the replicates) observations for each element is as follows: C(35/169), N(140/696), P(152/836), K(128/605), Ca(139/739), S(67/373), Mg(123/650), Fe(125/639), Zn(123/702), Cu(124/612) and Mn(101/493). An element is shown individually if the statistical power for a 5% effect size for the element is > 0.40. The 'ionome' bar reflects all the data on 25 minerals (all the elements in the dataset except of C and N). All the data are available at Dryad depository. Copies of all the original sources for the data are available upon request.

Figure 3. The effect of CO_2 on foliar tissues. Change (%) in the mean concentration of chemical elements in foliar tissues grown in eCO_2 relative to those grown at ambient levels. Average ambient and eCO_2 levels across all the foliar studies are 364ppm and 699ppm respectively. Error bars represent 95% CIs. The number of independent mean observations, *m*, for each element is shown with the respective statistical power. For each plant group, *m* equals the sum of mean observations over all the minerals (C and N are not included) for that group. Elements and plant groups for which the statistical power is >0.40 (for a 5% effect size) are shown.

Figure 4. The effect of CO_2 on edible tissues. Change (%) in the mean concentration of chemical elements in edible parts of crops grown in eCO_2 relative to those grown at ambient levels. Average ambient and elevated CO_2 levels across all the crop edible studies are 373ppm and 674ppm respectively. Other details are in the legends for Figs 2 and 3.

Figure 5. The effect of CO_2 in artificial enclosures. Change (%) in the mean concentration of chemical elements of plants grown in chambers, greenhouses, and other artificial enclosures under eCO_2 relative to those grown at ambient levels. Average ambient and eCO_2 levels across all the non-FACE studies are 365ppm and 732ppm respectively. Other details are in the legends for Figs 2 and 3.

Figure 6. The effect of CO_2 at FACE centers. Change (%) in the mean concentration of chemical elements of plants grown in Free-Air Carbon dioxide Enrichments (FACE) centers relative to those grown at ambient levels. Average ambient and eCO_2 levels across all the FACE studies are 376ppm and 560ppm respectively. Other details are in the legends for Figs 2 and 3.

Figure 7. The effect of CO_2 at various locations and latitudes. Locations of the FACE and Open Top Chamber (OTC) centers, which report concentrations of minerals in foliar or edible tissues, are shown as white dots inside colored circles. The area of a circle is proportional to the total number of observations (counting replicates) reported by the center. If the mean change is negative (decline in mineral content), the respective circle is blue; otherwise, it is red. The figure reflects data on 21 minerals in 57 plant species and cultivars. The shaded region (between 35 N and S latitudes) represents tropics and subtropics.

Figure 8. The systemic aspect of the CO_2 effect. Change (%) in the mean concentration of minerals in plants grown in eCO_2 relative to those grown at ambient levels. All the results in the figure reflect the combined data for the foliar and the edible tissues. The number of total *mean* observations for all the measured minerals across all the studies for each crop/plant group, experiment type, country or region is shown (*m*) with the respective statistical power. Country specific and regional results reflect all the FACE and Open Top Chamber (OTC) studies carried in any given country/region. The number of total observations of mineral concentrations (including all replicates, but not counting C and N) per country is as follows: Australia (926), China (193), Finland (144), Germany (908), and USA (1156). Other details are in the legends for Figs 2 and 3.

Figure 9. Testing for publication bias. A funnel plot of the effect size (the natural log of the response ratio) plotted against the number of replicates/sample sizes (*n*) for each study and each mineral in the dataset for C_3 plants. The plot provides a simple visual evaluation of the distribution of effect sizes. The blue line represents the mean effect size of eCO_2 on mineral concentrations: the decline of 8.39% (yielding the decline of 8.04% when back transferred from the log-form). The symmetrical funnel shape of the plot around the mean effect size indicates the publication bias in the dataset is insignificant (Egger et al. 1997).

Figure 1–source data 1. This table provides supportive data for Figures 1-8 and contains the outcomes of statistical analyses of various data subsets (see 'Materials and methods' section for details). All results, except one, are for C_3 plants. Means and 95% CIs are color-coded: statistically significant increases (red), statistically nonsignificant changes (black), and statistically significant decreases (blue). All results with the statistical power < 0.40 are shaded grey. Results for small subsets ($m < 7$) are included to illustrate the inaccuracy stemming from bootstrapping small samples. Note that

the same subset can appear multiple times in the table. For instance, only foliar non-FACE data are available for grasses. Hence, the grass data appears as 1) "grass", 2) "foliar, grass" and 3) "non-FACE, grass" subsets (95% CIs and power can slightly vary for each subset due to bootstrapping).

study/species	C:N	TNC:protein	Reference
Arabidopsis thaliana	25%	125%	Teng et al. (2006)
Bromus erectus	6%	26%	Roumet et al. (1999)*
Dactylis glomerata	17%	53%	Roumet et al. (1999)*
wheat grain (low N)	–10%	47%	Porteaus et al. (2009)
wheat grain (high N)	–18%	7%	Porteaus et al. (2009)
wheat grain	9%	6%	Högy et al. (2009)
27 C_3 species	28%	90%	Poorter et al. (1997)
meta-analysis	25%	54%	Robinson et al. (2012)
meta-analysis	27%	39%	Stiling & Cornelissen (2007)

*in lieu of protein, N content is used.

Table 1. Comparing the effects of CO2 on two plant quality indicators. CO2-induced changes (%) in C:N (a quality indicator often used in CO2 studies) and in TNC:protein (a rarely used but nutritionally important indicator) for wheat grains and foliar tissues of various plants. The results shows that in the same plant tissue, eCO2 can increase TNC:protein up to several-fold > C:N. Significant CO2-induced shifts in the ratio of major macronutrients are probable. This highlights the importance of measuring and reporting changes in TNC:protein for future CO2 studies.

Plant quality indicator	Effect of adding 5g of TNC	Effect of elevated CO_2
Grains & Tubers:		
TNC	2.6%	1-15%
TNC:protein	7%	6-47%
TNC:minerals	7%	6-28%
protein	–4.8%	–14% to -9%
minerals	–4.8%	–10% to -5 %
Foliar tissues:		
TNC	27%	15-75%
TNC:protein	33%	26-125%
TNC:minerals	33%	24-98%
protein	–4.8%	–19% to –14%
minerals	–4.8%	–12% to –5%

Table 2. Comparing the effect of CO_2 to the effect of adding ‘a spoonful of sugar’. Changes (%) in various plant quality indicators caused by: 1) Adding a teaspoon of TNC (~5g of starch-and-sugars mixture) per 100g of dry mass (DM) of plant tissue, and 2) growing plants in twice-ambient CO_2 atmosphere. Changes due to the addition of TNC are calculated assuming the baseline TNC content of 65% for grains & tubers, and 15% for foliar tissues. The C content is assumed to be ~42% in plant tissues and in TNC.

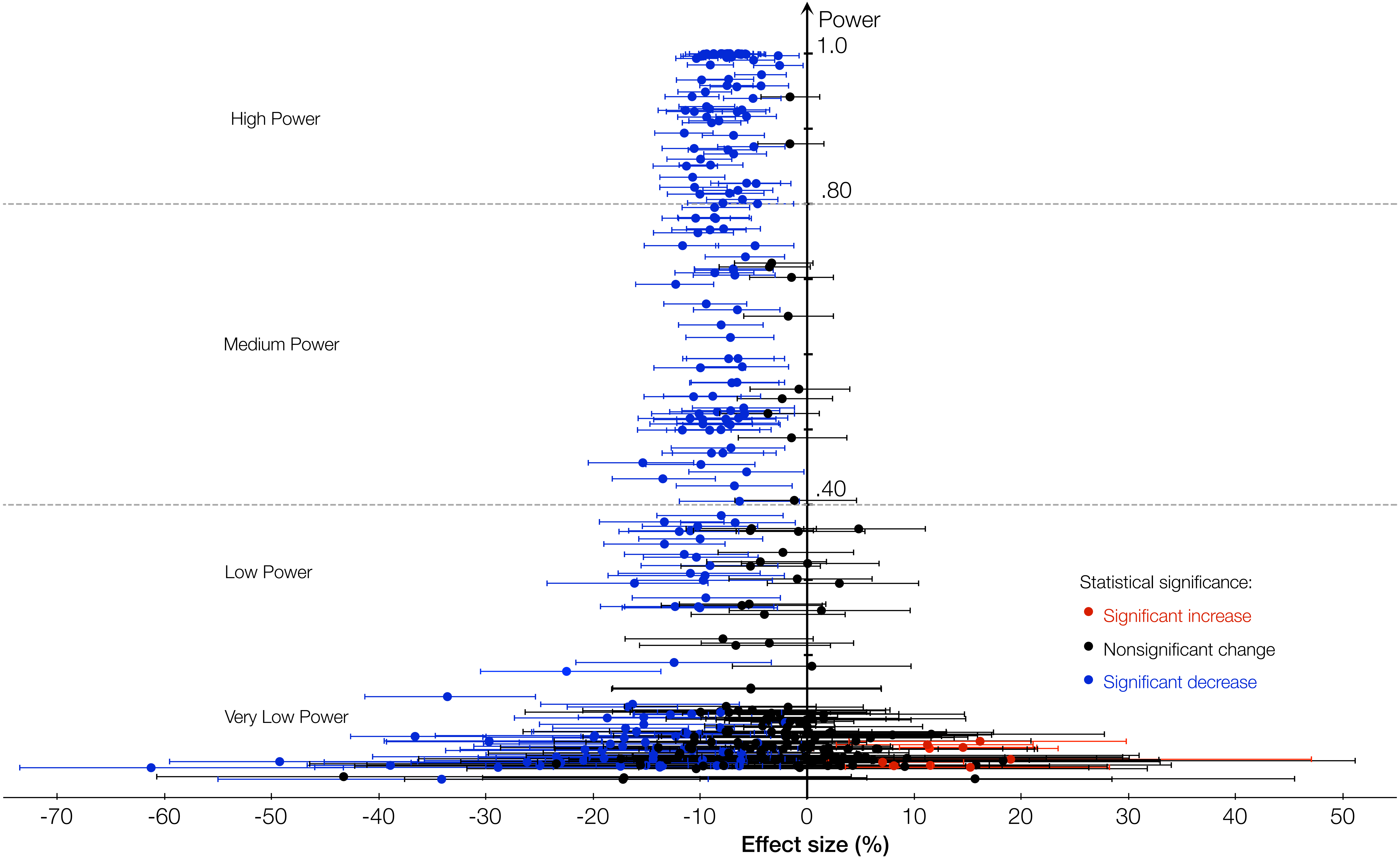
Species	Common name	Crop	+ CO2	Country	Reference
Acer pseudoplatanus	maple tree	No	260		Overdieck 1993
Acer rubrum	red maple tree	No	200	USA	Finzi et al 2001
Agrostis capillaris	grass	No	340	UK	Baxter et al 1994
Agrostis capillaris	grass	No	250		Newbery 1995
Alnus glutinosa	alder tree	No	350	UK	Temperton et al 2003
Alphitonia petriei	rainforest tree	No	440		Kanowski 2001
Ambrosia dumosa	shrub	No	180	USA	Housman et al 2012
Arabidopsis thaliana	thale cress	No	450		Niu et al 2013
Arabidopsis thaliana	thale cress	No	330		Teng et al 2006
Betula pendula 'Roth'	birch tree	No	349	Finland	Oksanen et al 2005
Bouteloua curtipendula	grass	No	230		Polley et al 2011
Bromus tectorum	cheatgrass	No	150		Blank et al 2006
Bromus tectorum	cheatgrass	No	150		Blank et al 2011
Calluna vulgaris	heather shrub	No	200		Woodin et al 1992
Cercis canadensis	red bud tree	No	200	USA	Finzi et al 2001
Chrysanthemum morifolium	chrysanth	No	325		Kuehny et al 1991
Cornus florida	dogwood tree	No	200	USA	Finzi et al 2001
Fagus sylvatica	beech tree	No	260		Overdieck 1993
Fagus sylvatica	beech tree	No	300		Rodenkirchen et al 2009
Festuca pratensis	meadow fescue	No	320		Overdieck 1993
Festuca vivipara	grass	No	340	UK	Baxter et al 1994
Flindersia brayleyana	rainforest tree	No	440		Kanowski 2001
Galactia elliottii	Elliott's milkpea	No	325	USA	Hungate et al 2004
Larix kaempferi	larch tree	No	335	Japan	Shinano et al 2007
Lepidium latifolium	peppergrass	No	339		Blank & Derner 2004
Liquidambar styraciflua	sweetgum tree	No	200	USA	Finzi et al 2001
Liquidambar styraciflua	sweetgum tree	No	167	USA	Johnson et al 2004
Liquidambar styraciflua	sweetgum tree	No	156-200	USA	Natali et al 2009
Liriodendron tulipifera	tulip tree	No	325		O'Neill et al 1987
Lolium perenne	grass	No	320		Overdieck 1993
Lolium perenne	grass	No	290	Germany	Schenk et al 1997
Lupinus albus	white lupin	No	550		Cambell & Sage 2002
Lycium pallidum	shrub	No	180	USA	Housman et al 2012
Nephrolepis exaltata	fern	No	650		Nowak et al 2002
Pelargonium x hortorum 'Maverick White'	geranium	No	330		Mishra et al 2011
Picea abies 'Karst.'	spruce tree	No	350		Pfirrmann et al 1996
Picea abies 'Karst.'	spruce tree	No	300		Rodenkirchen et al 2009
Picea abies 'Karst.'	spruce tree	No	300		Weigt et al 2011
Picea rubens	spruce tree	No	350		Shipley et al 1992
Pinus ponderosa	pine tree	No	346	USA	Walker et al 2000
Pinus ponderosa 'Laws.'	pine tree	No	350	USA	Johnson et al 1997
Pinus sylvestris	pine tree	No	331		Luomala et al 2005
Pinus sylvestris	pine tree	No	225	Finland	Utriainen et al 2000
Pinus taeda	loblolly pine tree	No	200	USA	Finzi et al 2001
Pinus taeda	pine tree	No	200	USA	Natali et al 2009

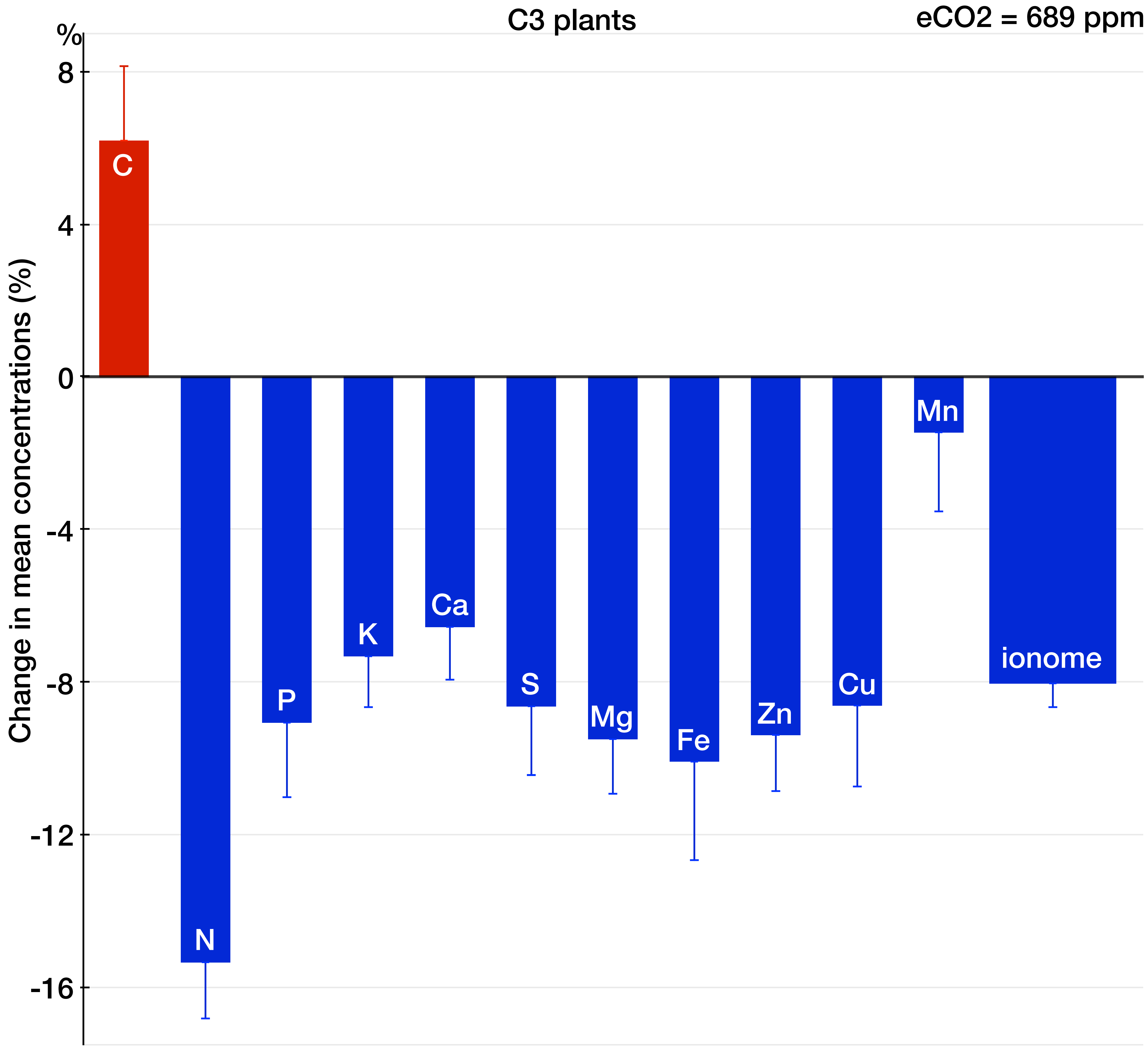
Poa alpina	grass	No	340	UK	Baxter et al 1994
Poa alpina	grass	No	340	UK	Baxter et al 1997
Pteridium aquilinum	fern	No	320		Zheng et al 2008
Pteridium revolutum	fern	No	320		Zheng et al 2008
Pteris vittata	fern	No	320		Zheng et al 2008
Quercus chapmanii	oak tree	No	350	USA	Natali et al 2009
Quercus geminata	oak tree	No	350	USA	Johnson et al 2003
Quercus geminata	oak tree	No	350	USA	Natali et al 2009
Quercus myrtifolia	oak tree	No	350	USA	Johnson et al 2003
Quercus myrtifolia	oak tree	No	350	USA	Natali et al 2009
Quercus suber	cork oak tree	No	350		Niinemets et al 1999
Schizachyrium scoparium	grass	No	230		Polley et al 2011
Sorghastrum nutans	grass	No	230		Polley et al 2011
Sporobolus kentrophyllus	grass	No	330		Wilsey et al 1994
Trifolium alexandrinum 'Pusa Jayant'	berseem clover	No	250	India	Pal et al 2004
Trifolium pratense	red clover	No	320		Overdieck 1993
Trifolium repens	white clover	No	320		Overdieck 1993
Trifolium repens	white clover	No	290	Germany	Schenk et al 1997
Trifolium repens	white clover	No	615		Tian et al 2013
Trifolium repens 'Regal'	white clover	No	330		Heagle et al 1993
Vallisneria spinulosa	macrophyte	No	610		Yan et al 2006
Apium graveolens	celery	Yes	670		Tremblay et al 1988
Brassica juncea 'Czern'	mustard	Yes	500	India	Singh et al 2013
Brassica napus 'Qinyou 8'	rapeseed	Yes	615		Tian et al 2013
Brassica napus 'Rongyou 10'	rapeseed	Yes	615		Tian et al 2013
Brassica napus 'Zhongyouza 12'	rapeseed	Yes	615		Tian et al 2013
Brassica napus 'Campino'	oilseed rape	Yes	106	Germany	Hogy et al 2010
Brassica rapa 'Grabe'	turnip	Yes	600		Azam et al 2013
Citrus aurantium	orange tree	Yes	300	USA	Penuelas et al 1997
Citrus madurensis	citrus tree	Yes	600		Keutgen & Chen 2001
Cucumis sativus	cucumber	Yes	650		Peet et al 1986
Daucus carota 'T-1-111'	carrot	Yes	600		Azam et al 2013
Fragaria x ananassa	strawberry	Yes	600		Keutgen et al 1997
Glycine max 'Merr.'	soybean	Yes	360	USA	Prior et al 2008
Glycine max 'Merr.'	soybean	Yes	200		Rodriguez et al 2011
Gossypium hirsutum 'Deltapine 77'	cotton	Yes	180	USA	Huluka et al 1994
Hordeum vulgare	barley	Yes	175	Germany	Erbs et 2010
Hordeum vulgare 'Alexis'	barley	Yes	334	Germany	Manderscheid 1995
Hordeum vulgare 'Arena'	barley	Yes	334	Germany	Manderscheid 1995
Hordeum vulgare 'Europa'	barley	Yes	400		Haase et al 2008
Hordeum vulgare 'Iranis'	barley	Yes	350		Perez-Lopez et al 2013
Hordeum vulgare 'Theresa'	barley	Yes	170	Germany	Wroblewitz et al 2013
Lactuca sativa 'BRM'	lettuce	Yes	308		Baslam et al 2012
Lactuca sativa 'Mantilla'	lettuce	Yes	350		Chagvardieff et al 1994
Lactuca sativa 'MV'	lettuce	Yes	308		Baslam et al 2012
Lactuca sativa 'Waldmann's Green'	lettuce	Yes	600		McKeehen et al 1996
Lycopersicon esculentum 'Astra'	tomato	Yes	600		Khan et al 2012
Lycopersicon esculentum 'Eureka'	tomato	Yes	600		Khan et al 2012

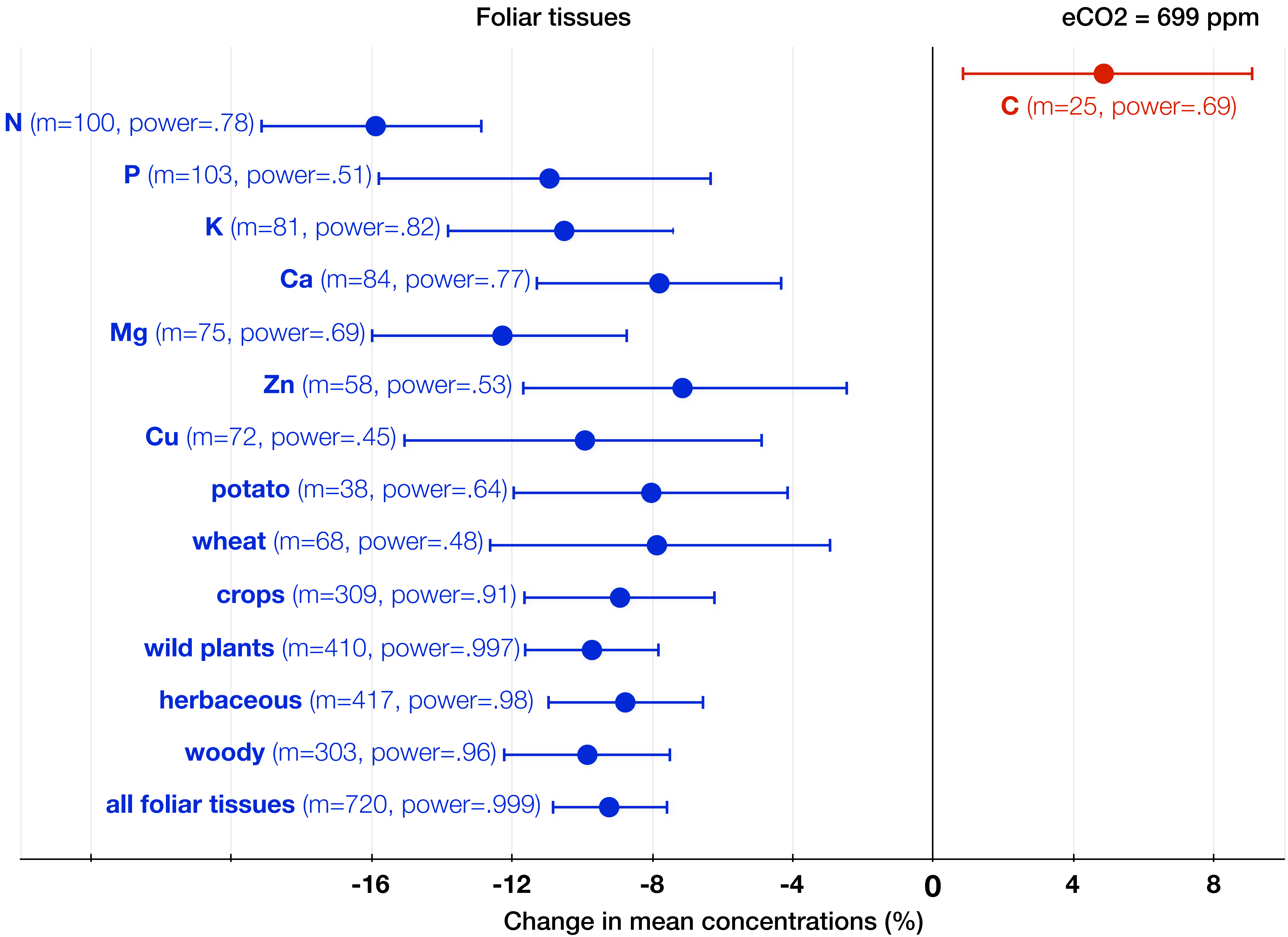
Lycopersicon esculentum 'Mill.'	tomato	Yes	360		Li et al 2007
Lycopersicon esculentum 'Zheza 809'	tomato	Yes	450		Jin et al 2009
Mangifera indica 'Kensington'	mango tree	Yes	350		Schaffer et al 1997
Mangifera indica 'Tommy Atkins'	mango tree	Yes	350		Schaffer et al 1997
Medicago sativa	alfalfa	Yes	615		Tian et al 2013
Medicago sativa 'Victor'	alfalfa	Yes	100	UK	Al-Rawahy et al 2013
Oryza sativa	rice	Yes	200	China	Pang et al 2005
Oryza sativa 'Akitakomachi'	rice	Yes	205-260	Japan	Lieffering et al 2004
Oryza sativa 'Akitakomachi'	rice	Yes	250	Japan	Yamakawa et al 2004
Oryza sativa 'BRRIdhan 39'	rice	Yes	210	Bangladesh	Razzaque et al 2009
Oryza sativa 'Gui Nnong Zhan'	rice	Yes	500		Li et al 2010
Oryza sativa 'IR 72'	rice	Yes	296	Philippines	Ziska et al 1997
Oryza sativa 'Japonica'	rice	Yes	200	China	Jia et al 2007
Oryza sativa 'Jarrah'	rice	Yes	350		Seneweera & Conroy 1997
Oryza sativa 'Khaskani'	rice	Yes	210	Bangladesh	Razzaque et al 2009
Oryza sativa 'Rong You 398'	rice	Yes	500		Li et al 2010
Oryza sativa 'Shakkorkhora'	rice	Yes	210	Bangladesh	Razzaque et al 2009
Oryza sativa 'Shan You 428'	rice	Yes	500		Li et al 2010
Oryza sativa 'Tian You 390'	rice	Yes	500		Li et al 2010
Oryza sativa 'Wu Xiang jing'	rice	Yes	200	China	Guo et al 2013
Oryza sativa 'Wuxiangjing 14'	rice	Yes	200	China	Ma et al 2007
Oryza sativa 'Wuxiangjing 14'	rice	Yes	200	China	Yang et al 2007
Oryza sativa 'Yin Jing Ruan Zhan'	rice	Yes	500		Li et al 2010
Oryza sativa 'Yue Za 889'	rice	Yes	500		Li et al 2010
Phaseolus vulgaris 'Contender'	bean	Yes	340		Mjwara et al 1996
Phaseolus vulgaris 'Seafarer'	bean	Yes	870		Porter & Grodzinski 1984
Raphanus sativus 'Mino'	radish	Yes	600		Azam et al 2013
Raphanus sativus 'Cherry Belle'	radish	Yes	380		Barnes & Pffirrman 1992
Raphanus sativus 'Giant White Globe'	radish	Yes	600		McKeehen et al 1996
Rumex patientia x R. Tianschanicus 'Rumex K-1'	buckwheat	Yes	615		Tian et al 2013
Secale cereale 'Wintergrazer-70'	rye	Yes	615		Tian et al 2013
Solanum lycopersicum '76R MYC+'	tomato	Yes	590		Cavagnaro et al 2007
Solanum lycopersicum 'rmc'	tomato	Yes	590		Cavagnaro et al 2007
Solanum tuberosum	potato	Yes	500		Cao & Tibbitts 1997
Solanum tuberosum 'Bintje'	potato	Yes	170	Germany	Hogy & Fangmeier 2009
Solanum tuberosum 'Bintje'	potato	Yes	278-281	Sweden	Piikki et al 2007
Solanum tuberosum 'Bintje'	potato	Yes	305-320	Europe	Fangmeier et al 2002
Solanum tuberosum 'Dark Red Norland'	potato	Yes	345	USA	Heagle et al 2003
Solanum tuberosum 'Superior'	potato	Yes	345	USA	Heagle et al 2003
Sorghum bicolor	sorghum	Yes	360	USA	Prior et al 2008
Spinacia oleracea	spinach	Yes	250	India	Jain 2007
Trigonella foenum-graecum	fenugreek	Yes	250	India	Jain 2007
Triticum aestivum	wheat	Yes	175	Germany	Erbs et 2010
Triticum aestivum 'Ningmai 9'	wheat	Yes	200	China	Ma et al 2007
Triticum aestivum 'Triso'	wheat	Yes	150	Germany	Hogy et al 2009
Triticum aestivum 'Triso'	wheat	Yes	150	Germany	Hogy et al 2013
Triticum aestivum 'Alcazar'	wheat	Yes	350		de la Puente et al 2000

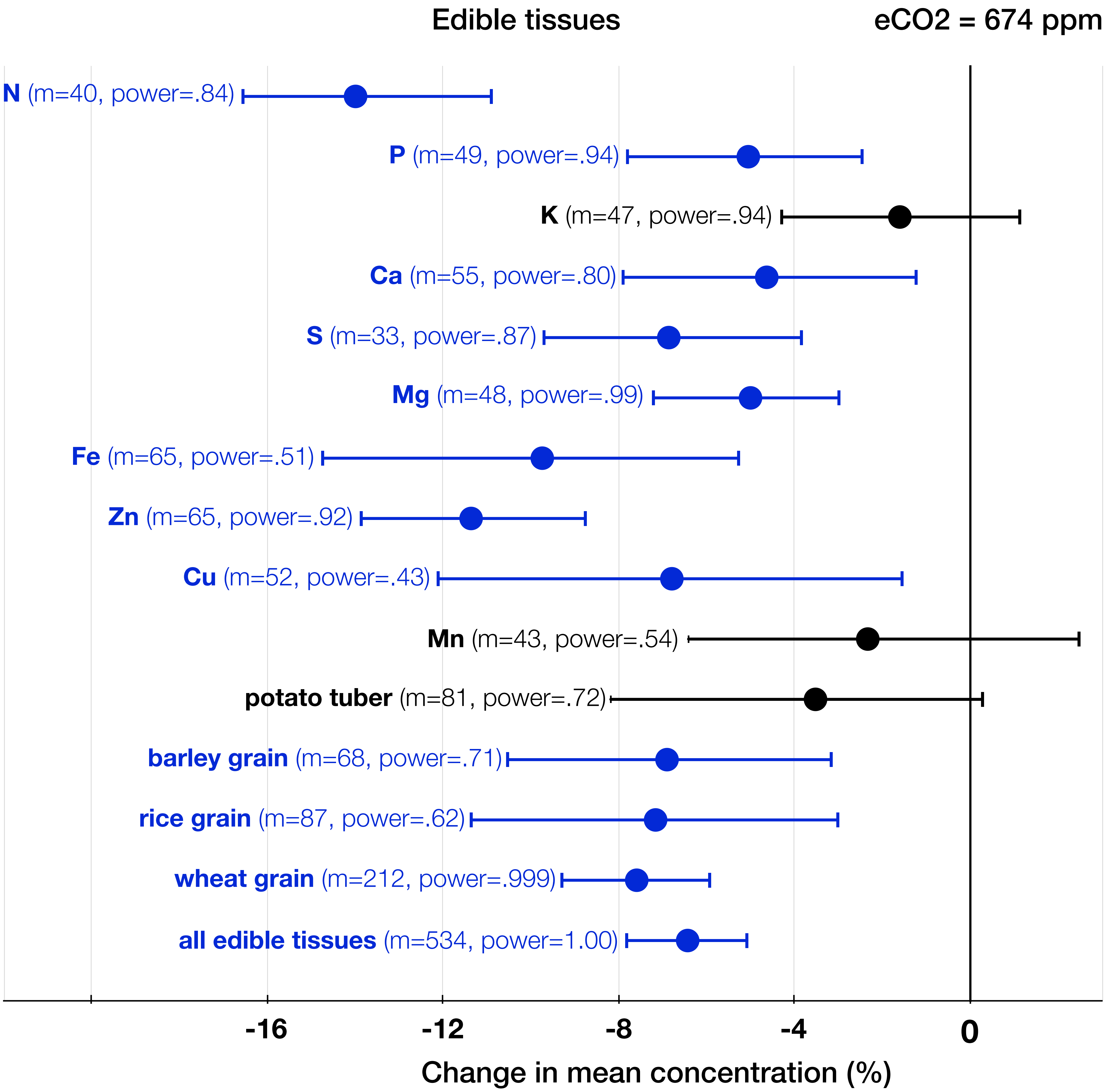
Triticum aestivum 'Batis'	wheat	Yes	170	Germany	Wroblewitz et al 2013
Triticum aestivum 'Dragon'	wheat	Yes	305320	Sweden	Pleijel & Danielsson 2009
Triticum aestivum 'HD-2285'	wheat	Yes	250	India	Pal et al 2003
Triticum aestivum 'Janz'	wheat	Yes	166	Australia	Fernando et al 2014
Triticum aestivum 'Jinnong 4'	wheat	Yes	615		Tian et al 2013
Triticum aestivum 'Minaret'	wheat	Yes	278	Germany	Fangmeier et al 1997
Triticum aestivum 'Minaret'	wheat	Yes	300	Europe	Fangmeier et al 1999
Triticum aestivum 'Rinconada'	wheat	Yes	350		de la Puente et al 2000
Triticum aestivum 'Star'	wheat	Yes	334	Germany	Manderscheid 1995
Triticum aestivum 'Turbo'	wheat	Yes	334	Germany	Manderscheid 1995
Triticum aestivum 'Turbo'	wheat	Yes	350		Wu et al 2004
Triticum aestivum 'Veery 10'	wheat	Yes	410		Carlisle et al 2012
Triticum aestivum 'Yangmai'	wheat	Yes	200	China	Guo et al 2013
Triticum aestivum 'Yitpi'	wheat	Yes	166	Australia	Fernando et al 2012a
Triticum aestivum 'Yitpi'	wheat	Yes	166	Australia	Fernando et al 2012b
Triticum aestivum 'Yitpi'	wheat	Yes	166	Australia	Fernando et al 2012c
Triticum aestivum 'Yitpi'	wheat	Yes	166	Australia	Fernando et al 2014

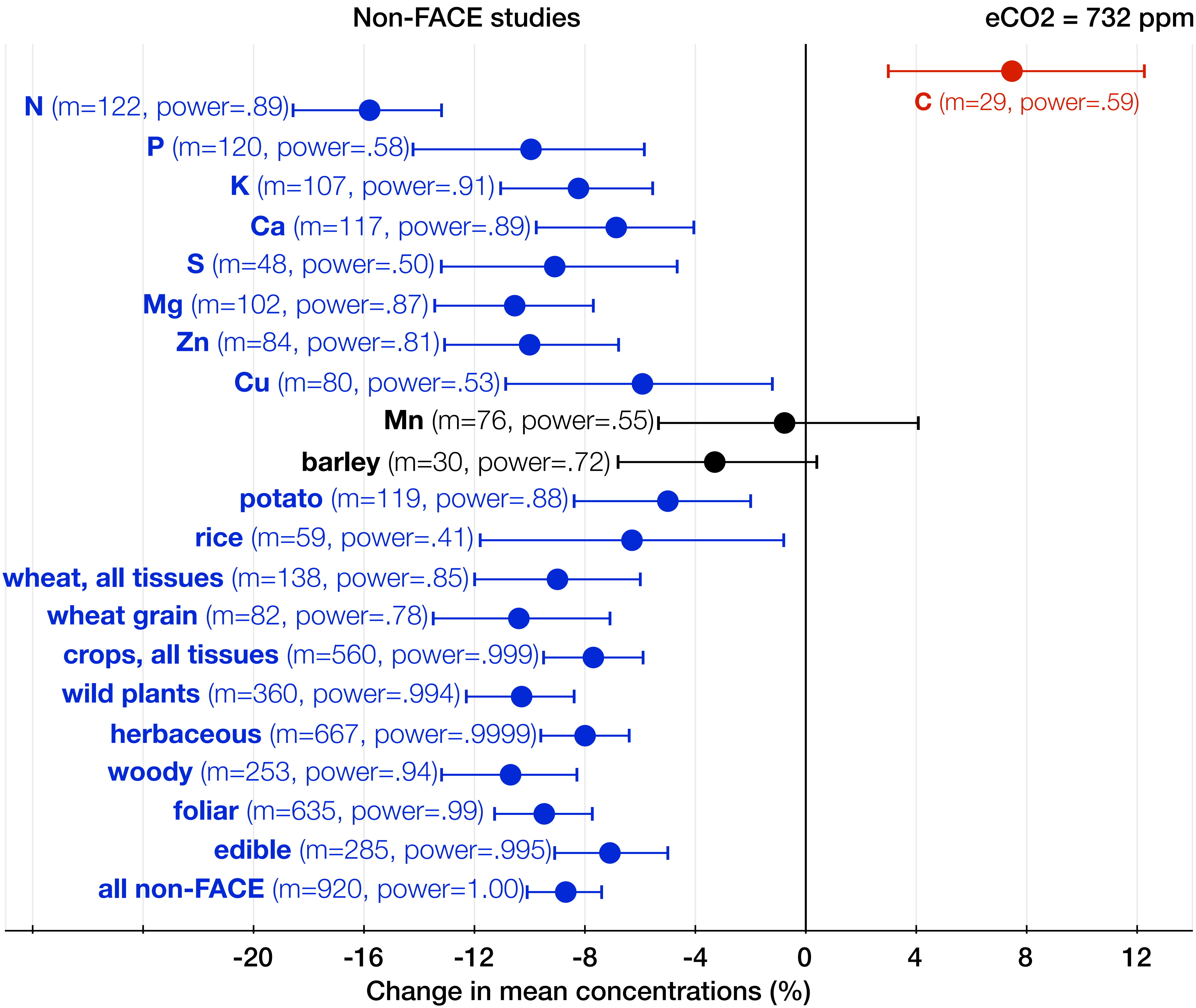
Table 3. Studies used in the meta-analysis of CO_2 effects on the plant ionome. The table provides species name, common name, the type of experimental set up, the level of CO_2 enrichment, and indicates whether the species is a crop. Countries are listed only for FACE and OTC type experiments with ‘Europe’ accounting for combined data from Belgium, Denmark, Finland, Germany, Sweden, and UK.

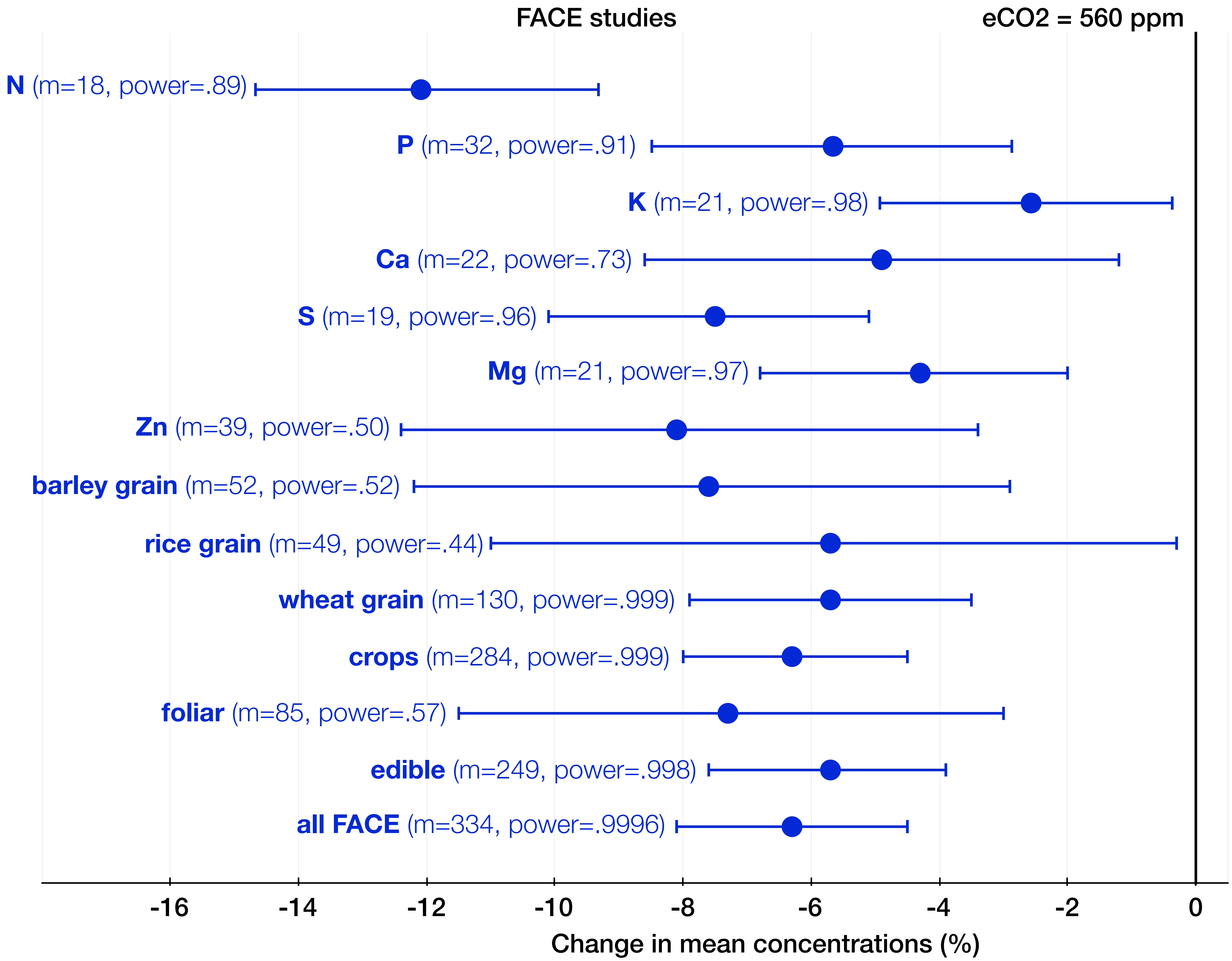

Power
1.0
.80
.40
High Power
Medium Power
Low Power
Very Low Power
Statistical significance:
● Significant increase
● Nonsignificant change
● Significant decrease
-70
-60
-50
-40
-30
-20
-10
0
10
20
30
40
50
Effect size (%)

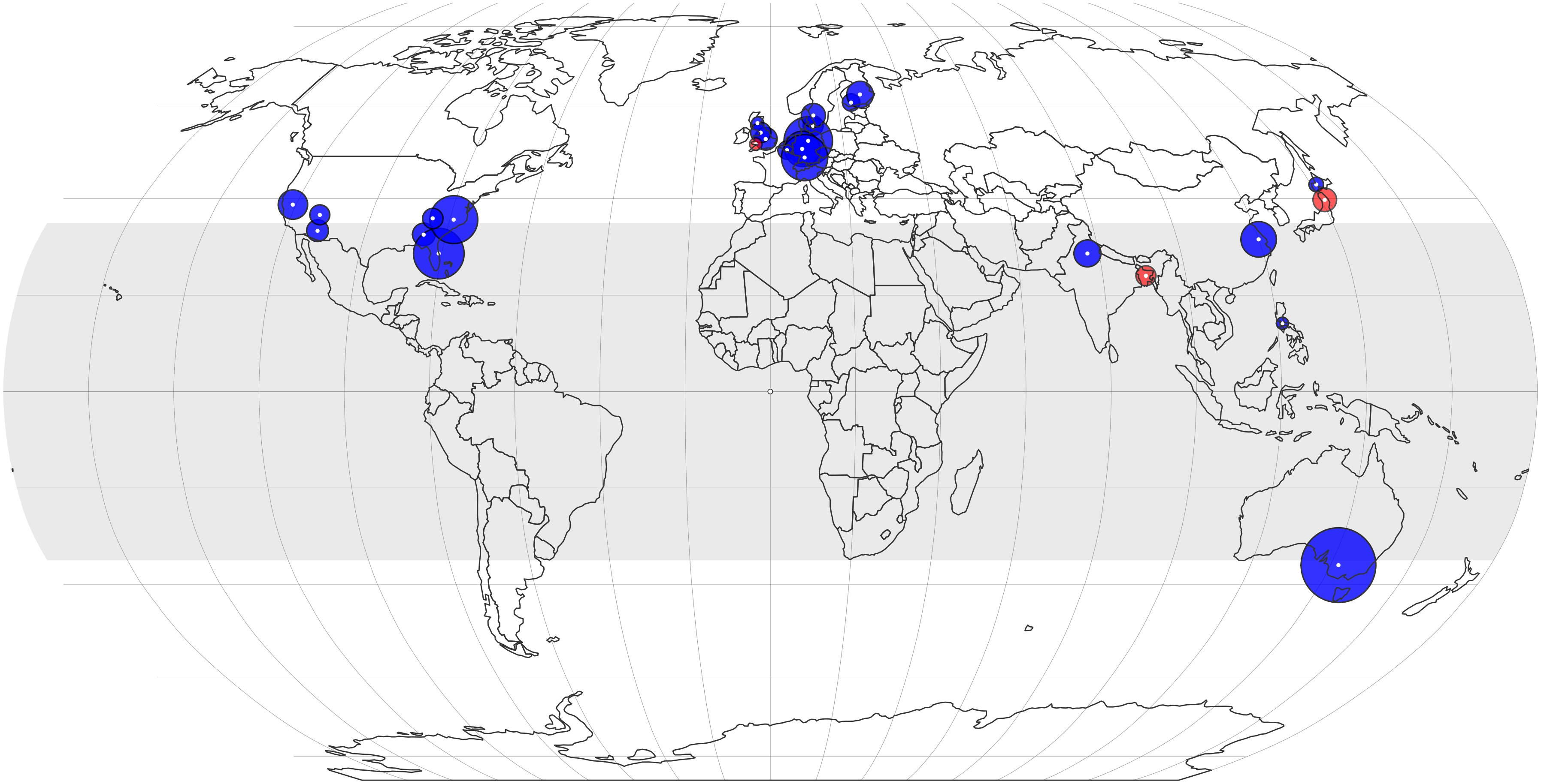

C3 plants
eCO2 = 689 ppm
%
8
4
0
-4
-8
-12
-16
Change in mean concentrations (%)
C
N
P
K
Ca
S
Mg
Fe
Zn
Cu
Mn
ionome

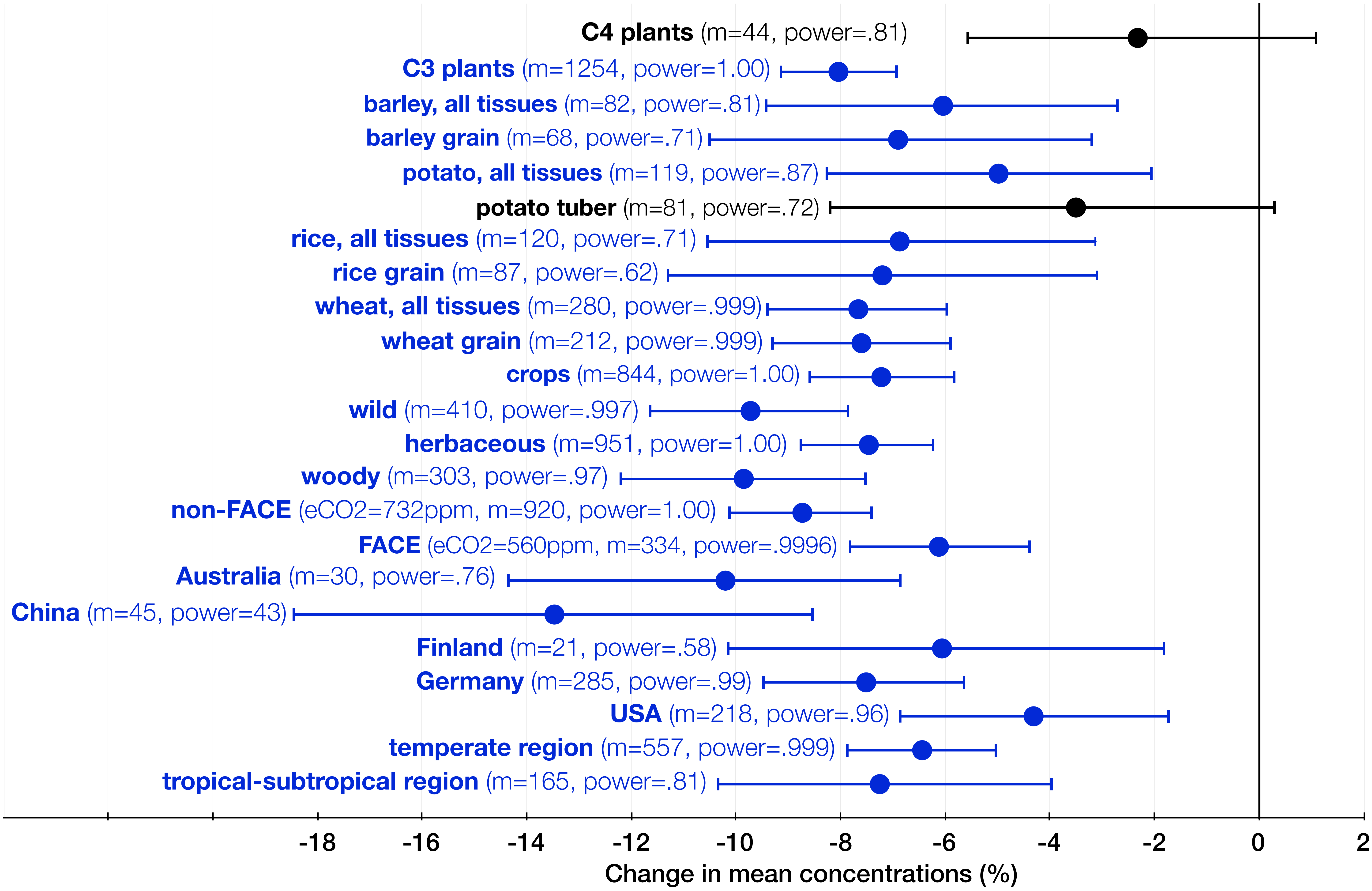

Foliar tissues
eCO2 = 699 ppm
C (m=25, power=.69)
N (m=100, power=.78)
P (m=103, power=.51)
K (m=81, power=.82)
Ca (m=84, power=.77)
Mg (m=75, power=.69)
Zn (m=58, power=.53)
Cu (m=72, power=.45)
potato (m=38, power=.64)
wheat (m=68, power=.48)
crops (m=309, power=.91)
wild plants (m=410, power=.997)
herbaceous (m=417, power=.98)
woody (m=303, power=.96)
all foliar tissues (m=720, power=.999)
-16
-12
-8
-4
0
4
8
Change in mean concentrations (%)

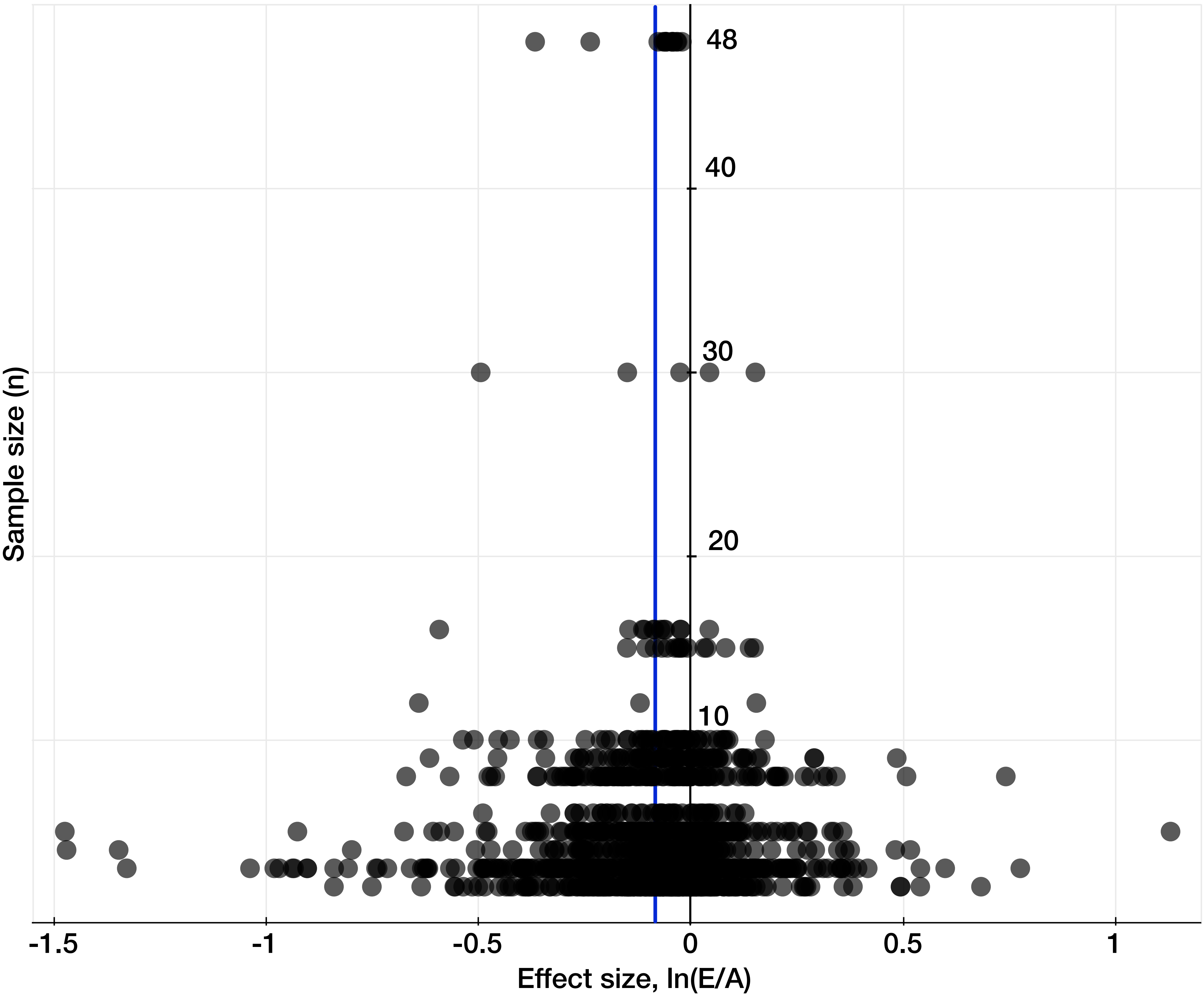

Edible tissues
eCO2 = 674 ppm
N (m=40, power=.84)
P (m=49, power=.94)
K (m=47, power=.94)
Ca (m=55, power=.80)
S (m=33, power=.87)
Mg (m=48, power=.99)
Fe (m=65, power=.51)
Zn (m=65, power=.92)
Cu (m=52, power=.43)
Mn (m=43, power=.54)
potato tuber (m=81, power=.72)
barley grain (m=68, power=.71)
rice grain (m=87, power=.62)
wheat grain (m=212, power=.999)
all edible tissues (m=534, power=1.00)
-16
-12
-8
-4
0
Change in mean concentration (%)


Non-FACE studies
eCO2 = 732 ppm
C (m=29, power=.59)
N (m=122, power=.89)
P (m=120, power=.58)
K (m=107, power=.91)
Ca (m=117, power=.89)
S (m=48, power=.50)
Mg (m=102, power=.87)
Zn (m=84, power=.81)
Cu (m=80, power=.53)
Mn (m=76, power=.55)
barley (m=30, power=.72)
potato (m=119, power=.88)
rice (m=59, power=.41)
wheat, all tissues (m=138, power=.85)
wheat grain (m=82, power=.78)
crops, all tissues (m=560, power=.999)
wild plants (m=360, power=.994)
herbaceous (m=667, power=.9999)
woody (m=253, power=.94)
foliar (m=635, power=.99)
edible (m=285, power=.995)
all non-FACE (m=920, power=1.00)
-20
-16
-12
-8
-4
0
4
8
12
Change in mean concentrations (%)


FACE studies
eCO2 = 560 ppm
N (m=18, power=.89)
P (m=32, power=.91)
K (m=21, power=.98)
Ca (m=22, power=.73)
S (m=19, power=.96)
Mg (m=21, power=.97)
Zn (m=39, power=.50)
barley grain (m=52, power=.52)
rice grain (m=49, power=.44)
wheat grain (m=130, power=.999)
crops (m=284, power=.999)
foliar (m=85, power=.57)
edible (m=249, power=.998)
all FACE (m=334, power=.9996)
-16
-14
-12
-10
-8
-6
-4
-2
0
Change in mean concentrations (%)




C4 plants (m=44, power=.81)
C3 plants (m=1254, power=1.00)
barley, all tissues (m=82, power=.81)
barley grain (m=68, power=.71)
potato, all tissues (m=119, power=.87)
potato tuber (m=81, power=.72)
rice, all tissues (m=120, power=.71)
rice grain (m=87, power=.62)
wheat, all tissues (m=280, power=.999)
wheat grain (m=212, power=.999)
crops (m=844, power=1.00)
wild (m=410, power=.997)
herbaceous (m=951, power=1.00)
woody (m=303, power=.97)
non-FACE (eCO2=732ppm, m=920, power=1.00)
FACE (eCO2=560ppm, m=334, power=.9996)
Australia (m=30, power=.76)
China (m=45, power=43)
Finland (m=21, power=.58)
Germany (m=285, power=.99)
USA (m=218, power=.96)
temperate region (m=557, power=.999)
tropical-subtropical region (m=165, power=.81)
-18
-16
-14
-12
-10
-8
-6
-4
-2
0
2
Change in mean concentrations (%)


48
40
30
20
10
Sample size (n)
-1.5
-1
-0.5
0
0.5
1
Effect size, ln(E/A)