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Global Food Security

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https://doi.org/10.1016/j.gfs.2022.100631

Global Food Security 33 (2022) 100631

Contents lists available at ScienceDirect

Global Food Security

journal homepage: www.elsevier.com/locate/gfs

Global analysis of nitrogen fertilization effects on grain zinc and iron of major cereal crops.

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ARTICLE INFO

Keywords:
N supply
Grain micronutrient density
Wheat
Rice
Maize

ABSTRACT

Human zinc (Zn) and iron (Fe) deficiencies can partly be alleviated by enhancing cereal concentrations of these micronutrients. Soil nitrogen (N) levels codetermine cereal grain yields and Zn and Fe nutrition of plants and grains. Grain Zn and Fe concentrations have been reported to be affected by both yield dilution and enhanced acquisition and grain allocation of Zn and Fe. A global meta-analysis of 100 publications concerning wheat, maize, and rice providing 785 records of Zn and 506 records of Fe allowed us to assess their relative importance and quantify the concentrations and bioavailability of Zn and Fe in major cereal grains over a wide range of N fertilization levels. Compared with the no N controls, N application significantly increased grain Zn and Fe concentrations in all crops except maize Zn. The increase in grain protein concentration correlated positively with the increases in Zn and Fe concentrations in all cereals except Zn in maize. In rice, the grain Zn and Fe concentration increase was independent of the rate of N applied. Grain concentrations of Zn and Fe in wheat and Fe in maize were positively correlated with N rate but were only higher than those in the controls above 40–60 kg N ha^{-1}. At lower N rates, the dilution effect was thus stronger than the enhancement effect. N supply had a larger effect on Zn and Fe concentrations in loamy textured soils or at lower soil available N and phosphorus (P), or higher soil organic matter and available Zn contents or with P and Zn fertilization, but the effect sizes differed among crops. Reductions in phytic acid concentration after N fertilization occurred in wheat, potentially improving micronutrient bioavailability. Thus, our findings indicate that N fertilization could be managed in ways that simultaneously support high grain yields and enhance nutritional quality for major cereals.

1. Introduction

Deficiencies of zinc (Zn) and iron (Fe), also known as “hidden hunger”, represent serious public health concerns and cause adverse impacts on social and economic development worldwide (Godecke et al., 2018). It has been estimated that 17% of the global population severely suffers from Zn malnutrition (Wessells and Brown, 2012). Approximately 800 million children under 5 years old and women of reproductive age worldwide show symptoms of anaemia (Stevens et al., 2013). Hidden hunger is tightly associated with inadequate dietary intake of micronutrients, particularly for populations that have a low dietary diversity and high consumption of cereal-based foods in developing countries and rural areas (Bouis et al., 2011). Cereal grains are high in caloric value but are regarded as poor sources of micronutrients as a consequence of their intrinsically low concentrations and low bioavailability due to abundant antinutrients such as phytic acid (PA), which chelates Zn and Fe and inhibits their absorption in the human body (Garcia-Oliveira et al., 2018; Gupta et al., 2015). Therefore, enhancing our understanding of what can contribute to improving grain Zn and Fe concentrations is needed to alleviate Zn and Fe malnutrition in affected regions.

Nitrogen (N) fertilization is critically important for guaranteeing crop productivity and global food security. Three major cereals, wheat, rice and maize, contribute up to 60% of the dietary calorie intake and account for 50% of the total fertilizer N use in the world (Tilman et al., 2002; Ladha et al., 2016). From 1961 to 2010, total production of major cereals increased approximately 3.4 times, but fertilizer N input increased 9.8 times, showing imbalances and inefficiencies of N use from regional to global scales (FAO, 2021; Ladha et al., 2016; Mueller et al.,

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https://doi.org/10.1016/j.gfs.2022.100631
Received 23 December 2021; Received in revised form 15 March 2022; Accepted 17 March 2022
Available online 30 March 2022

2014). In addition to its effect on yield, N status also affects grain Zn and Fe nutrition. Good N nutrition was found to positively affect micronutrient uptake, translocation, remobilization and thereby grain Zn and Fe concentrations (Khampuang et al., 2021; Zhang et al., 2020; Manzeke et al., 2020; Xue et al., 2019; Kutman et al., 2011). Conversely, it has also been reported that yield increases resulting from N supply dilute and decrease grain micronutrient concentrations (Miner et al., 2018; Gu et al., 2015; Gao et al., 2012). Changes in the concentrations of grain Zn and Fe rely upon whether micronutrient dilution caused by increased yields is offset by the N-dependent synergistic effects enhancing crop Zn and Fe uptake and grain allocation. Speciation and localization studies on cereal grains have shown that grain proteins constitute a physiological sink for Zn and Fe (Persson et al., 2016; Cakmak and Kutman, 2018). Therefore, the increase in grain protein concentration is plausibly a key parameter affecting Zn and Fe accumulation upon N application. Nevertheless, crop responses in previous studies varied strongly in both direction and magnitudes. Hence, there is a need for a quantitative summary of N fertilization effects on grain nutritional quality in terms of Zn and Fe concentrations and bioavailability on a global scale. Combining this knowledge with the known N effects on grain energy and protein yields, further optimization will be possible between serving human nutritional needs and mitigating damages of N use on ecosystems and human health, such as biodiversity loss, poor air and water quality, soil acidification, and increases in greenhouse gas emissions (Stevens, 2019).

Several factors have been reported to cause a variation in the response of grain Zn and Fe concentrations to fertilizer N supply, including the rate and timing of N fertilization, the production environment, and the supply of other fertilizers. For example, field experiments conducted on calcareous soils in northern China showed that the concentrations of Zn and Fe in wheat grain first increased and then remained stable with increasing N application rates (Xia et al., 2018; Chen et al., 2017; Shi et al., 2010). However, under comparable N application levels, an absence of effects or even adverse effects on wheat Zn and Fe were found in Canada, the USA, and Australia, probably due to differences in soil type, inherent nutrient status and climate conditions (Gao et al., 2012; Moraghan et al., 1999; Brennan, 1996). For instance, Gao and Grant (2011) found that the grain Zn concentration across N levels tested in two locations was generally lower in fine sandy loam soils than in clay loam soils, reflecting soil Zn availability. Soil pH, organic matter, and available N and phosphorus (P) contents have a significant influence on plant growth and might directly or indirectly affect the solubility and mobility of Zn and Fe in the soil and the capability of micronutrient uptake by roots (Moreno-Jiménez et al., 2019; Hamnér et al., 2017; Monasterio and Graham, 2000). Zn fertilization is a particularly crucial factor, given that the contribution of N supply to grain Zn accumulation greatly depends on Zn nutritional status (Kutman et al., 2010). P fertilization could also dramatically decrease the concentration and bioavailability of grain Zn as a result of the antagonistic interaction between P and Zn and increased grain PA concentrations (Zhang et al., 2021). Therefore, a comprehensive meta-analysis could help determine the role of environmental and management factors that moderate N effects on grain micronutrients and identify the key drivers.

The present work aims to quantitatively evaluate the effects of N fertilization on Zn and Fe nutrition (concentrations and bioavailability) in the grain of major cereals and to elucidate the underlying mechanisms and dominant influencing factors. We therefore conducted a meta-analysis based on the literature on grain Zn and Fe concentrations in wheat, maize, and rice and collected information on N fertilization rate and timing, soil properties, climate conditions, P application rate, and Zn fertilizer supply.

2. Materials and methods

2.1. Data compilation

Web of Science (WoS) all databases and Chinese National Knowledge Infrastructure (CNKI) databases were searched through the CAU library to identify relevant peer-reviewed journal articles published between January 1990 and December 2021. The search string was (*wheat* OR *maize* OR *corn* OR *rice*) AND (*N* OR *nitrogen*) AND (*zinc* OR iron OR *Zn* OR *Fe* OR *micronutrient** OR *trace element**). All publications matching this string were further scrutinized and retained in this study if (a) the study was conducted under field conditions (greenhouse and hydroponic experiments were excluded), (b) the study included both a control (without any N application) and one or more N application treatments, (c) field management practices other than N supply were the same for all treatments, (d) the study was carried out with at least three replicates per treatment, and (e) the grain concentrations of Zn and/or Fe were reported (grain Zn and Fe concentrations in the no N control below 5 mg kg^{-1} or, respectively higher than 60 mg kg^{-1} and 80 mg kg^{-1} were considered outliers and therefore excluded). If a paper reported multiple independent experiments (e.g., two experiments at separate locations, in different years, or multiple crops), each experiment was considered an individual study which may have multiple observations.

Based on the above criteria, our search yielded 52 (518 observations), 28 (134 observations), and 18 (133 observations) papers for grain Zn in wheat, maize, and rice, respectively, and 27 (248 observations), 20 (133 observations), and 16 (125 observations) papers for grain Fe, respectively. The studies span 23 countries across East and South Asia, Europe, North America, and Australia. However, few data were collected from Southeast Asia, Africa, Argentina, and parts of Russia, all of which are also important cereal cultivation areas. See Table S6 and Methods S1 for further details.

For each paper, the dry matter weights and the concentrations or uptake of N, P, Zn, and Fe in the grain, straw, and shoots of cereal crops, as well as the number of replicates and standard deviations (SD), were collected for each treatment either directly from tables or figures using GetData Graph Digitizer (version 2.25) (Table S1). The SD was either reported or calculated from the standard error (SE) and sample size (n) according to Equation (1).

$$SD = SE\sqrt{n}, \quad (1)$$

As potential moderator variables, environmental factors included climate zone (tropical, arid, temperate, cold), soil texture (sand, loam, clay), initial soil pH, organic matter, and available N, P, Zn and Fe contents. Fertilization factors included the rate and timing (sowing, vegetative and reproductive growth stage) of N application, P application rate, and Zn fertilizer application method (soil or foliar) (Table S2). For each study, the climate zone was obtained from Köppen-Geiger climate classification based on geographic coordinates (Peel et al., 2007). The soil texture was classified according to USDA (1999). When soil organic carbon content was reported, we converted it to soil organic matter by multiplying the value by 1.724 (Oldfield et al., 2019). The sum of the soil NO_3^--N and NH_4^+-N contents was referred to as soil available N. The reported Olsen-extractable P content in the soil was termed soil available P. The reported diethylene triamine pentaacetic acid (DTPA)-extractable Zn and Fe contents were termed soil available Zn and Fe. The grain protein concentration was calculated by multiplying the grain N concentration by 5.70, 6.25, and 5.95 for wheat, maize, and rice, respectively (Charmet et al., 2005; Oktem et al., 2010). The PA-P to total P ratio in the grain was assumed to be 0.7 (Raboy, 2007). The bioavailability of Zn and Fe was estimated by the molar ratios of PA to Zn and PA to Fe, respectively (Magallanes-López et al., 2017). The Zn or Fe harvest index referred to the proportion of grain Zn or Fe uptake to total shoot Zn or Fe uptake at maturity. The methods used to calculate the relative changes in the uptake and remobilization of Zn during the pre-anthesis or post-anthesis period in response to N application are given in Table S1.

2.2. Statistical analyses

The response ratio (RR) was used to assess the effect of N fertilization on the concentrations and uptake of Zn and Fe in the grain and straw in comparison with those of the no-N control. The natural logarithm of the RR (lnR) was used as the effect size, as shown in Equation (2) (Lipsey and Wilson, 2001):

$$\ln R_k = \ln\left(\overline{X}_{kt} / \overline{X}_{kc}\right) = \ln\left(\overline{X}_{kt}\right) - \ln\left(\overline{X}_{kc}\right) \quad (2)$$

where $\overline{X}_{kt}$ and $\overline{X}_{kc}$ are the mean values of the N treatment and of the control, respectively, for a given response variable X in each observation k. The variance (v) of ln R_k is estimated by Equation (3) as follows:

$$v_k = \frac{SD_{kt}^2}{\overline{X}_{kt}^2 \times n_{kt}} + \frac{SD_{kc}^2}{\overline{X}_{kc}^2 \times n_{kc}} \quad (3)$$

where SD_{kt} and SD_{kc} are the standard deviations of $\overline{X}_{kt}$ and $\overline{X}_{kc}$, respectively, and n_{kt} and n_{kc} are the number of replicates of $\overline{X}_{kt}$ and $\overline{X}_{kc}$, respectively. For studies in which the SD or SE was not reported, SD_{kt} and SD_{kt} were estimated by the "Bracken (1992)" approach using the *metagear* package for R(Lajeunesse, 2016). The total variance ($v_k^{'}$) for each observation k was the summation of within-study variance (v_k) and between-study variance (τ^2; Equation (4)). τ^2 was estimated by the restricted maximum likelihood (REML) method (Veroniki et al., 2016).

$$v_k^{'} = v_k + \tau^2 \quad (4)$$

The weighting factor w_k was calculated as the inverse of the pooled variance ($1/v_k^{'}$). The weighted effect size (ln $R^{'}$ (Equation (5)) and mean effect size ($\overline{\ln\ R^{'}}$ (Equation (6)) of all observations were then estimated as follows:

$$\ln R_k^{'} = w_k \times \ln R_k, \quad (5)$$

$$\overline{\ln\ R^{'}} = \sum_k \ln\ R_k^{'} \Big/ \sum_k w_k, \quad (6)$$

To facilitate understanding, the results are reported as percentage changes by back-transforming $\overline{\ln\ R^{'}}$ to unlogged ratios using Equation (7).

$$\left(e^{\overline{\ln\ RR^{'}}} - 1\right) \times 100\% \quad (7)$$

For all analyses, we used hierarchical models to account for nonindependence, as implemented in the package *metafor* version 2.4.0 (Viechtbauer, 2010) in R version 4.0.3 (R Core Team, 2020). 'Observation' was nested in 'paper' as a random effects structure in this model. Analyses were performed for all crops together and separately for wheat, maize, and rice.

First, we used a random effects model to test the significance of the mean effect with 95% confidence intervals (CIs). Effect sizes were considered to be significant at the level of $p < 0.05$ when their 95% CI did not include zero. The residual heterogeneity in this model for grain Zn ($Q = 6774.8$, $p < 0.0001$) and grain Fe ($Q = 2335.5$, $p < 0.0001$) was significant, so we further tried to explain it with moderator variables. Second, we used a mixed effects model to test the influences of categorical and continuous factors. In this model, the total heterogeneity (Q_T) of the effect size consisted of the explained variance by the moderator (Q_M) and residual error (Q_E). For the categorical factors, differences between subgroups were considered significant if one or more of the 95% CIs did not overlap one another. For the continuous factors, we reported the statistical results by p value. The N application rate was log-transformed to account for nonlinear relationships. Publication bias was assessed using Rosenthal's fail-safe number (N_{fs}) (Rosenthal, 1979).

3. Results

3.1. Overall effect sizes of cereal Zn and Fe nutrition

Compared with the no-N control, the Zn concentration in cereal grains in response to N application increased on average by 9.4% (95% CI: 5.5%–13.5%), and the differences between crops were not significant. The increase in grain Zn concentration was significant in wheat (11.8%, 95% CI: 6.8%–17.1%) and rice (12.7%, 95% CI: 2.5%–24.0%) but nonsignificant in maize (1.7%, 95% CI: −5.0%–8.9%). The grain concentration of Fe in all crops significantly increased in response to N supply on average by 12.8% (95% CI: 8.7%–17.1%) (Fig. 2A). Straw Fe concentration significantly increased in rice but decreased in maize. The other straw Zn and Fe concentrations showed no differences (Fig. 2B). The uptake of Zn and Fe in grain, straw, and shoot significantly increased in all crops (Fig. 2D, E, and F). The micronutrient harvest index (HI) significantly increased for Fe but not for Zn (Fig. 2C). Compared with threshold values, the calculated fail safe numbers for grain Zn and Fe concentrations were large enough to consider that the estimates were robust and reliable (Table S3).

Averaged across all crops, grain and straw dry matter weights significantly increased by 50.0% and 45.4%, respectively, and the N concentrations in grain and straw increased by 21.5% and 34.5%, respectively (Fig. S2).

3.2. Effects of N fertilization rate and timing

According to the mixed effects models, the effect sizes of grain concentrations of Zn and Fe in wheat and of Fe in maize increased with an increase in the N application rate ($p < 0.0001$). The effect sizes of wheat Zn, wheat Fe, and maize Fe were negative at lower N rates and then increased to 0 at approximately 50, 41, and 60 kg N ha^{-1}, respectively. Above these N rates, Zn and Fe concentrations increased compared with those of the control, and the increase was higher with higher N input (Fig. 3). The effect sizes of grain Zn concentrations in maize and rice and Fe concentrations in rice did not change significantly across N rates. Split applications of N during the vegetative and/or reproductive growth stage generally had greater effect sizes for Zn but similar effect sizes for Fe than single N application before sowing (Fig. 4). The effect size of wheat grain Fe was negatively related to the proportion of basal N rate to the total N rate ($p = 0.0003$; Table 1).

Only a limited subset of data allowed evaluation of the contribution of pre-anthesis uptake and post-anthesis remobilization to Zn and Fe accumulation in grains in response to different N levels. These analyses should therefore be considered indicative at best. For wheat (n = 44), N supply markedly increased the quantity and proportion of pre-anthesis Zn uptake by 200% and 23%, respectively. The share of grain Zn accumulation provided by Zn remobilization increased by 28%. For maize (n = 11), the N supply significantly increased pre-anthesis Zn uptake by 64%. No analysis was performed on rice Zn and cereal Fe because of insufficient data.

3.3. Relationships between grain protein concentrations and Zn or Fe concentrations

The increase in grain protein concentrations positively correlated with the increases in Zn and Fe concentrations upon N application in all cereal grains (except for Zn in maize, Fig. 6). A positive relationship between actual protein concentrations and Zn and Fe concentrations was only observed in wheat grains (Fig. 5).

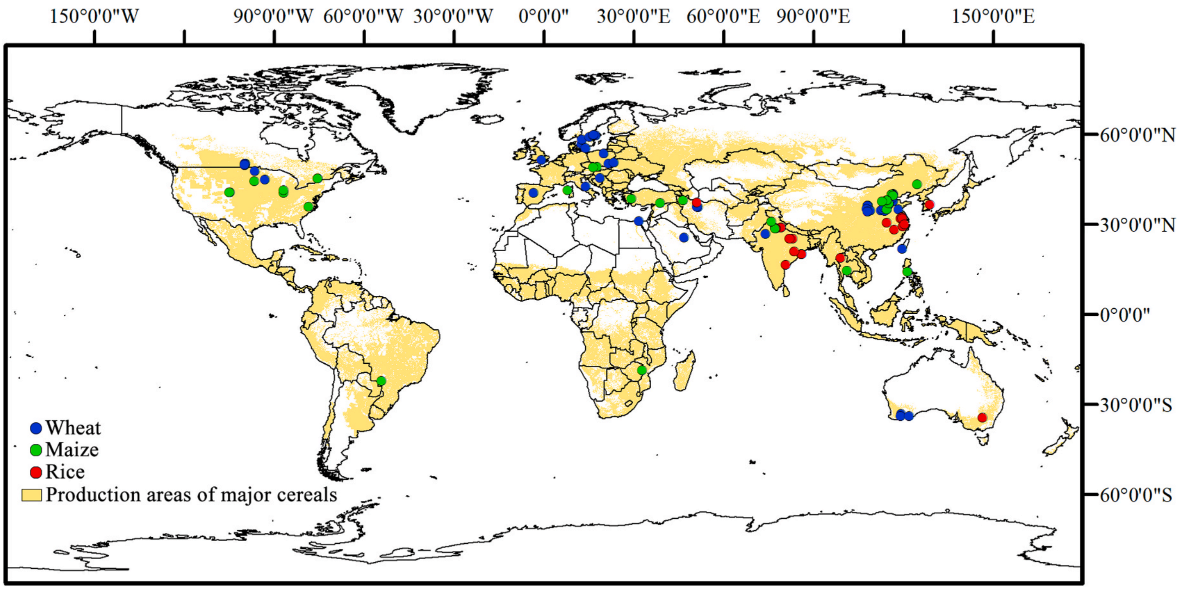

Fig. 1. Location of the study sites included in this meta-analysis and the areas of wheat, maize, and rice production (map adjusted from http://www.earthstat.org/harvested-area-yield-175-crops/, Monfreda et al., 2008).

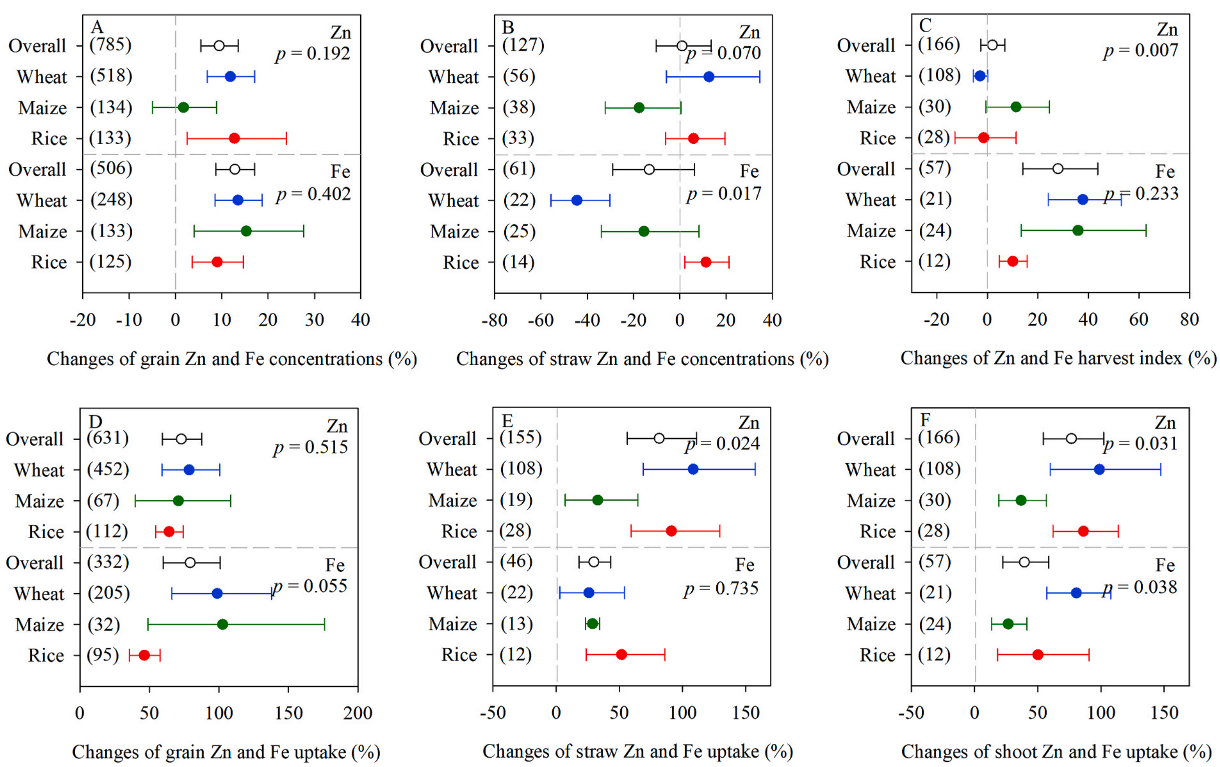

Fig. 2. Changes of Zn and Fe concentrations in grain (A) and straw (B), changes of Zn and Fe harvest index (C), and changes of Zn and Fe uptake by grain (D), straw (E) and shoot (F) of cereal crops in response to N application compared with no N control. Error bars represent 95% confidence intervals (CIs). Values in parentheses indicate the number of observations. The *p* values for the differences between wheat, maize, and rice are shown in the panel.

3.4. Effects of soil, climate, and other fertilization variables

The overall changes in grain Zn and Fe in crops grown on soil with a loamy texture (Zn: 12.0%; Fe: 18.6%) were higher than those grown on soils with sandy (Zn: 5.0%; Fe: 11.6%) and clayey (Zn: 8.8%; Fe: 8.5%) textures, while the differences were not statistically significant (Fig. 7). The effect sizes of grain Zn and Fe were not different when grown in different climate zones for any crop species (Fig. S5). Moreover, the effect size of wheat grain Zn was negatively related to the initial soil available N ($p = 0.0345$) and available P ($p = 0.0002$) contents but positively related to the soil available Zn ($p = 0.0238$) content. The effect size of maize grain Zn was positively related to the soil organic matter content ($p = 0.0494$). The effect size of wheat grain Fe was positively related to the P application rate ($p = 0.0227$). Soil pH and available Fe content did not have a significant impact (Table S5). Regardless of whether Zn fertilizer was applied, N had a positive effect

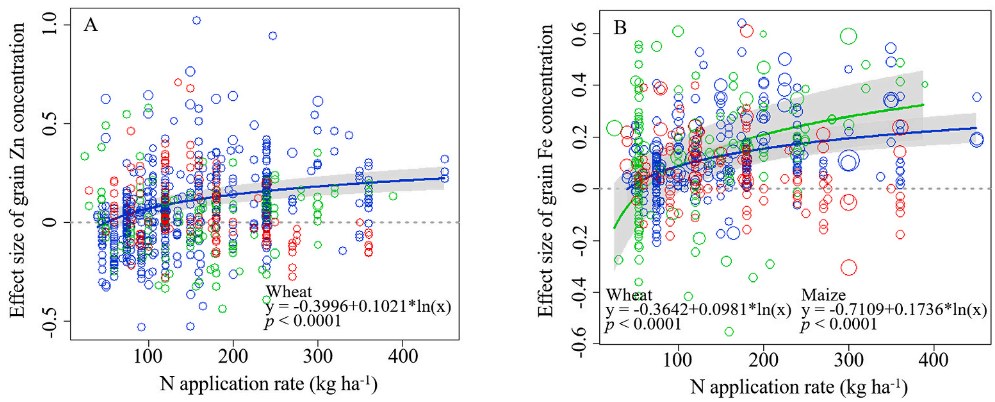

Fig. 3. Changes of grain Zn (A) and Fe (B) concentrations compared to the control for wheat (blue points), maize (green points) and rice (red points) in response to N application rate. Effect size = 0, dashed gray line; predicted mean effect size (with 95% CI in gray), solid lines. Size of data points is proportional to the sampling variance. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

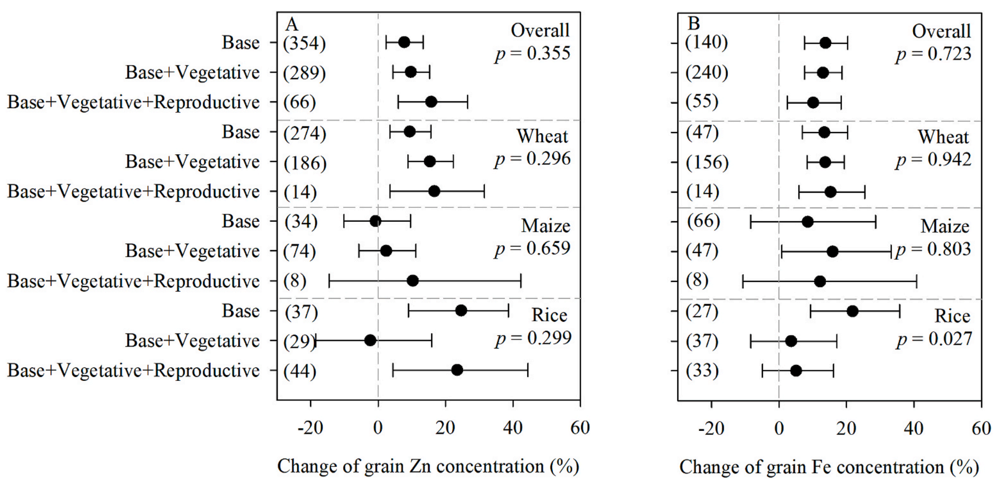

Fig. 4. Effects of N application on grain Zn (A) and Fe (B) concentrations of cereal crops as related to N application regime. Base represents single application of N fertilizer at sowing. Base + Vegetative represents split applications of N fertilizer at sowing and vegetative growth stage. Base + Vegetative + Reproductive represents split applications of N fertilizer at sowing, vegetative and reproductive growth stage. Error bars represent 95% confidence intervals (CIs). Values in parentheses indicate the number of observations. The *p* values for the differences between groups within each cereal are shown in the panels.

Table 1
Significant fertilization and soil property moderators affecting the effect sizes of grain Zn and Fe concentrations of cereal crops. Statistical results were reported as moderator heterogeneity (Q_M) and residual error (Q_E) from mixed-effects model. The relationship is indicated only if significant at $p < 0.05$. Numbers of the observations (papers) are given as n.

Crop	Moderator	n	Q_E	Q_M	Intercept distance	Slope	p
Effect size of grain Zn concentration							
Wheat	N rate[a]	517 (51)	4344.8	32.7	−0.3996	0.1021	<0.0001
Wheat	Soil available N	176 (15)	342.2	4.5	0.2253	−0.0098	0.0345
Wheat	Soil available P	390 (43)	2055.9	14.1	0.1909	−0.0030	0.0002
Wheat	Soil available Zn	330 (35)	1809.3	5.1	0.0878	0.0295	0.0238
Maize	Soil organic matter	93 (20)	630.7	3.9	−0.1440	0.0075	0.0494
Effect size of grain Fe concentration							
Wheat	N rate[a]	247 (26)	756.2	38.8	−0.3642	0.0981	<0.0001
Wheat	Proportion of basal N rate	247 (26)	752.9	12.8	0.2243	−0.1738	0.0003
Wheat	P rate	227 (22)	758.4	5.2	0.0449	0.0009	0.0227
Maize	N rate[a]	133 (20)	836.3	17.5	−0.7109	0.1736	<0.0001

[a] log-transformed data.

on grain Zn concentrations in wheat and rice (Fig. 8). The combination of N application with soil Zn application enhanced the positive effect of N application in wheat (no Zn: 9.1%; soil Zn: 26.5%) but not in rice or maize, whereas foliar Zn application did not further enhance the N effect on grain Zn in any crop.

3.5. Effects on the bioavailability of grain Zn and Fe

For wheat, N application decreased the grain phytic acid (PA) concentration by 8.4% and decreased the molar ratios of PA to Zn by 16.7% and of PA to Fe by 21.8%. The molar ratio of PA to Fe in maize also decreased by 18.8%, implying that N application resulted in potentially better Zn and Fe bioavailability to humans. No significant effect was found on the PA concentration or molar ratio of PA to either micronutrient in the rice grain (Fig. 9).

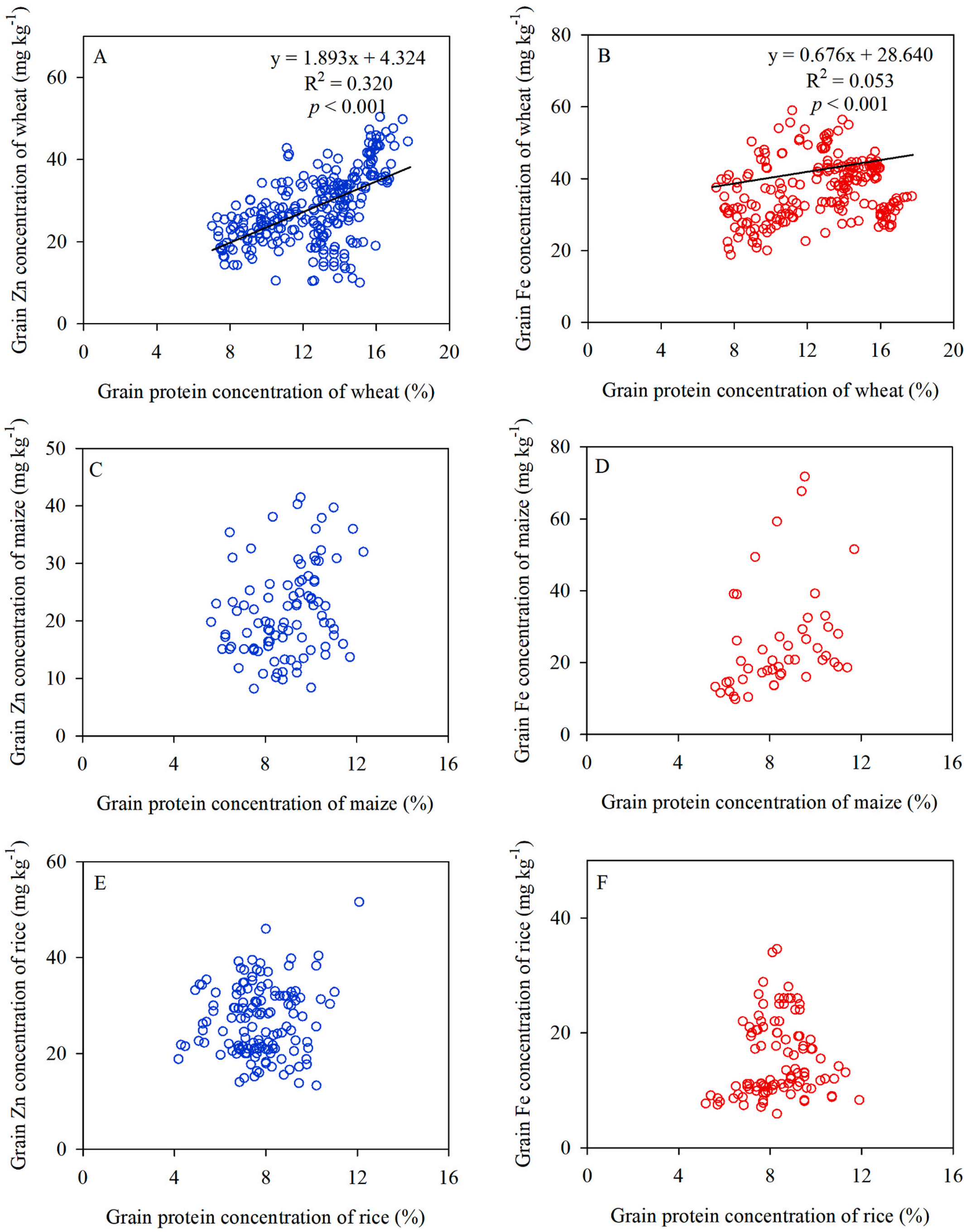

Fig. 5. Relationships between grain protein concentration and grain Zn and Fe concentrations in wheat (A and B), maize (C and D), and rice (E and F).

4. Discussion

4.1. N fertilization improves the Zn and Fe nutritional quality of cereal grains

This meta-analysis provided quantitative evidence that N fertilization enhanced grain Zn and Fe concentrations in major cereals on a global scale and could be seen as an effective agronomic approach to improve productivity and slightly increase grain nutritional quality (Fig. 2). Overall, it therefore appears that any dilution effects related to the enhanced productivity following N application are more than balanced by the increase in Zn and Fe uptake and grain allocation accompanied by higher N supply to the cereals. The only exception was maize grain Zn, the concentration of which was not influenced by N supply.

Because crops differ in their physiological and morphological traits, the potential trade-offs between yield dilution and enhanced acquisition and grain allocation of Zn and Fe could vary among crops under different N supplies. Generally, by boosting root growth, stimulating microbial activity and root exudation of organic acids or phytosiderophores, and increasing mycorrhizal colonization and the expression level of root Zn and Fe transporter proteins, N could improve the mobilization and uptake of Zn and Fe (Hui et al., 2022; Nie et al., 2019; Xue et al., 2014; Paterson et al., 2006). Within plants, N has also been reported to enhance the activities of transporter proteins and nitrogenous compounds such as peptides, hence facilitating Zn and Fe transport in plants and their loading into grains (Diaz-Benito et al., 2018; Nozoye, 2018; Shi et al., 2012; Erenoglu et al., 2011). Additionally, grain protein

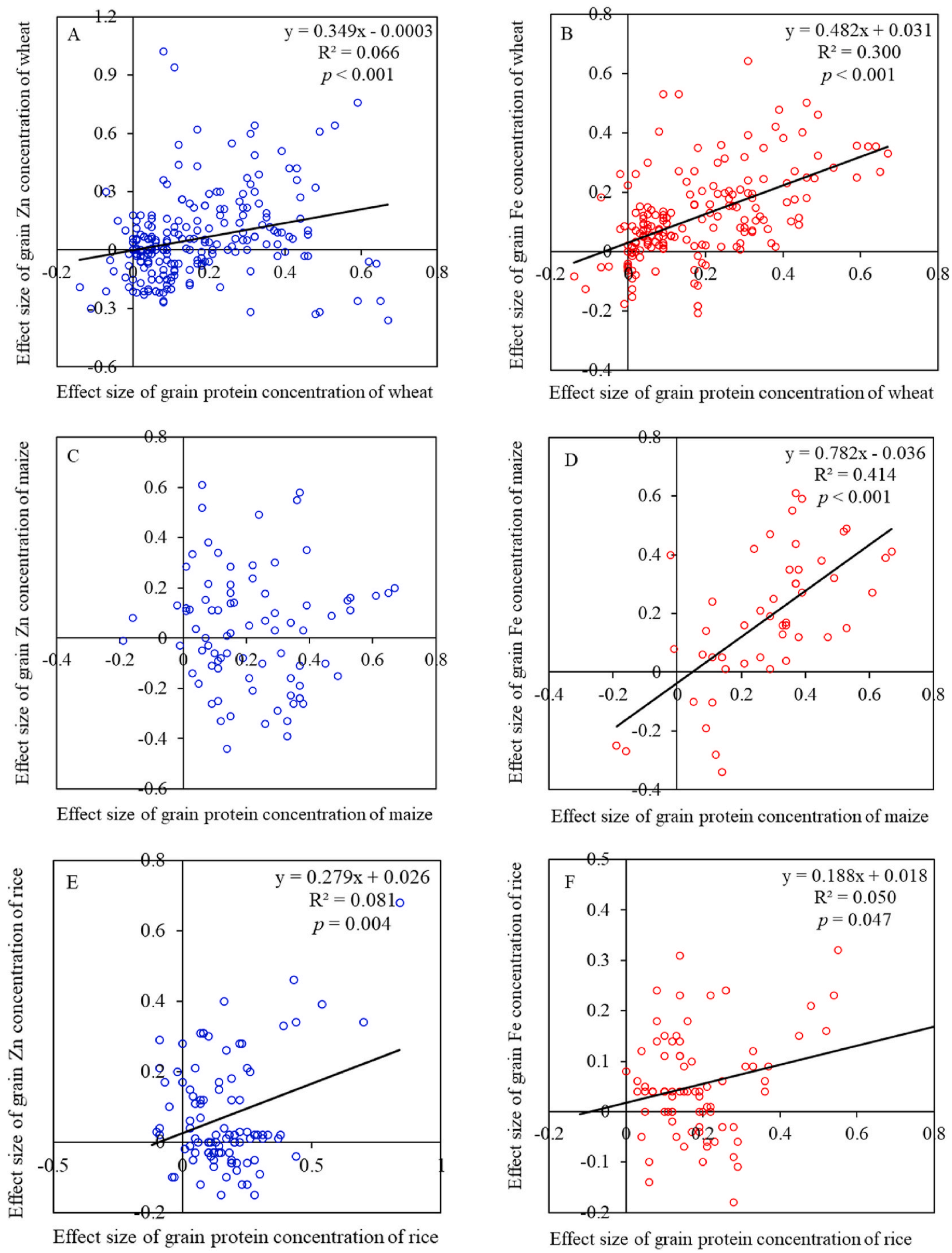

Fig. 6. Relationships between the effect sizes of grain protein concentration and the effect sizes of grain Zn and Fe concentrations in wheat (A and B), maize (C and D), and rice (E and F) in response to N application compared to the control.

concentrations can be effectively enhanced by N application, which is valuable in itself from a human nutrition perspective. The increased protein levels have been suggested to result in a larger storage capacity for Zn and Fe in grain tissues (Persson et al., 2009, 2016; Cakmak et al., 2010), which was confirmed as a contributing process by the observed positive relationships in the present study (Fig. 6). It was found that at N rates below approximately 60 kg ha^{-1}, there was an initial decline in grain concentrations of wheat Zn and Fe and maize Fe because of the higher increase in grain weight than in grain Zn and Fe uptake, leading to dilution (Fig. 3 and Fig. S4). When the increase in grain Zn and Fe uptake exceeded the increase in grain weight at N rates above 60 kg ha^{-1}, an increasingly positive effect of N on grain Zn and Fe concentrations was detected. This lower uptake of Zn and Fe in crops under low N supply compared with sufficient N supply has been reported earlier (Erenoglu et al., 2011; Kutman et al., 2011). For wheat Zn, increasing N primarily enhanced pre-anthesis Zn uptake. The observed higher post-anthesis remobilization was caused by the higher amount of Zn stored in the vegetative biomass, rather than by a higher remobilization efficacy, as wheat Zn HI decreased (Fig. 2 and Table S4).

Dilution effects seem to be limited or always more than compensated by enhancement effects in rice, and the two are in balance for Zn in maize (Fig. 3). The results from the N rate subgroup analysis showed

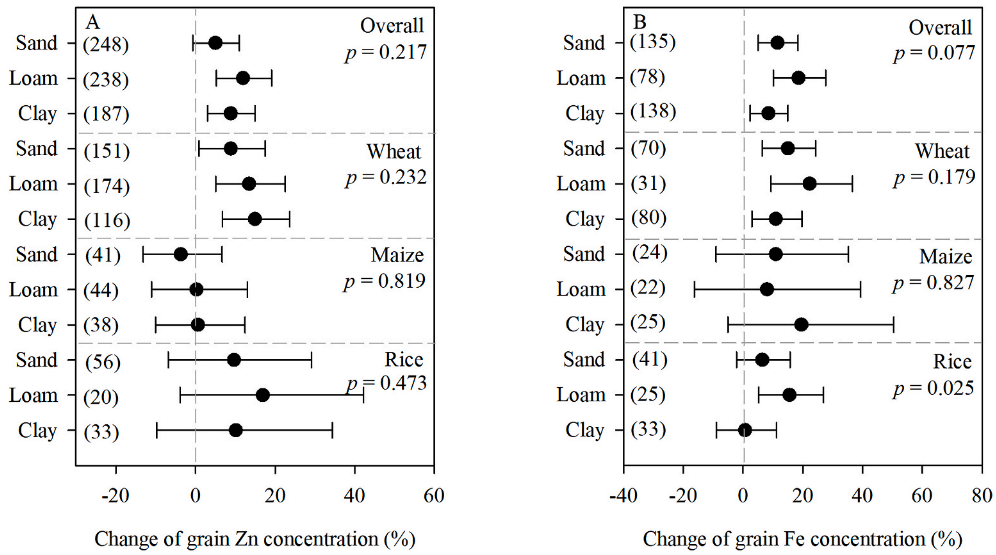

Fig. 7. Effects of N application on grain Zn (A) and Fe (B) concentrations of cereal crops as related to soil texture. Error bars represent 95% confidence intervals (CIs). Values in parentheses indicate the number of observations. The *p* values for the differences between groups within each cereal are shown in the panels.

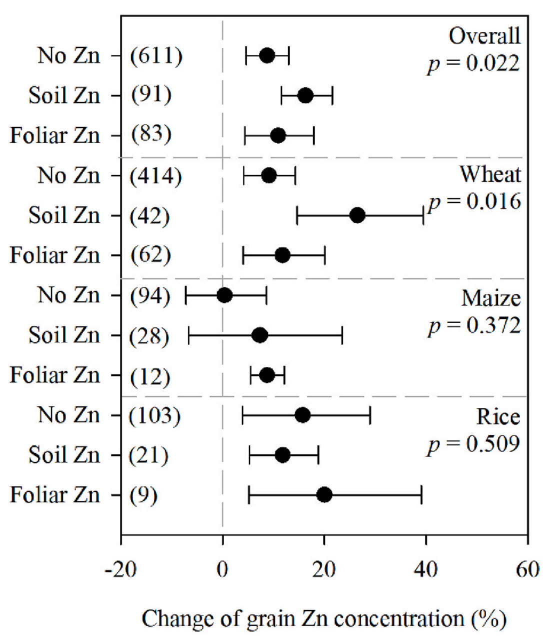

Fig. 8. Changes of grain Zn concentration of cereal crops when N was applied without Zn fertilization or in combination with soil or foliar applied Zn. Points show means of changes of grain Zn concentration in response to N application compared with no N control for the different Zn application methods, bars show the 95% confidence intervals (CIs). Values in parentheses indicate the number of observations. The p values for the differences between groups are shown in each panel.

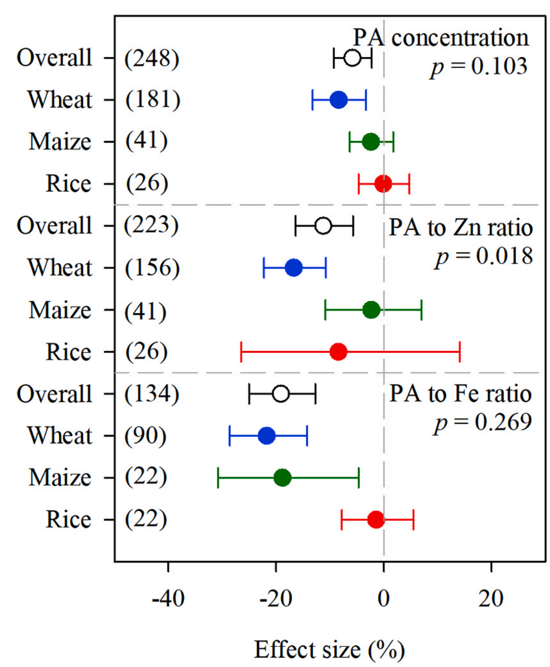

Fig. 9. Changes of the PA concentration and molar ratios of PA to Zn and Fe in grain of cereal crops in response to N application compared to the control. Points show means of treatments, bars show the 95% confidence intervals (CIs). Values in parentheses indicate the number of observations. The p values for the differences between wheat, maize, and rice are shown in the panel.

that the effect sizes of rice Zn and Fe appeared to show a quadratic response to N rate and to decrease at very high N rates, with a maximum increase achieved in the $120 < N \leq 180$ kg ha^{-1} group (Figs. S3 and S4). Unlike in wheat, rice xylem is continuous at the base of grain, so Zn and Fe can enter the grain directly from the xylem (Stomph et al., 2009). This makes continued root uptake of Zn and Fe through xylem an important process for grain deposition after flowering (Sperotto, 2013). However, soils in flooded rice cultivation are often drained during the final weeks of grain filling and maturation, which may also restrict xylem transportation, making phloem transportation of remobilized Zn and Fe important towards the end of grain filling (Sperotto, 2013). The nonsignificant response of maize Zn could be explained by the following. Shoot Zn uptake in maize increased far less than that in wheat and rice (Fig. 2F). In addition, maize showed the smallest grain protein gain and the largest grain yield gain by N application among the three crops (Fig. S2; van Grinsven et al., 2022), suggesting that the grain sink strength for Zn may not have been much improved. These two effects make maize grain Zn more susceptible to dilution as N rates increase (Miner et al., 2018). However, no net decrease in maize grain Zn was observed as Zn remobilization was simultaneously enhanced, given that the Zn HI increased by 11.4% (Table S4). This higher remobilization efficiency lowered the remaining Zn concentration in maize straw which decreased by 17.5% after N application (Fig. 2B). In summary, the increases in grain Zn concentrations in wheat and rice were attributed to the increase in shoot Zn uptake rather than Zn remobilization. In contrast, the grain Zn loading in maize was more effectively increased than the shoot Zn uptake. The increases in grain Fe concentrations in all three crops were likely due to the higher Fe HI. The underlying mechanisms remain to be further elucidated.

Sustainable crop production requires both a proper amount of N input and spatial and temporal synchrony between N supply and crop N requirements (Cui et al., 2010). Split applications of N can realize better yields, maximize grain protein quality, increase N use efficiency, and decrease the chances of N losses (Cakmak and Kutman, 2018; Snyder et al., 2014). Our meta-analysis adds N impacts on grain nutritional value in terms of Zn and Fe as a further aspect. Our finding indicates that split applications of N during periods of rapid growth (i.e., the jointing stage of wheat and rice and the six-leaf stage of maize) and flowering favour both plant uptake and grain accumulation of Zn and Fe (Fig. 4; Singh et al., 2018).

The bioavailability of micronutrients in wheat increased to some extent (Fig. 9). The substantial decrease in wheat PA concentration lowering molar ratios of PA to Zn and Fe might be a yield dilution consequence caused by high N levels (Magallanes-López et al., 2017). However, the average molar ratios of PA to Zn and PA to Fe in wheat calculated in this meta-analysis changed from 39 to 33 and from 28 to 23 after N fertilization (data not shown), respectively, implying that Zn and Fe bioavailability remained poor as the molar ratios were far above the critical values for substantially promoting Zn and Fe absorption in the human gut (<15 for Zn and <1 for Fe) (Hurrell and Egli, 2010; Gibson, 2006). Therefore, more efforts are needed towards breeding cultivars with reduced PA at unchanged total grain P levels or developing post-harvest processing methods for the removal of PA from grains (Gupta et al., 2015).

4.2. Dominant influencing factors

Overall, the effect sizes of grain Zn and Fe between individual studies differed greatly, ranging from −41.1% to 177.3% and −42.3% to 90.0%, respectively, suggesting that factors other than N application, including plant genotype, play an important role in different agroecological areas worldwide. Our integrative analysis further highlights as key drivers soil texture; soil organic matter; available N, P, and Zn contents; and P and Zn fertilizer supplies and their interactions. These could be used to develop regional-scale N management strategies in view of different agronomic practices and environmental conditions.

The highest increases in grain Zn and Fe in response to N supply were observed in loamy soils (Fig. 7). The low contents of clay and organic matter of sandy soils in some cases combined with high pH and $CaCO_3$ content often lead to limited availability and uptake of Zn and Fe (Alloway, 2009). Meanwhile, compared with fine-textured (clay) soils, loamy soils support better root system growth. For wheat Zn, we found that the effect sizes were more pronounced under lower initial soil N availability but decreased with increasing soil N levels (Table 1). Also Hui et al. (2022) observed a reduced increase in wheat grain Zn concentration at higher soil available N. This is in line with the reduced increase observed at increased N application (Fig. 3A). A higher inherent soil N level is equivalent to a higher application of N, which supports proposals that rather than applied N, the total available N in the system should be used in designing fertilization strategies (Hui et al., 2022; Gao et al., 2012). Soil P availability also influences Zn nutrition in crops (Ova et al., 2015), and the enrichment of wheat Zn by N was hindered by higher available soil P contents (Table 1). A main reason for P–Zn antagonism could be the reduced root colonization by arbuscular mycorrhizal fungi under increased P supply, since Zn absorption by wheat roots is largely dependent on this symbiosis (Zhang et al., 2021). This highlights the importance of simultaneously considering N input and available soil P levels to achieve yield and grain Zn quality (Hui et al., 2019, 2022).

Zn fertilization is often regarded a short-term agronomic practice to improve cereal grain Zn concentrations (Cakmak et al., 2010). We observed across the available literature that wheat grain Zn gains by N supply were limited at low soil Zn availability (Table 1), as earlier suggested in individual studies on wheat (Erenoglu et al., 2011; Kutman et al., 2010). While N fertilization can considerably increase grain Zn concentrations in wheat and rice, this positive effect of N was strongly enhanced by soil Zn supply but not by foliar Zn supply for wheat (Fig. 8). Nitrogen interacted more positively with soil than foliar Zn application plausibly because of the N effect on root system size and/or functioning, leading to uptake of the extra Zn provided by soil Zn supply, thus further increasing the amount of root Zn uptake. Additionally, prolonged uptake might have played a role here. Wheat is often cultivated on calcareous and alkaline soils with low Zn availability (Gregory et al., 2017), implying the necessity of an external Zn supply. The lack of a positive interactive effect of N and Zn on grain Zn in maize and rice could be partly because of limited data for maize and the specific conditions of flooded rice cultivation. The direct effects of soil versus foliar Zn application on grain Zn concentration compared with no Zn application were not assessed in this study, yet warrant further analyses.

The present work showed that factors such as soil pH, soil available Fe, and climate did not affect the effect size independently for any of the crops (Table S5, Fig. S5). The amount of plant-available Zn and Fe has been found to be strongly suppressed by a high soil pH (Bhatt et al., 2019; Kumar et al., 2016). Since there were enough soil pH data available ($n = 673$) covering a wide enough range (4.3–8.7), the main plausible reason could be that pH interacts with other soil properties (e.g., soil organic matter contents and redox potential), complicating the analysis of its effect in a meta-analysis (Kumar et al., 2016).

4.3. Implications and perspectives

Inequalities of N use present major challenges from global to local scales (Stevens, 2019). Efforts have predominantly focused on managing N for high productivity and N use efficiency, and to limit environmental costs, but have hardly considered food quality changes from a nutritional health perspective (He et al., 2021; Chen et al., 2014). The present quantification of the N-related changes in cereal Zn and Fe nutrition may fill that gap and could serve as input for policymakers considering fertilization as a tool to achieve United Nations' Sustainable Development Goal 2 (zero hunger) by 2030 (Balié, 2020). Our results highlight that overall grain micronutrient quality is not compromised by N supply, as the dilution effect is generally balanced or overruled by enhanced Zn and Fe uptake, translocation and remobilization. However, for maize and wheat at low N application rates, we observed a stronger dilution than enhancement effect. Maize is a major staple in Africa, where yields and fertilizer applications are much lower than elsewhere and the prevalence of human micronutrient deficiencies is higher (Bonilla-Cedrez et al., 2021; Balié, 2020). Yet there were hardly any relevant data from Africa (Fig. 1), revealing a major knowledge gap and emphasizing the need to check our findings there to more accurately establish potential trade-offs between yield gains and nutritional quality at low N application rates. The current research data are essentially about N as a chemical fertilizer, but comparable positive effects can be expected when N is applied partially or wholly as organic fertilizer and through rotation with legumes, the more so as both enhance soil organic carbon in the longer run and contain organic forms of Fe and Zn. The effects of these organic N sources on the bioavailability of Fe and Zn for uptake in major cereals are poorly understood and merit further analyses.

With soil- and site-specific N management strategies, opportunities for grain productivity and quality improvement exist across reported countries (Fig. 1). For countries with a negative N balance, the immediate priority is to improve soil fertility and increase N use for higher crop yields (He et al., 2021). Our study indicates that a minimum N application rate of 60 kg N ha^{-1} is recommended to boost yield and avoid the potential yield dilution effect on grain Zn and Fe, which would often aggravate hidden hunger. For countries with a positive N balance, high N surpluses could lead to a severe resource waste and environmental damage. Nitrogen application levels should be limited to 150–200 kg N ha^{-1} per crop, which would be sufficient to enhance grain Zn and Fe nutrition without sacrificing yield (van Grinsven et al., 2022). At levels of N beyond, although further increases in yield and Zn and Fe concentrations may be observed, at least for wheat, but N losses through leaching and volatilization will be enhanced such that the trade-offs of the total system are beyond the optimum for food and environmental health.

In addition, we need to be realistic about these nutrition improvements that can be reached with N supply. According to the target values for biofortification proposed by HarvestPlus, Zn concentrations in wheat and rice grains should be 52% and 75% higher than baseline contents, respectively (Bouis et al., 2011). Even the maximum Zn increases observed in wheat and rice (17% and 24%) are thus very limited compared to the required levels, let alone the neutral effect on maize Zn (Fig. 2A), which means that N application is not to be considered a major way to improve grain micronutrient concentrations. However, it is good to understand that N application also does not pose a general threat to grain nutritional values. Taken together, future fertilization strategies should pay more attention to the balance between the quantity and quality of food production through the combination of improving soil fertility, optimizing N management, avoiding overuse of P fertilizer and possible soil or foliar supplying of Zn fertilizer.

Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Qingyue Zhao reports a relationship with China Scholarship Council that includes: funding grants.

Acknowledgments

The authors thank all the individuals and institutions that contributed available datasets to this work. We also appreciate the reviewers for their constructive suggestions and comments on our manuscript. This work was supported by the National Maize Production System of China (grant number CARS-02-24) and the China Scholarship Council (grant number 202006350124).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gfs.2022.100631.

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