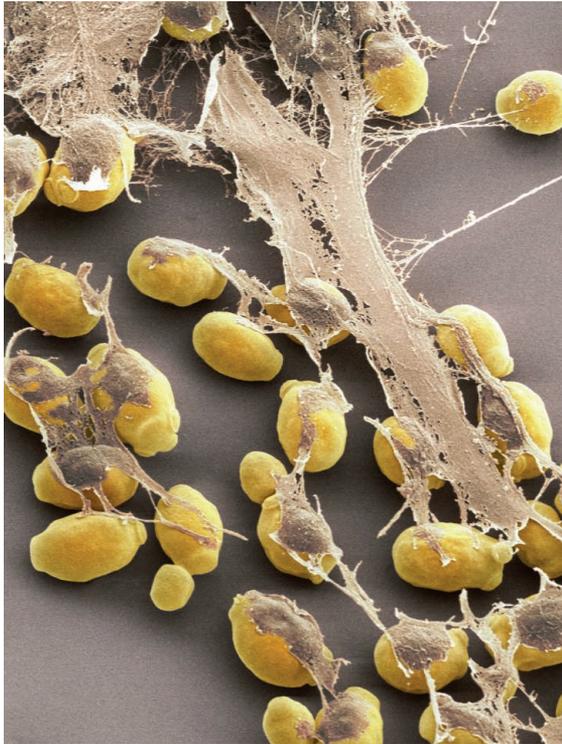


in strong inflammasome activation. The observations suggest a two-step inflammasome activation process (see the first figure) in murine plaque macrophages in which NETs prime a macrophage for inflammasome activation and pro-IL-1 β production. Cholesterol crystals then induce lysosomal damage, which is sensed by the macrophage inflammasome called NOD-like receptor family, pyrin domain containing 3



Deploying NETs. Colored scanning electron micrograph of neutrophil extracellular traps (NETs, brown) capturing spores from the yeast *Candida albicans* (yellow).

(NLRP3). NLRP3 activates caspase-1, which subsequently leads to proteolytic cleavage and release of IL-1 β (5).

Cholesterol crystal-induced NETosis as a macrophage inflammasome stimulator adds to the growing knowledge on neutrophil activity in atherosclerosis, including the role of neutrophils in augmenting monocyte recruitment (7) and the pro-thrombotic actions of NETs in the setting of plaque erosion (8). Do these interactions occur in human atherosclerotic plaque? Although Warnatsch *et al.* provide compelling human *in vitro* data, and NETs are present on the surface of eroding human plaque (8), it will be important to verify that the observed murine phenotype translates to patients. Additionally, it is unknown if similar interactions between neutrophils and macrophages also occur in other organs, as these cells travel far and hypercholesterolemia is systemic. Hence,

it will be imperative to determine whether the phenotype observed in *Apoe*^{-/-}/*Ela2*^{-/-}/*Prtn3*^{-/-} mice is exclusive to NETosis; other leukocytes, including macrophages, also express proteinase-3 (9). The high turnover of plaque macrophages (10) and the observation of NETosis in diabetes (11), a common risk factor for atherosclerosis, mean the striking phenotype reported by Warnatsch *et al.* could depend on additional mechanisms that still await discovery.

Warnatsch *et al.* introduce an interesting new facet to our understanding of how neutrophils and macrophages communicate. Macrophage activation through NETosis contrasts with neutrophil-macrophage interaction during resolution of inflammation. When macrophages engulf apoptotic neutrophils, a noninflammatory macrophage phenotype supports healing and a return to a steady state (1). Thus, the presence of cholesterol crystals dramatically influences cell-cell interactions and macrophage function. In considering possible therapies, inhibiting NETosis, or at least eliminating extracellular DNA, may prove beneficial. An alternative approach could reduce neutrophils by limiting their production in the bone marrow, migration, and/or recruitment. Both strategies would edit the instructions that macrophages receive from their tissue microenvironment, possibly curbing inflammasome activation and

promoting inflammation resolution. Further downstream in the pathway, inhibiting the active form of IL-1 β with a neutralizing antibody is a promising strategy currently being tested in patients with atherosclerosis (12). ■

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GLOBAL NUTRITION

Metrics for land-scarce agriculture

Nutrient content must be better integrated into planning

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Over the past half-century, the paradigm for agricultural development has been to maximize yields through intensifying production, particularly for cereal crops (1). Increasing production of high-yielding cereals—wheat, rice, and maize—has replaced more nutrient-rich cereals, which has eroded the content of essential dietary nutrients in the world's cereal supply. New approaches are needed to produce healthy foods, rich in essential nutrients, with efficient use of land.

Standard yield metrics that measure the quantity of production are inadequate to assess progress toward this goal; thus, we propose alternative metrics of nutritional yields.

Intensification of agriculture through multiple crops per year, high-yielding seed varieties, synthetic fertilizer, mechanization, and other inputs increases yields and improves the efficiency of using land to produce food. In the last 50 years, intensification of cereal production has increased the world's cereal supply by a factor of almost 3.2, outpacing the 2.3-fold increase in population growth (2). Intensification was critical for averting food shortages that loomed on the horizon in the 1960s.

Intensification has spared 18 to 27 million hectares that would have been required to produce the same amount of cereals with yields equivalent to those in the mid-1960s (1). But intensification can exacerbate land-clearing in the absence of appropriate policies and enforcement (3). Moreover, intensification relies on high inputs of energy, fertilizer, pesticides, and water (4). Environmental consequences include runoff of excess fertilizer that damages water quality, toxicity from pesticides, nitrous oxide emissions, and degradation of habitat for biodiversity.

With increasing competition for land (e.g., for carbon storage, watershed protec-

tion, conservation, and other ecosystem services apart from food production), future food demand will be met largely through further intensification rather than expansion of agriculture into uncultivated areas (5). Agricultural methods that minimize environmental damage, as well as diets that reduce demand for resource-intensive foods, have been recognized as approaches to “sustainable intensification” (6, 7). Analyses of trade-offs and synergies between ecosystem services and food production at local (8) and global (9, 10) scales generally use crop yield or calories as a metric to compare strategies for fulfilling food demand. But nutritional needs for a wide range of essential nutrients in the human diet have generally not been included in considerations of sustainable

intensification. Access to food with high nutritional quality is a primary concern, particularly for 2 to 3 billion people who are undernourished, overweight, or obese or deficient in micronutrients (11).

We illustrate the need for new metrics in the context of cereal production in the global food supply, as well as for (i) India, which has undergone substantial intensification; (ii) least-developed countries (LDCs), which have yet to undergo major intensification; and (iii) China, where cereals are increasingly used for animal feed. These three cases collectively make up about half of the global population (2). Although we focus on the effects of intensification that have promoted high-yielding over nutrient-dense cereals, other factors may alter the nutritional composition of

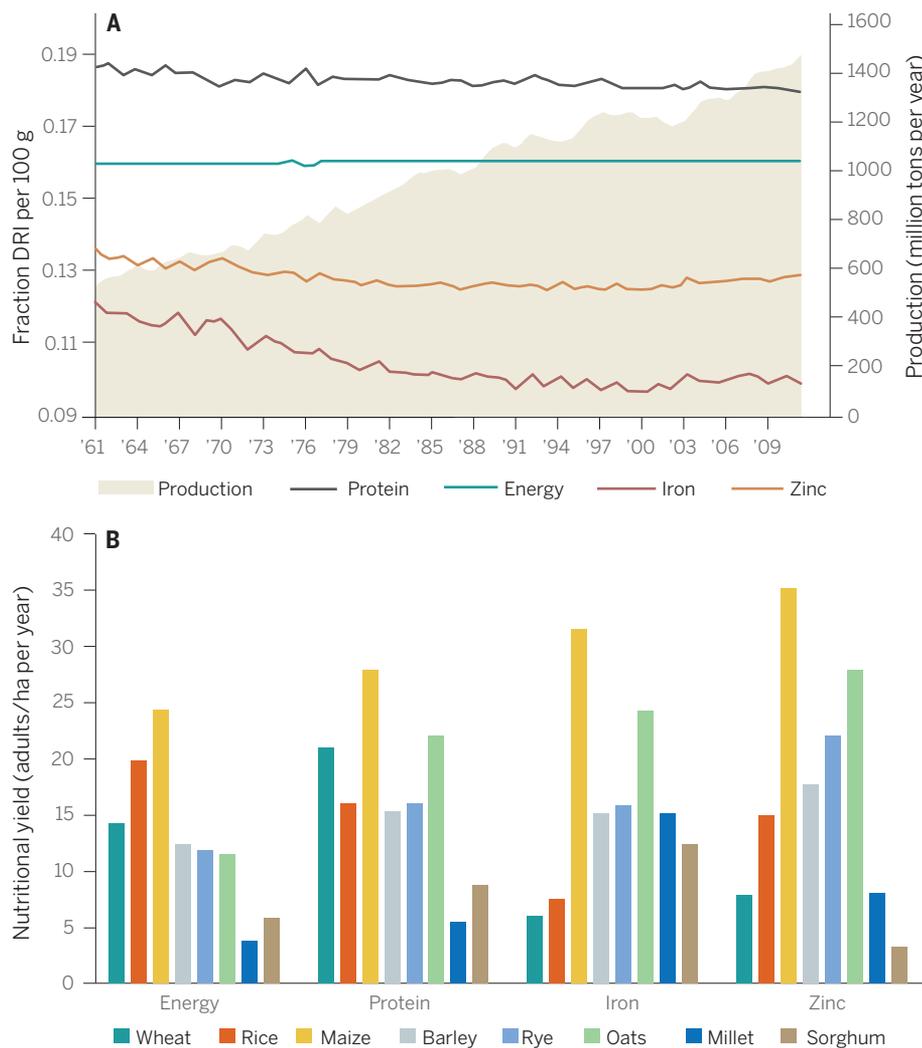
cereals, including changes in atmospheric composition (12), increasing consumption of refined cereals, and changing crop varieties.

NUTRITIONAL COMPOSITION. In addition to energy from calories, other macronutrients (such as proteins and fats), and micronutrients (such as iron and zinc) are essential for healthy diets. Micronutrient deficiencies can occur from a lack of dietary quality and diversity, even if the supply of macronutrients is sufficient. For example, the percentage of females of reproductive age with iron deficiencies range from 12% in Northern America to 50% in Western Africa (11). The prevalence of other micronutrient insufficiencies, such as zinc, is less well quantified but is believed to be widespread in low-income settings. These deficiencies are associated with compromised immunity and growth, poor cognitive development, reduced learning capacity and worker productivity, and other detrimental effects (13).

Despite increasing diversion of cereals for animal feed, cereals compose a major component of human diets, particularly in India and LDCs where diets are predominantly based on starches (fig. S1). Consequently, the nutritional content of the cereal supply reverberates into the nutritional status of the population, especially in low-income settings. The importance of nutrition from cereals is compounded by relatively low bioavailability (proportion of the nutrient that is absorbed and metabolized through normal pathways) of micronutrients in cereals compared with those from animal products (14).

Globally, land area devoted to high-yielding cereals increased over the past 50 years, with rice, wheat, and maize collectively increasing from 66% to 79% of all cereal area between 1961 and 2013. This was at the expense of other cereals, with barley, oats, rye, millet, and sorghum collectively declining from 33% to 19% (2) (fig. S2). The cereals that declined in area generally have higher micronutrient contents than rice, wheat, and maize. For example, the iron content per 100 g of millet is nearly four times that for rice. Similarly, zinc content is more than quadruple for oats compared with wheat (fig. S3).

At the global scale, the energy density of the cereal supply (excluding cereals used to feed livestock) stayed fairly constant between 1961 and 2011 because of similar caloric contents of different cereals. However, the protein, iron, and zinc content in the global, directly consumed cereal supply declined by 4%, 19%, and 5%, respectively (see the graph, A) (fig. S5 for India, China, and LDCs). Diversion of cereals for feed, mostly maize, reduced the global supply of iron compared with a hypothetical case of all cereals consumed directly. However, because



Nutritional content of global cereal supply has declined as production has increased since 1960. (A) Fraction of DRI provided by 100 g dry weight from a mix of eight cereals (barley, oats, maize, millet, rice, rye, sorghum, and wheat) from 1961 to 2011 for macronutrients (energy and protein) and micronutrients (iron and zinc). Values were calculated from production quantity (excluding cereals used for livestock feed) and nutritional composition for each cereal crop (figs. S2 to S4). DRI does not account for differences among cereals in bioavailability (14) or refining, both of which would further reduce DRI values. (B) Nutritional yields (number of adults who can obtain 100% of annual DRI from 1 ha per year) of eight cereals for energy, protein, iron, and zinc for global supply in 2013. See SM for details.

the proportion of maize diverted for feed remained fairly stable over the time period, the change in the mix of cereal types had an even larger effect on reducing the nutritional content of the global, directly consumed cereal supply than the diversion to feed (table S1 and fig. S4).

In other words, the amount of cereals that a person would need to consume to fulfill the daily dietary reference intake (DRI) has increased for protein, iron, and zinc, based on a mix of cereals in proportion to the production of each type. In 1961, 533, 821, and 735 g of cereals were needed to satisfy requirements for protein, iron, and zinc, respectively. By 2011, the amount required increased to 556, 1013,

compensate for eroding nutritional content of cereals but requires more land because of low conversion efficiencies of animal feed to protein (16). Moreover, low-income populations have limited access to substantial amounts of animal products.

NEW METRICS. The standard yield metric of agricultural production by weight per unit land neglects the importance of human nutritional needs as a critical factor for sustainable intensification. We propose a metric of “nutritional yield,” the number of adults who would be able to obtain 100% of their recommended DRI of different nutrients for 1 year from a food item produced annually on one

tons and energy per hectare than rice, wheat, and maize (see the graph, B). In India and LDCs, drought-tolerant millet and sorghum provide nutritional yields for iron higher than rice, despite relatively low yields in terms of metric tons per hectare. In China, wheat and rice have the lowest nutritional yields of all cereals for iron (fig. S6).

Decisions about the desired mix of crops to achieve efficient use of land differ according to the priority: quantity of production or quality to produce essential dietary nutrients. The nutritional yield metric can guide decisions to simultaneously address both priorities at multiple scales. At the field and farm scales, the metric can quantify benefits of improved, nutrition-sensitive agricultural practices, such as the use of biofortified varieties and integrated soil fertility management. At a landscape or national scale, the metric can be applied to formulate policies that promote a mix of crops that balance productivity in terms of quantity and nutritional needs of the respective populations. At the global scale, the metric could be included in projections of food demand and requirements for micronutrients and other macronutrients beyond energy.

With growing pressures on land resources, food systems will be called upon to use land efficiently. At the same time, scarce land resources need to provide adequate nutrition for the world's population and alleviate micronutrient deficiencies. This confluence of imperatives calls for new alliances, metrics, and analyses for incorporating human nutrition as a primary consideration for sustainable agriculture. ■

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SUPPLEMENTARY MATERIALS

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Healthy foods are needed. They must be rich in essential nutrients produced with efficient use of land. Sacks filled with wheat in Punjab, India.

and 777 g. Grams required to satisfy energy requirements remained nearly unchanged at 625 to 623 g over this time period. The nutrient-to-calorie ratio in our directly consumed cereal supply has declined, with less nutrient-dense cereals contributing to high levels of micronutrient deficiencies, particularly in low-income settings with cereal-based diets. Although our analysis did not address bioavailability, our estimates of amounts needed to meet requirements would be expected to increase because of the relatively low bioavailability of micronutrients in grains, which depends strongly on processing and cooking procedures.

Declining nutritional content of cereals could be compensated by trade and increased consumption of other foods (15). Diversion of cereals for livestock increases consumption of animal products and can

hectare [see supplementary materials (SM)]. Conversely, the inverse of the metric indicates the land area required to grow enough food to supply one person with 100% of recommended daily requirement of different nutrients from a food item for 1 year.

In reality, people do not obtain 100% of recommended nutrient intake from a single food item, and processing and cooking further affect the nutrients available for human consumption (14). However, the metric allows comparison among different crops and production systems to evaluate nutritional value produced from a given land area. The metric could be compiled over different food items and along food value chains to measure nutritional yield for a food system as a whole.

In 2013, for example, on average one hectare of rice produced 4.5 metric tons/year, which is the equivalent of providing the annual energy requirement for 19.9 adults. Millet produced only 0.9 metric tons/ha per year, the annual energy requirement for 4.0 adults. However, a hectare of rice fulfills the annual iron requirement for only 7.6 adults, compared with 15.3 for millet. Similarly, oats yield more zinc per ha than all other cereals except maize, despite providing fewer metric

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