Trends in
Plant Science

CellPress

Review

# Low glycemic index rice: a healthier diet for countering diabetes epidemic in Asia

Rhowell N. Tiozon Jr.,[1,2], Bert Lenaerts[3], Sakshi Kor[1], Matty Demont[3], Alisdair R. Fernie[2], and Nese Sreenivasulu[1,*]

**The prevalence of type 2 diabetes is rising worldwide, particularly in Asia, where rice is a dietary staple. Hence, it is essential to consume low glycemic index (GI) food. Here, we review the potential of low GI and high resistant starch (RS) of rice to mitigate diabetes risk. Progress has been made in lowering the GI of rice without compromising yield and grain quality through marker-assisted breeding techniques. To enhance RS content, mutation breeding and genome editing were used. Deployment of these new varieties in global food systems remains critical through policy initiatives such as 'Seeds without Borders' and the widespread deregulation of genome editing plants that can expedite the wider adoption of low-GI and high-RS rice.**

## Highlights

To lower the glycemic index of rice and increase resistant starch without compromising yield and sensory attributes, it is essential to understand the role of starch biosynthetic genes and other regulatory networks.

Most gene-edited lines with high amylose content and resistant starch have not been tested for their glycemic index properties, leading to their underutilization.

Developing low-glycemic index rice is crucial, and deploying it in the global food systems through initiatives like the 'Seeds without Borders' policy can help mitigate the growing prevalence of diabetes in Asia.

## Importance of breeding low-GI rice as a healthier dietary choice

The substantial burden of diabetes on healthcare systems worldwide is underscored by estimates from the International Diabetes Federation (IDF) suggesting that in 2021, 537 million individuals were affected by diabetes, resulting in global health expenditures of US$966 billion, a figure projected to exceed US$1054 billion by 2045 [1]. The escalating prevalence of diabetes mellitus worldwide is particularly pronounced in low- and middle-income countries (LMICs), where 80% of cases occur, underscoring the challenge of limited resources for prevention and management [2]. This global increase in diabetes has been accelerated by the nutritional shift toward a more calorie-dense diet, coupled with increased consumption of sugary drinks, ultraprocessed foods, and refined carbohydrates [e.g., white rice (*Oryza sativa*) and polished wheat (*Triticum aestivum*)][2]. In many LMICs, due to undergoing rapid economic development and nutritional transition, white rice serves as a staple food. However, an elevated consumption of white rice has been linked to a heightened risk of diabetes, especially notable in Asian countries (Table S1 in the supplemental information online) [3]. The Global Burden of Disease (GBD) study of 2017 linked the development of diabetes to poor diet and 12 other risk factors [4]. In mitigating the risk of diabetes, a diet characterized by the regular consumption of all five food groups, with an emphasis on introducing whole grains and enhancing the quality of starch to lower the **GI** (see Glossary) in starchy staples while promoting the diverse range of dairy, fruits, and vegetables, is crucial [5,6].

Whole grain rice varieties present a viable alternative owing to their generally lower GI than white rice, which can be attributed to their elevated fiber content and reduced absorption rate. However, challenges pertaining to shelf-life and palatability have hampered their adoption in regions where milled rice constitutes a major dietary staple. Several efforts have focused on modifying starch-related genes to increase **RS** content [7,8], as higher RS levels result in a more controlled release of glucose and gradual rise in blood sugar levels [7]. However, increasing RS content often comes with a trade-off in texture, which has posed challenges to integrating these traits into breeding programs. In a molecular sense, high RS content and elevated amylose levels

[1]Consumer-Driven Grain Quality and Nutrition Center, Rice Breeding and Innovation Department, International Rice Research Institute, Los Baños 4030, Philippines
[2]Max-Planck-Institute of Molecular Plant Physiology, Am Mühlenberg 1, Potsdam-Golm 14476, Germany
[3]Sustainable Impact through Rice-Based Systems Department, International Rice Research Institute, Los Baños 4030, Philippines

*Correspondence:
n.sreenivasulu@irri.org (N. Sreenivasulu).

https://doi.org/10.1016/j.tplants.2024.11.003

can form strong hydrogen bonds, which can lead to a firmer and more gel-like consistency when cooked. Since texture is a key factor in consumer preference for rice worldwide [9], a more focused breeding approach is essential, using advanced breeding strategies to lower the GI of white rice without impairing palatability. Currently, only a few cultivars with low GI properties are available in the market (Table S2 in the supplemental information online), highlighting the need for breeding strategies aimed at developing mapping populations capable of producing rice with low GI properties without compromising grain quality and yield. Such a strategy holds great promise in mitigating the risk of type 2 diabetes, particularly in countries heavily reliant on white rice as their staple food. It can also contribute to poverty reduction by enabling smallholder farmers to capture high-value market opportunities for nutritionally enhanced rice.

Here, we review the genetic traits that produce low-GI and high-RS rice varieties. These traits can help convert popular rice varieties to optimize slow caloric release, addressing the health benefits for Asian and African populations that rely heavily on milled rice as a dietary staple amid the rapid rise in diabetes rates.

## Facing the prevalence of diabetes in Asia and preventing a possible future epidemic in Africa

The Green Revolution launched in the 1960s through the introduction of high-yielding semidwarf varieties transformed food production, reduced poverty, and sustained the caloric needs of millions by achieving food security of Asian populations [10,11]. In the post-Green Revolution period, Asia lost the wider cultivation of indigenous crops, like some legumes, millets, and sorghum, between 1961 and 2017[i]. A massive population in Asia shifted from a diet prominently featuring millet, a grain rich in fiber and micronutrients, to a cereal-based diet with very high capita rice consumption of milled rice. The GBD study of 2021 projects that developing countries will witness a more than twofold increase in diabetes prevalence rates by 2050 (Figure 1A). Several meta-analyses have shown that the consumption of polished rice is associated with the prevalence of type 2 diabetes (Table S1 in the supplemental information online) [12,13]. We quantified potential impacts following standard methods based on **disability-adjusted life-years (DALYs)** as a metric [14,15]. We modeled apparent relative nutrient intake levels by inversing the normalized relationship between undernourishment and relative calorie intake [16] and applying the functional form to DALYs lost due to diabetes to calculate high-GI intake. The three largest consumers of rice suffer significantly from the burden of diabetes: India suffers the most with 11.2 million DALYs, followed by China with 10.0 million DALYs and then Indonesia with 4.4 million DALYs [13]. Since per capita consumption of white rice as a staple food in many countries of Asia is very high, it is likely the predominant contributor to dietary glycemic load. In fact, high dietary glycemic load is associated with elevated risk of diabetes [17]. A Lancet study reported India as a hotspot for increasing prevalence of diabetes, projecting a surge of more than 101 million cases by 2023 [18]. In some regions of China, white rice accounts for 73.9% of the dietary glycemic load, with incidences of diabetes of more than 141 million cases, with over 50% of cases undiagnosed [17,19]. Regrettably, the associated mortality in China stands at nearly 1.4 million, and diabetes-related health expenditures have soared to US$165.3 billion, reflecting a substantial economic burden [19]. The cumulative cases of diabetes in India and China collectively represent 60% of the total population living with diabetes in Asia. In addition, there is a high prevalence of diabetes cases in other rice-consuming countries in Southeast Asia and this is projected to rise by 68%, reaching 152 million individuals by 2045 [12]. Generally, Asian diabetic patients face an elevated risk of developing long-term complications associated with diabetes due to the earlier onset of the disease [20]. Food as medicine sits at the cross roads of healthcare and nutrition, where high-quality carbohydrate low-GI rice varieties will likely bring healthier diet options in Asia.

## Glossary

**Amylose content:** refers to the proportion of amylose, a linear polymer of glucose, in starch. It affects the texture and digestibility of starchy foods.

**Disability-adjusted life year (DALYs):** a measure used to assess the overall burden of disease. It combines years of life lost due to premature mortality and years lived with disability, providing a comprehensive view of the impact of health conditions on a population.

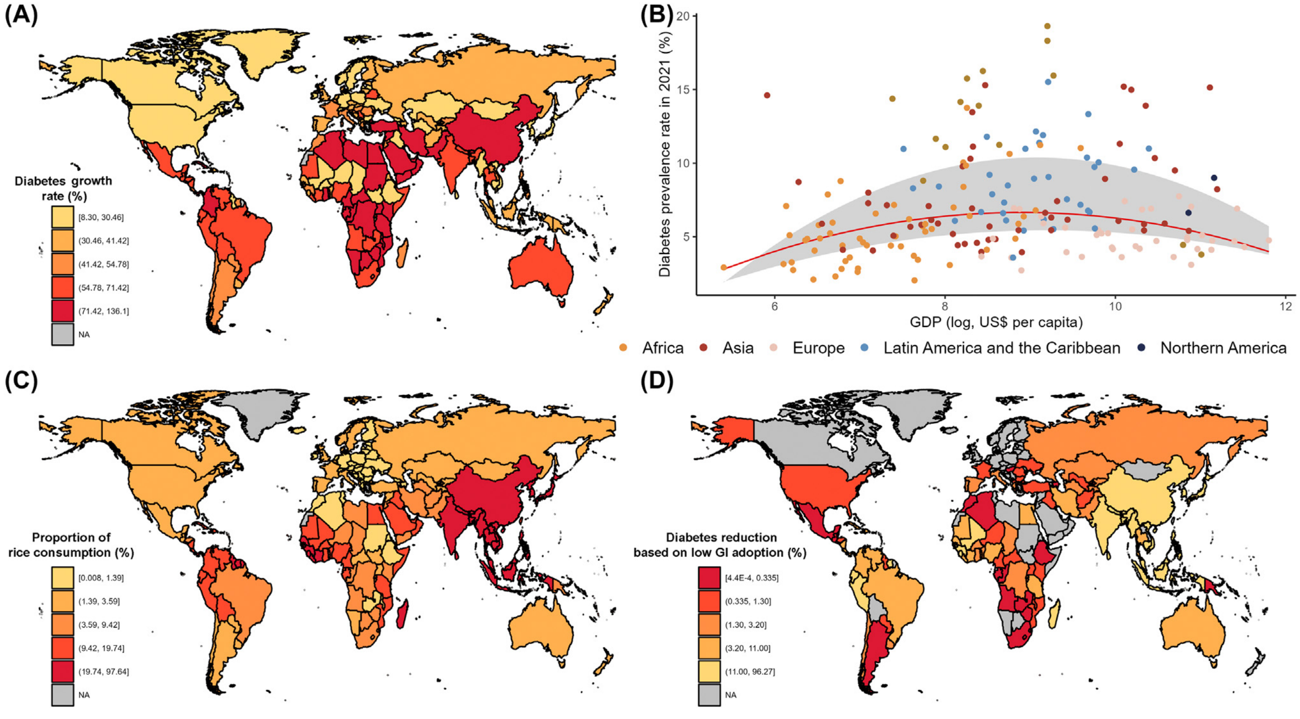
**Genome-wide association study:** a research method used to identify genetic variations associated with specific traits by scanning the genomes of many individuals.

**Glycemic index (GI):** a measure of how quickly a carbohydrate-containing food raises blood glucose levels after being consumed.

**Resistant starch (RS):** a type of starch that resists digestion in the small intestine and ferments in the large intestine, acting like dietary fiber.

**Starch branching enzymes (SBE):** enzymes that catalyze the formation of branch points in starch molecules by breaking and reattaching the glucose chains. This branching is essential for creating the highly branched structure of amylopectin, a major component of starch.

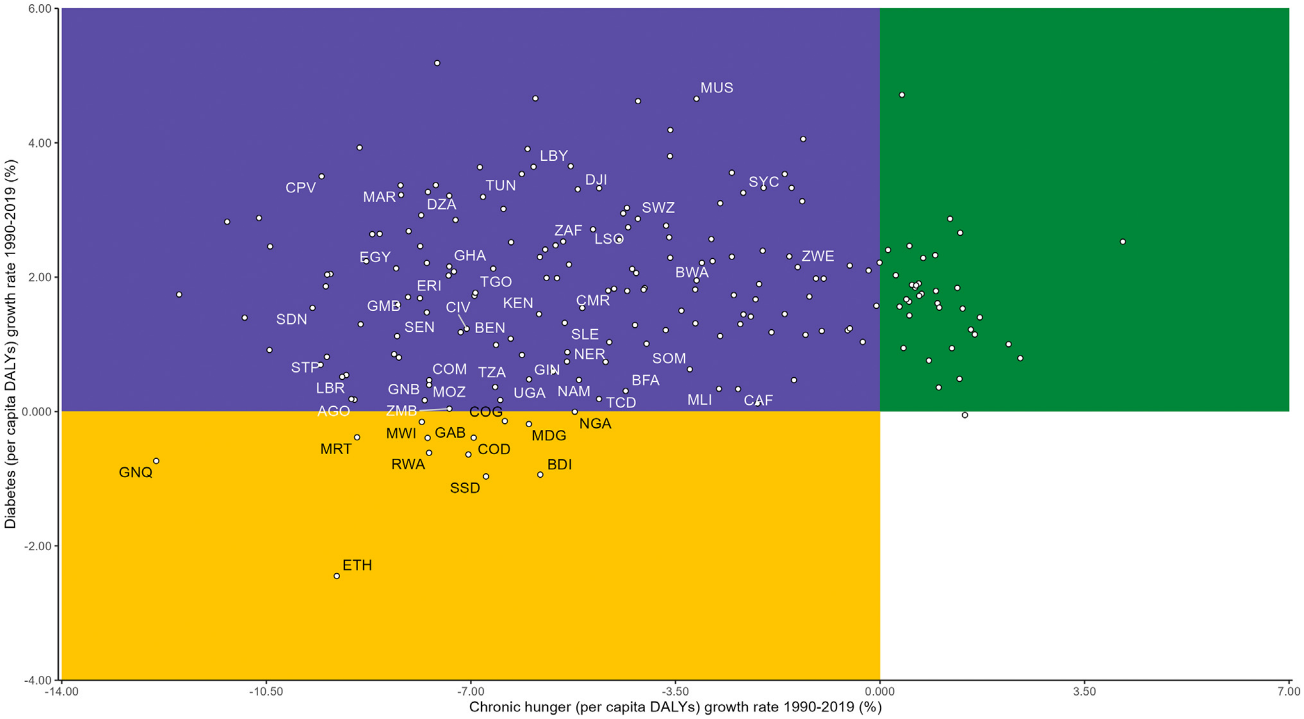
**Transcriptome-wide association study:** a research approach that links gene expression data with genetic variations to identify genes associated with traits or diseases.



Trends in Plant Science

Figure 1. Trends in diabetes prevalence and rice consumption. (A) Projected relative change (%) in diabetes prevalence from 2021 to 2050 indicates a rising incidence of type 2 diabetes across Asia, with Africa also expected to experience a significant increase in diabetes prevalence by 2050. (B) Scatter plot illustrating the relationship between diabetes prevalence rate and gross domestic product (GDP) shows that low- to middle-income countries bear a higher burden of type 2 diabetes than both very low- and high-income countries. (C) Proportion of total caloric intake derived from rice (%) reveals that Asia has the highest rice consumption, followed by South America and Africa. (D) Estimated percent reduction in diabetes burden (disability-adjusted life-years) resulting from the adoption of low-glycemic index rice highlights potential health benefits for rice-consuming countries.

African diets historically centered on staple crops like coarse grains (e.g., maize and sorghum) and tubers such as cassava. However, there has been a gradual shift toward increased rice consumption attributed to economic growth and the corresponding preference of consumers for fine grains such as rice [21]. The demand for rice quadrupled from approximately 10 million metric tons to 40 million metric tons between 1990 and 2018, driven by rapid population growth (+113%) and changing diets. By 2050, demand for rice in Africa will reach approximately 150 million metric tons due to continued population growth and an increase in rice consumption per capita [22]. Historically, countries with higher reductions in the per capita burden of chronic hunger also experienced higher rises in the per capita burden of diabetes (Figure 2). If these past trends persist, future reductions in undernutrition will be more than offset by increases in calorie-rich-associated noncommunicable diseases (NCDs) [23]. Diabetes prevalence rates are expected to more than double in the Middle East (Oman, Syria, United Arab Emirates, and Iran) and Africa (Kenya, Tanzania, Libya, Sudan, Zimbabwe, and Botswana; Figures 1A and 2). The IDF estimates that 24 million people are living with diabetes in Africa, a number predicted to increase by 129% to 55 million[ii]. Furthermore, 59.7% of diabetes cases in Africa remain undiagnosed, representing the highest percentage of undiagnosed cases in the world. Higher proportions of undiagnosed cases are found in low-income countries than in middle-income countries[ii]. Despite various initiatives, including national strategies aimed at improving the availability of medicines for diabetes, up to 75% of diabetic patients face challenges in accessing the necessary medications (e.g., insulin) [24].



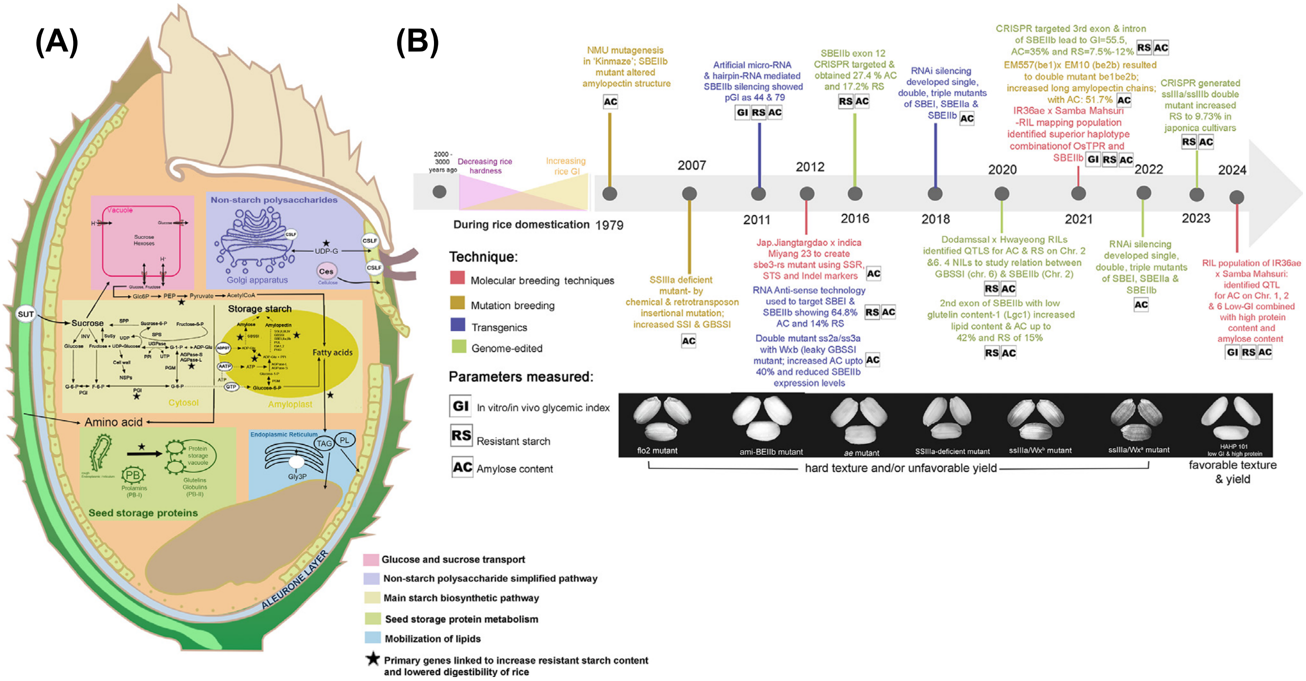
Trends in Plant Science

Figure 2. Scatter plot illustrating the annualized growth (1990–2019) in the per capita burden of diabetes versus the annualized growth in the per capita burden of chronic hunger reveals that future reductions in undernutrition are expected to be outweighed by increases in noncommunicable diseases associated with calorie-rich diets. Note, African countries are labeled using their ISO3 country code. Abbreviation: DALYs, disability-adjusted life-years.

Diabetes prevalence rates tend to follow an inverted U-shaped 'Kuznets' curve, where rates initially increase as countries become wealthier but later decline as governments implement public health policies (Figure 1B). Recent studies highlight the role of public policy in fostering healthy habits, particularly in children, by promoting physical activity and nutritious diets to counteract the harmful effects of processed food consumption and sugary drinks as well as reduced physical movement [23,25]. In response, nutritional interventions should focus on two key strategies: (i) converting starchy staples into healthier carbohydrates that are rich in RS and dietary fiber and possess low-GI properties and (ii) diversifying diets by introducing nutritious crops through crop rotations to ensure access to high-quality food products that provide more than just calories, thus addressing the double burden of malnutrition. One promising approach is to deploy rice varieties with a low GI that are enriched with fiber and antioxidants and maintain superior grain quality without sacrificing yield. These varieties could help combat the growing diabetes epidemic, particularly in low- and middle-income populations in Asia and Africa.

## Widespread adoption of the intermediate- to low-GI trait in breeding rice with acceptable texture

To breed low-GI varieties, two different breeding strategies must be deployed. The first approach includes deploying important landrace with a low-GI phenotype with good texture to create recombinant inbred and near-isogenic lines. The second approach is deploying the mutation breeding strategies to develop low-GI varieties with high RS content (Figures 3 and 4). Developing low-GI rice lines while simultaneously considering good texture with low chalk and higher head rice yield via conventional breeding is critical to meet the consumer demand. The ratio of amylose

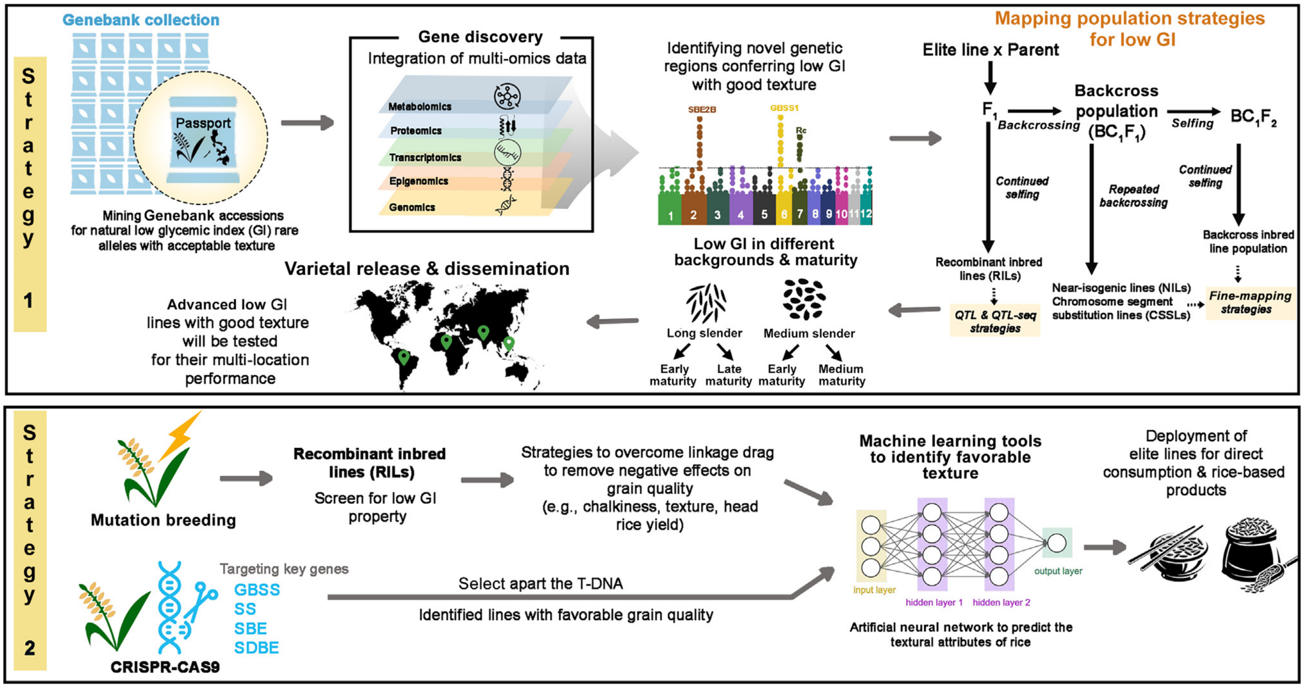


Trends in Plant Science

Figure 3. Development of low glycemic index (GI) and high resistant starch (RS) rice. (A) The impact of increasing amylose content (AC) and RS on reducing the GI of rice is primarily driven by key starch biosynthetic genes. These genes, along with those involved in amino acid metabolism, lipid synthesis, and nonstarch polysaccharide formation, contribute to lowering the overall digestibility of rice. The schematic representation was adapted from Butardo and Sreenivasulu [53]. (B) Timeline of high-RS and low-GI rice development through mutation breeding strategies and genome editing and RNA interference (RNAi) technology, illustrating the key targeted genes and the associated penalties on yield and sensory attributes over recent decades. Abbreviations: BE, branching enzyme; Chr, chromosome; EM, ethyl methanesulfonate; GBSS, granule-bound starch synthase; Indel, insertion/deletion; NIL, near-isogenic line; pGI, predictive glycemic index; QTL, quantitative trait loci; RIL, recombinant inbred lines; SBE, starch branching enzyme; SS, starch synthase; OsTPR, nuclear pore anchor similarity to translocated promote region.

to amylopectin is an important factor of starch quality that plays a pivotal role in determining the glycemic response and the textural attributes [7,26]. Amylose is characterized by elongated chains of glucans connected by α-1,4-glycosidic bonds, forming a linear structure. By contrast, amylopectin consists of highly branched glucans of β-1,6-glycosidic bonds linked to linear chains of α-1,4-glycosidic bonds. Enzymatic degradation by amylases can act at a single endpoint in amylose, resulting in slower digestion. Besides main starch components [8], oligosaccharides can contribute to low-GI properties of rice by resisting digestion in the small intestine, leading to slower glucose release into the bloodstream [27].

Historically, the amylose/amylopectin ratio was considered the sole factor influencing the GI. However, a nonsignificant correlation between the GI and **amylose content** unraveled within an indica diversity panel of 305 indica rice landraces with only three germplasms found to possess characteristic low-GI features [28]. Besides starch components, dietary fiber (primarily composed of pectin, arabinogalactan, and xylan) is crucial in lowering the GI of rice [29]. Within temperate japonica, screening 25 Italian rice varieties for their *in vivo* GI measurements in humans by measuring blood glucose levels determined that only five varieties were low GI [30]. Although *in vivo* GI measurements accurately measure the GI of rice, this process is laborious and expensive, a fact that greatly restricts its use in breeding programs. A recently established *in vitro* GI measurement approach with a high correlation to *in vivo* methods ($r^2$ = 0.96–0.97) provides a considerably more rapid and more economical alternative, enabling breeding programs to



Trends in Plant Science

Figure 4. Breeding strategies in developing low glycemic index (GI)-rice. (A) Strategy 1 involves conventional breeding by developing mapping populations in different background and maturity. (B) Strategy 2 involves mutation breeding or gene editing that focuses on the main starch biosynthetic genes to increase amylose content and resistant starch, thereby lowering rice digestibility, and deploy machine learning tools to overcome the barrier of grain quality.

effectively identify low-GI germplasms during prebreeding [31]. Once validated through *in vitro* GI measurements, continuous glucose monitoring for *in vivo* GI measurements can be deployed to determine the human GI response of the food matrix [32].

The GI of high-yielding varieties of rice are in the range of intermediate to high in glycemic response ranging from 65 to 94, with very few varieties possessing characteristic features of low-GI germplasm (Table S2 in the supplemental information online) [33]. During the postdomestication process, there has been a global shift from high- to low-amylose rice selection, which matches the preference for a smooth texture, leading to preferential selection of the mutated $Wx^b$ allele of granule-bound starch synthase (*GBSS1*) in japonica varieties at the 5' splice site of the exon/intron boundary while retaining the $Wx^a$ allele in indica from weedy rice [28,34]. This has inadvertently led to the rapid digestibility of rice with high-GI values [35]. A **transcriptome-wide association study** coupled with a **genome-wide association study** identified the genomic region *GI6.1* on chromosome 6 responsible for lowering the GI in rice [28]. This region includes 26 genes, among which *GBSS1*, substandard starch grain 6, and glucan endo-1,3-β-glucosidase 7 were related to the starch and dietary fiber pathways. To breed intermediate GI with soft texture, a novel 2-SNP haplotype of the *GBSS1* gene that is critical for consumer preference due to a balance between starch digestibility and textural attributes was identified [28]. The alternative splicing allele (the G allele of $Wx^a$) primarily influences GI variation, while exon 10 (C allele) is related to low final viscosity with higher initial starchy coating texture. The GC haplotype of *GBSS* is associated with intermediate GI and soft texture among indica populations, suitable for consumption in East and Southeast Asian countries, while the GT haplotype is linked to intermediate GI with a hard and cohesive texture preferentially enriched in South Asian countries [36]. Indeed, an expanding body of evidence has brought to light the complexity of GI as a trait, indicating that it is not only influenced by starch but is also impacted by various factors such as fiber, protein, lipids, and secondary metabolites [26,37]. These advances in rice starch genetics are pivotal in transforming popular rice varieties into low-GI options. Furthermore, the progress made in reducing the GI of rice can provide valuable insights for developing methods to lower the GI of other starchy staples and tubers.

## Strategies for enhancing the RS content of milled rice using mutation breeding and genome editing techniques

For over two decades, concerted efforts have been directed toward comprehending and elucidating the intricate factors that govern the RS, which most likely contributes to the lower complex glycemic trait (Figure 4), primarily centering on starch manipulation by altering the flux from amylopectin to amylose [7,38].

### Mutation breeding methods

The double-mutant population created by crossing EM557 (*be1*) of Taichung 65 and EM10 (*be2b*) of the Kinmaze mutant lines of branching enzyme (designated *be1 + be2b)* revealed a decrease in intermediate-length amylopectin chains [degree of polymerization (DP) 10–20] and an increase in long amylopectin chains (DP > 21), with a maximal amylose content of 51.7% [39]. Additionally, severely tampering with starch structure usually leads to reduced starch content and grain weight, subsequently affecting the overall grain yield (Figure 4). To address the yield barrier, Pasion *et al.* developed recombinant inbred line pyramiding of the ultralow GI trait in a high-yielding background with the superior haplotype combination of *OsTPR* (responsible for higher upper secondary rachis branching) and the recessive allele of the *sbeIIb* gene (for the ultralow GI phenotype) [40]. Badoni *et al.* identified candidate genes located on chromosome 2 (qGI2.1, spanning the region from 18.62 Mb to 19.95 Mb) that exert influence on the ultralow GI and a remarkable increase in protein content of 14–16% (more than twofold compared with its recipient line) [41]. These ultralow GI lines (GI ≤ 44) have comparable sensorial attributes as the recipient line [41]. Metabolomic analysis revealed that in ultralow (GI ≤ 45) and low-GI rice (GI ≤ 55), the flow of metabolites shifts from carbohydrate metabolism toward flavonoid and amino acid metabolism, potentially contributing to reduced digestibility. Mechanistically, the metabolic reflux observed could be attributed to the activation of certain genes involved in flavonoid and amino acid biosynthesis. For example, the downregulation of *OsbZIP58*, a key regulator of starch and protein synthesis, has been shown to directly activate the expression of several storage protein genes, including *GluA1*, *GluA2*, *GluA3*, *GluB1*, and *GluD1*, and 10-, 13-, and 16-kDa prolamins [42].

### Genome editing methods

Further, the utilization of advanced precision breeding tools such as CRISPR/Cas9 genome editing expedites the development of low-GI rice with high RS by targeting the **starch branching enzyme (SBE)** and starch synthase (SS) genes involved in amylopectin biosynthesis (Table 1 and Box 1). CRISPR/Cas9 knockout of *ssIIIa* and *ssIIIb* genes resulted in an increase in RS content from 0.5% to 5% in *ssIIIa* mutants; however, there was no significant difference in RS content observed in the *ssIIIb* mutant. With that said, the *ssIIIa/ssIIIb* double mutant showed increased RS content of up to 9.73% in *japonica* cultivars due to the synergistic effect of *ssIIIb* knockout on the *ssIIIa* mutant in increasing RS content [43,44]. The *ssII-2* and *ssII-3* CRISPR/Cas9-mediated knockout studies along with RNA interference unraveled the importance of *ssII-2* in the regulation of both amylose and amylopectin synthesis, thus finding it to be essential to maintain the balance for eating and cooking quality [45]. Suppressing the *sbeIIb* gene at exon 12 resulted in an increase in RS of 17.2% [46]. Using a similar approach, Wang *et al.* targeted the third exon and intron, which lead to a decreased GI to 55.5 and increased RS of up to 7.5% in heterozygous lines [47]. Badoni *et al.* targeted the 15th exon of *sbeIIb* to lower the GI to 54 in the high-yielding

Table 1. Gene-edited lines targeted in increasing amylose and resistant starch thereby lowering digestibility[a]

| Target gene (site) | Background | Changes observed | Pleiotropic effect observed | Refs |
|---|---|---|---|---|
| *sbeIIb* (exon 12) | – | Endosperm amylose 27.4% (1.4 times higher); RS: 17.2% | Decreased grain size, weight; increased interstitial space and round starch granules; opaqueness | [46] |
| *sbeI* (exon 1) and *sbeIIb* (exon 3) | Kitaake (japonica) | 22–26% AC compared with 15% WT in the *sbeIIb* mutant; no change in *sbeI*; RS: 9.8% for *sbeIIb* | No change in weight, width, and thickness of *sbeI* while it decreased for *sbeIIb* with higher gelatinization temperature and increased longer chains (DP > 14) and decreased SCAP (DP –12) and opaque | [54] |
| Exon 1 *sbeI*, exon 1 of *sbeIII*, exon 1 of *sbeIIb* and exon 3 for *sbeIIa* | Presidio rice | 22–42% higher endosperm AC; 2.4 times higher; 10–15% higher RS | Decreased total starch content, length, thickness, and weight; spherical starch granules; heterozygous; opaque | [49] |
| *sbeIIb* (exon 2)/*Lgc1* (low glutelin content 1) japonica rice | | 1.8-fold change increase in AC; 32.4–34.2%; RS: 5.6–6%; increased lipid content and amylose–lipid complexes | | |
| *sbeIIb* (third exon and third intron) | TNG82 (japonica) | GI lowered from 77 to 55.5 in homozygous and 68.5 in heterozygous; 15.8% to 31–35% AC; RS for homozygous is 6.7–7.5% and for heterozygous is 11.6–12% | Opaque in homozygous and chalky in heterozygous | [48] |
| SSII-2 (*ssIIb*) sixth exon, SSII-3 (*ssIIa*) second exon | Nipponbare | SSII-2 mutant affected the levels of the *Wx* gene along with SSII-2 and SSII-3, while SSII-3 and double mutants had no effect on the *Wx* gene; AC decreased for s2, with no significant change in s3 and s23 mutants; SSII-2 mutant increased DP 10–12 and >34 while decreasing short chains DP 5–9 and 13–33 | Not reported | [45] |
| *ss3a*, *ss3b* | Nipponbare | RS of *ss3a* raised to 4.76–5.01% from 0.58% (WT); TDS content and digestion rate decreased; RS for the *ss3a/ss3b* double mutant increased to 9.54–9.73%; AM1 increased; amylopectin B2 chains (DP 22–37) increased in *ss3a*; A chains DP 6–9 and B1 chains DP 12–21 decreased in *ss3a* and *ss3a* – *ss3b* | Increased chalky grain percentage in all single and double mutants; decreased 1000-grain weight and grain thickness; abnormal starch granule morphology in *ss3a* and *ss3a* – *ss3b* mutants while the *ss3b* mutant not much change compared with WT | [43] |
| *ssIIIa*, *ssIIIb* | ZH11; Jia58 japonica varieties | *ssIIIa* G-to-A point mutation leading to alternative splicing; *ssIIIb* with 2-bp del have premature stop codon; *ssIIIa* increased RS from 1.7 to 5.8% and *ssIIIb* no effect; double mutant (rs4) increased RS of 10.8%; rs4 mutant AAC, lipids, amylose–lipid complexes increased | Irregular starch granules with rounded shape; irregular surfaces leading to poor eating and cooking quality; white core floury endosperm; reduced grain yield | [44] |
| *GBSS1* | – | GBSS activity was not completely abolished; increase in *GBSS2* transcripts; amylose content declined to 8–12% in heterozygous seeds while <5% in homozygous seeds | Abnormal cellular organization in aleurone layer; amorphous starch grain structure | [55] |
| First intron of the $Wx^{b}$ allele of *GBSS1* | – | 10% increase in KY131 and X32 mutant lines harboring $Wx^{b}$ | X32 intron-deleted mutants more transparent that X32; KY131 intron-deleted mutant poor quality in appearance | [56] |

[a] Abbreviations: AC, amylose content; AM1, amylose1; bp, base pair; del, deletion; DP, degree of polymerization; SCAP, short-chain amylopectin; TDS, total digestible starch; WT, wild type.

IRRI 154 background [41]. Targeting the second exon of *sbeIIb* along with low glutelin content-1 (*Lgc1*) increased the lipid content and increased amylose up to 42% with an RS of 15% [48]. This strategy of enhancing the amylose content and simultaneously increasing lipid content is a valuable way to increase the grain RS content due to amylose–lipid interaction. Interestingly, no significant change in RS content was noted for the *sbeI* mutant, while *sbeIIb* increased the amylose content up to 26% and RS up to 9.8%. CRISPR multiplexing to target all four *SBE* genes (*sbeI*, *sbeIII*, *sbeIIb*, and *sbeIIa*) led to a very high increase in amylose content of 42% and increased the RS content to 15% [49].

### Box 1. Genetic engineering to lower the GI in rice

Through RNA technology, suppressing amylopectin biosynthesis genes, such as the various isoforms of SBE or SS enzymes, shifted the starch composition toward higher amylose or longer amylopectin chains, thus lowering the GI. Using artificial microRNA (ami-RNA)- and hairpin RNA (hp-RNA)-mediated RNA silencing targeting the *sbeIIb* gene achieved a reduced predicted GI value of 44 for ami-*BEIIb* and 79 for hp-*BEIIb* compared with 85 of wild type [57]. RNA antisense technology can suppress *sbeI* and *sbeIIb*, resulting in increased amylose content as high as 64.8% compared with 27.2% in wild type, thus increasing the RS from 0 to 14% [58]. Targeting all SBEs in the *sbeI/sbeIIa/sbeIIb* triple mutant dramatically reduced the seed weight and increased short-chain amylopectin, while *sbeI* and *sbeIIa* single mutations did not result in extreme phenotypes. These results clearly suggest that among the SBEs, *sbeIIb* is the governing factor for lowering the GI by diverting the amylopectin flux to amylose. More than 40% of amylose content was achieved in the endosperm of transgenic seeds that introduced the $Wx^a$ gene into the *ss2a/ss3a* double mutant line harboring $Wx^b$ (leaky mutant of *GBSS1*) and reduced levels of *sbeIIb* expression [59]. Although many of these mutants exhibited substantial increases in RS content, they were low yielding and possessed opaque and cracked endosperms after polishing (see Figure 3B in main text). Hence, their flour is targeted to developing cookies and other extruded food products tailored for the health-conscious market [39]. To overcome these limitations, it is imperative to develop a comprehensive understanding of these enzymes and use a combinatorial approach to target the genes, facilitating the attainment of low-GI characteristics while maintaining satisfactory eating and cooking qualities.

### Outstanding questions

How can rice with high RS and amylose content be developed to maintain a low GI without compromising yield and sensory attributes?

What are the specific genes and regulatory networks involved in determining the GI properties of rice?

What conventional breeding techniques and gene-editing strategies can be used to develop rice varieties with low GI, high RS, and high amylose content?

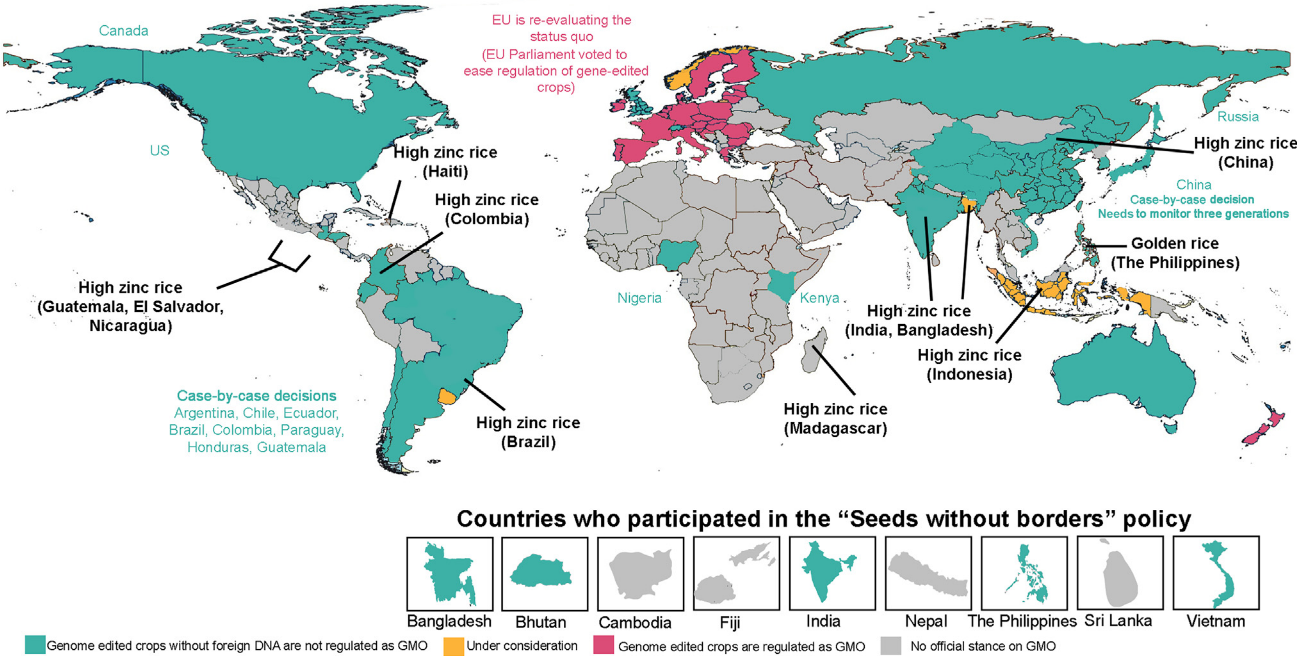
How can low-GI rice be effectively integrated into global food systems, and what strategies can ensure consumer acceptance?

## Concluding remarks and future perspectives

The emerging initiative of promoting ‘food as medicine’ underscores the potential of dietary-based interventions in treating a diverse range of chronic conditions, including diabetes [50]. Currently, the introduction of low-GI rice holds the greatest potential impact in Southern, Eastern, and Southeastern Asia, given the high diabetes rates and substantial consumption of (white) rice (Figure 1C) in these parts of the world. Currently, three low-GI rice varieties, namely BR-16, BRRI-46, and BRRI-69, were deployed in Bangladesh, and among the released varieties in the Philippines, IRRI-147 and IRRI-125 were shown to possess characteristic features of low-GI lines, exhibiting salt tolerance and resilience to extreme weather conditions. Furthermore, IRRI initiated the Seeds Without Borders project[iii], a regional seed policy agreement designed to expedite the distribution of modern rice varieties across countries in Southern Asia and Southeast Asia. This initiative is expected to be instrumental in deploying low-GI rice varieties[iv] and already released biofortified micronutrient zinc rice varieties in other parts of Asia [14,15], specifically targeting diabetes and other NCDs. This policy will facilitate the integration of the climate-resilient low-GI rice varieties in countries such as Bangladesh, Bhutan, Cambodia, Fiji, India, Nepal, the Philippines, Sri Lanka, and Vietnam (Figure 5). This will not only contribute to food security and nutrition [16] but also promote poverty reduction and improve livelihoods by providing smallholder farmers with access to high-value markets for nutritious rice. Additionally, Asian countries with high rates of protein deficiency and higher rates of diabetes prevalence can directly benefit from ultralow GI and high-protein rice, as the inclusion of high-protein foods in the diet is strongly associated with improved insulin response and reduced diabetes risk.

In the future, the same policy intervention will be pivotal in Africa to adopt nutritious rice varieties within a high-yielding background. Impact estimates for low-GI rice, assuming a 25% national adoption rate by farmers and a 25% reduction in the ‘rapid sugar spike’ content, indicate that diabetes prevalence in Asia could decrease substantially depending on factors such as the existing diabetes rates, rice consumption, and production levels (Figure 1D). By 2050, economic growth will likely shift the burden of hunger from undernutrition to higher NCDs, particularly diabetes, especially in Africa. Therefore, deploying low-GI measures early on could play a crucial role in mitigating future risks of diabetes and combating malnutrition overall. In other words, it can prevent countries from having to go through the Kuznets curve as they become wealthier (Figure 1B).

Although various mutants with high amylose and low GI have been developed [38,51], a common challenge associated with these mutants is their hardness, which renders them less suitable for



Trends in Plant Science

Figure 5. Global regulation of genome editing and genetically modified organisms (GMOs) and deployment of healthier rice varieties. This map illustrates the varying regulations surrounding genome editing and GMOs across different regions, alongside the deployment locations for newly developed rice varieties. It also highlights countries participating in the 'Seeds Without Borders' policy, which may facilitate easier access to low glycemic index (GI) and high zinc rice varieties developed through non-GMO. The policy expedites the spread of already released variety in one country to be notified among signatory countries in Asia, especially in South and Southeast Asia.

direct consumption [51]. In the past, these lines have been transformed into food products that can fetch a premium in the market, such as coingredients in nongluten products [7]. Additionally, the high amylose rice starches have been explored for various nonfood applications, including functional packaging, drug delivery systems, and catalytic templates [52]. These advances should catalyze the establishment of a collaborative ecosystem that nurtures the entire value chain, encompassing research and cultivation alongside processing and marketing. Currently, low-GI rice varieties with favorable textural properties have been released in some Asian countries[iv]. Forging partnerships across the entire value chain is imperative to seamlessly integrate low-GI rice and rice-based products into the global food system. This involves empowering the production of low-GI rice, reinforcing processing and distribution channels, and prioritizing consumer health awareness. Governments should actively facilitate market connections for farmers producing high-RS and low-GI rice, thereby contributing to rural poverty reduction. Moreover, private companies will delve into developing value-added products using high-RS rice, with a specific focus on nongluten products. At present, low-GI is a niche premium market. For instance, Doongara, an Australian low-GI rice variety, fetched a higher value for farmers of US$1700 per metric ton compared with milled nonbroken white high-GI rice being sold at US$350 per metric ton [38]. Collectively, the collaborative efforts across the entire value chain will contribute to the broader adoption and commercial success of these low-GI rice varieties, thereby simultaneously contributing to consumers' nutrition and farmers' incomes when this technology is brought to scale.

The emergence of genome editing technology will accelerate the process of tailoring low-GI varieties in other starch staples and tubers. Deploying gene-edited rice with high RS and low GI

(Table 1), along with other crop varieties, can best be tested and disseminated in regions with less strict genetically modified organism (GMO) regulations, such as Asia, North America, and Latin America as well as selected African countries (e.g., Kenya, Nigeria, and Ghana). For instance, products of SDN1 and SDN2 genome editing methods that are similar to naturally occurring events and do not carry exogenous DNA should be exempt from the Indian GMO laws. This approach is expected to create a series of low GI varieties across staples through genome editing to bring healthier dietary choices and counter the rising prevalence of diabetes. However, for other African countries, revisiting GMO laws will be necessary to facilitate the adoption of gene-edited low-GI rice varieties. In its broadest sense, research and investment in improving rice varieties will not only drive agricultural innovation but also address growing public health concerns. This can be achieved through proactive collaboration among research institutions within the Consortium of International Agricultural Research Centers, regulatory bodies supported by the government, and health policymakers (see Outstanding questions).

## Acknowledgments

N.S. acknowledges funding from the Foundation for Food and Agricultural Research (CA-21-SS-0000000157), Department of Agriculture and Farmers Welfare, Government of India, and The Indian Council of Agricultural Research. R.N.T. acknowledges the Academy for International Agricultural Research (ACINAR) for funding his PhD. ACINAR, commissioned by the German Federal Ministry for Economic Cooperation and Development, is being carried out by the Council for Tropical and Subtropical Agricultural Research e.V. on behalf of the Deutsche Gesellschaft für Internationale Zusammenarbeit GmbH.

## Declaration of interests

No interests are declared.

## Resources

[i] www.fao.org/faolex/opendata/en/

[ii] https://idf.org/about-diabetes/diabetes-facts-figures

[iii] www.irri.org/news-and-events/news/new-countries-asia-and-pacific-join-seeds-without-borders-initiative

[iv] www.irri.org/news-and-events/news/irri-reveals-scientific-breakthrough-low-and-ultra-low-glycemic-index-rice

## Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.tplants.2024.11.003.

## References

1. Sun, H. *et al.* (2022) IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* 183, 109119
2. GBD (2021) Diabetes Collaborators. (2023) Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 402, 203–234
3. Villegas, R. *et al.* (2007) Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. *Arch. Intern. Med.* 167, 2310–2316
4. GBD (2017) Risk Factor Collaborators. (2018) Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392, 1923–1994
5. Sreenivasulu, N. *et al.* (2023) Metabolic signatures from Genebank collections: an underexploited resource for human health? *Annu. Rev. Food Sci. Technol.* 14, 183–202
6. Thompson, A.S. *et al.* (2024) Higher habitual intakes of flavonoids and flavonoid-rich foods are associated with a lower incidence of type 2 diabetes in the UK Biobank cohort. *Nutr. Diabetes* 14, 32
7. Tiozon, R.J.N. *et al.* (2023) More than the main structural genes: regulation of resistant starch formation in rice endosperm and its potential application. *J. Plant Physiol.* 285, 153980
8. Shen, L.S. *et al.* (2022) Resistant starch formation in rice: genetic regulation and beyond. *Plant Commun.* 3, 100329
9. Custodio, M.C. *et al.* (2019) Rice quality: how is it defined by consumers, industry, food scientists, and geneticists? *Trends Food Sci. Technol.* 92, 122–137
10. Pingali, P.L. (2012) Green revolution: impacts, limits, and the path ahead. *Proc. Natl. Acad. Sci. U. S. A.* 109, 12302–12308
11. Khush, G.S. (2001) Green revolution: the way forward. *Nat. Rev. Genet.* 2, 815–822
12. Bhavadharini, B. *et al.* (2020) White rice intake and incident diabetes: a study of 132,373 participants in 21 countries. *Diabetes Care* 43, 2643–2650
13. Ren, G. *et al.* (2021) Association between intake of white rice and incident type 2 diabetes—an updated meta-analysis. *Diabetes Res. Clin. Pract.* 172, 108651
14. Stein, A.J. *et al.* (2005) Analyzing the health benefits of biofortified staple crops by means of the disability-adjusted life years approach: a handbook focusing on iron, zinc and vitamin. *Int. Food Policy Res. Inst. (IFPRI)* 4, 2005
15. Zimmermann, R. and Qaim, M. (2004) Potential health benefits of Golden Rice: a Philippine case study. *Food Policy* 29, 147–168

16. Robinson, S. *et al.* (2015) The international model for policy analysis of agricultural commodities and trade (IMPACT): model description for version 3. *Int. Food Policy Res. Inst. (IFPRI)* 1483,
17. Hu, E.A. *et al.* (2012) White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. *BMJ* 344, e1454
18. Anjana, R.M. *et al.* (2023) Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). *Lancet Diabetes Endocrinol.* 11, 474–489
19. Liu, X. *et al.* (2023) Trends in economic burden of type 2 diabetes in China: based on longitudinal claim data. *Front. Public Health* 11, 1062903
20. Ramachandran, A. *et al.* (2012) Trends in prevalence of diabetes in Asian countries. *World J. Diabetes* 3, 110–117
21. Arouna, A. *et al.* (2021) Moving toward rice self-sufficiency in sub-Saharan Africa by 2030: lessons learned from 10 years of the Coalition for African Rice Development. *World Dev. Perspect.* 21, 100291
22. Yuan, S. *et al.* (2024) Intensifying rice production to reduce imports and land conversion in Africa. *Nat. Commun.* 15, 835
23. Chong, B. *et al.* (2023) The global syndemic of metabolic diseases in the young adult population: a consortium of trends and projections from the Global Burden of Disease 2000–2019. *Metabolism* 141, 155402
24. Godman, B. *et al.* (2020) Review of ongoing activities and challenges to improve the care of patients with type 2 diabetes across Africa and the implications for the future. *Front. Pharmacol.* 11, 108
25. Popkin, B.M. *et al.* (2020) Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet* 395, 65–74
26. Parween, S. *et al.* (2020) Balancing the double-edged sword effect of increased resistant starch content and its impact on rice texture: its genetics and molecular physiological mechanisms. *Plant Biotechnol. J.* 18, 1763–1777
27. An, R. *et al.* (2022) Effects of oligosaccharides on the markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Food Funct.* 13, 8766–8782
28. Anacleto, R. *et al.* (2019) Integrating a genome-wide association study with a large-scale transcriptome analysis to predict genetic regions influencing the glycaemic index and texture in rice. *Plant Biotechnol. J.* 17, 1261–1275
29. Kosik, O. *et al.* (2020) Diversity of content and composition of cell wall-derived dietary fibre in polished rice. *J. Cereal Sci.* 96, 103122
30. Haxhari, F. *et al.* (2023) Endosperm structure and glycemic index of japonica Italian rice varieties. *Front. Plant Sci.* 14, 1303771
31. Pautong, P.A. *et al.* (2022) Evaluation of *in vitro* digestion methods and starch structure components as determinants for predicting the glycemic index of rice. *LWT* 168, 113929
32. Zeevi, D. *et al.* (2015) Personalized nutrition by prediction of glycemic responses. *Cell* 163, 1079–1094
33. Fitzgerald, M. *et al.* (2011) Identification of a major genetic determinant of glycaemic index in rice. *Rice* 4, 66–74
34. Huang, X. *et al.* (2021) Novel *Wx* alleles generated by base editing for improvement of rice grain quality. *J. Integr. Plant Biol.* 63, 1632–1638
35. Sreenivasulu, N. *et al.* (2022) Post-genomics revolution in the design of premium quality rice in a high-yielding background to meet consumer demands in the 21st century. *Plant Commun.* 3, 100271
36. Buenafe, R.J.Q. *et al.* (2021) Deploying viscosity and starch polymer properties to predict cooking and eating quality models: a novel breeding tool to predict texture. *Carbohydr. Polym.* 260, 117766
37. Brotman, Y. *et al.* (2021) The genetics underlying metabolic signatures in a brown rice diversity panel and their vital role in human nutrition. *Plant J.* 106, 507–525
38. Jukanti, A.K. *et al.* (2020) Low glycemic index rice—a desired trait in starchy staples. *Trends Food Sci. Technol.* 106, 132–149
39. Wada, T. *et al.* (2018) Development and characterization of a new rice cultivar, 'Chikushi-kona 85', derived from a starch-branching enzyme IIb-deficient mutant line. *Breed. Sci.* 68, 278–283
40. Pasion, E.A. *et al.* (2021) OsTPR boosts the superior grains through increase in upper secondary rachis branches without incurring a grain quality penalty. *Plant Biotechnol. J.* 19, 1396–1411
41. Badoni, S. *et al.* (2024) Multiomics of a rice population identifies genes and genomic regions that bestow low glycemic index and high protein content. *Proc. Natl. Acad. Sci.* 121, e2410598121
42. Ying, Y.N. *et al.* (2025) Multi-omics analyses reveal mechanism for high resistant starch formation in an indica rice mutant. *Carbohydr. Polym.* 347, 122708
43. Huang, L. *et al.* (2024) Creating high-resistant starch rice by simultaneous editing of SS3a and SS3b. *Plant Biotechnol. J.* 22, 787–789
44. Wang, A. *et al.* (2023) Loss of function of SSIIIa and SSIIIb coordinately confers high RS content in cooked rice. *Proc. Natl. Acad. Sci. U. S. A.* 120, e2220622120
45. Huang, L. *et al.* (2021) Improving rice eating and cooking quality by coordinated expression of the major starch synthesis-related genes, SSII and Wx, in endosperm. *Plant Mol. Biol.* 106, 419–432
46. Baysal, C. *et al.* (2020) Inactivation of rice starch branching enzyme IIb triggers broad and unexpected changes in metabolism by transcriptional reprogramming. *Proc. Natl. Acad. Sci. U. S. A.* 117, 26503–26512
47. Wang, H.-C. *et al.* (2021) Production of high amylose and resistant starch rice through targeted mutagenesis of starch branching enzyme Iib by CRISPR/Cas9. 8, 298
48. Guo, D. *et al.* (2020) Evaluation of the quality of a high-resistant starch and low-glutelin rice (*Oryza sativa* L.) generated through CRISPR/Cas9-mediated targeted mutagenesis. *J. Agric. Food Chem.* 68, 9733–9742
49. Biswas, S. *et al.* (2023) Increasing the level of resistant starch in 'Presidio' rice through multiplex CRISPR–Cas9 gene editing of starch branching enzyme genes. *Plant Genome* 16, e20225
50. Anon. (2023) Food as medicine: translating the evidence. *Nat. Med.* 29, 753–754
51. Tao, K. *et al.* (2019) High-amylose rice: starch molecular structural features controlling cooked rice texture and preference. *Carbohydr. Polym.* 219, 251–260
52. Tiozon, R.J.N. *et al.* (2021) Enhancing the functional properties of rice starch through biopolymer blending for industrial applications: a review. *Int. J. Biol. Macromol.* 192, 100–117
53. Butardo Jr., V.M. and Sreenivasulu, N. (2016) Tailoring grain storage reserves for a healthier rice diet and its comparative status with other cereals. *Int. Rev. Cell Mol. Biol.* 323, 31–70
54. Sun, Y. *et al.* (2017) Generation of high-amylose rice through CRISPR/Cas9-mediated targeted mutagenesis of starch branching enzymes. *Front. Plant Sci.* 8, 249451
55. Perez, L. *et al.* (2019) CRISPR/Cas9 mutations in the rice *Waxy/GBSSI* gene induce allele-specific and zygosity-dependent feedback effects on endosperm starch biosynthesis. *Plant Cell Rep.* 38, 417–433
56. Liu, X. *et al.* (2022) Targeted deletion of the first intron of the Wx b allele via CRISPR/Cas9 significantly increases grain amylose content in rice. *Rice* 15, 1
57. Butardo, V.M. *et al.* (2011) Impact of down-regulation of starch branching enzyme IIb in rice by artificial microRNA- and hairpin RNA-mediated RNA silencing. *J. Exp. Bot.* 62, 4927–4941
58. Zhu, L. *et al.* (2012) High-amylose rice improves indices of animal health in normal and diabetic rats. *Plant Biotechnol. J.* 10, 353–362
59. Crofts, N. *et al.* (2012) Lack of starch synthase IIIa and high expression of granule-bound starch synthase I synergistically increase the apparent amylose content in rice endosperm. *Plant Sci.* 193-194, 62–69