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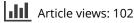
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# Could High-Amylose Wheat Have Greater Benefits on Diabesity and Gut Health than Standard Whole-wheat?

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#### ABSTRACT

Diets which have a low glycaemic index (GI) and high levels of dietary fibre are generally considered to be beneficial for promoting weight loss and improving insulin sensitivity, and are therefore recommended for the management of diabesity (the coexistence of obesity and type 2 diabetes mellitus). In addition, high dietary fibre intake is also positively associated with gut health. High-amylose wheat (HAW) is a type of wheat which has a lower GI value and contains higher amounts of dietary fibre, including resistant starch, compared with standard wheat, and therefore has potential applications as a functional food for improving metabolic and gut health. The aim of this review is to describe the characteristics of HAW and the current evidence in support of its potential effects on metabolic and gut health, as well as identifying important areas for future research. **KEYWORDS** 

Obesity; type 2 diabetes mellitus; high-amylose wheat; gut function

## The issue of diabesity

Obesity is a major public health challenge worldwide, with over one-third of the world's adult population being classified as overweight or obese in 2013.<sup>[1]</sup> Australia is one of the nations with the highest prevalence of overweight and obesity and according to the latest Australian Health Survey, 63.4% of Australian adults were overweight or obese when the survey was conducted (2014–2015).<sup>[2]</sup> Obesity arises from the complex interaction between environmental, socioeconomic and genetic factors. Ultimately, however, weight gain is the result of a chronic imbalance between energy intake and energy expenditure. The consumption of calorie-dense but nutrient-poor foods in conjunction with low levels of physical activity has been widely recognised as a major factor contributing to the dramatic rise in obesity rates worldwide.<sup>[3]</sup>

Overweight and obese individuals are at an elevated risk of developing a range of debilitating complications that can impact negatively on quality of life and result in premature mortality. Health consequences of obesity include dyslipidaemia, insulin resistance, osteoarthritis, sleep apnoea, asthma, impaired fertility, cardiovascular disease (CVD), hypertension, some cancers and psychological problems.<sup>[3]</sup> Type 2 diabetes mellitus (T2DM) is a particularly serious comorbidity associated with overweight and obesity<sup>[4]</sup> and the prevalence of T2DM

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has increased at an alarming rate, paralleling global overweight and obesity trends. In the latest Australian Health Survey, over 1.2 million Australian individuals were reported to have T2DM.<sup>[2]</sup> The coexistence of obesity and T2DM in the same individuals is more detrimental to health than either condition alone, since T2DM also confers an elevated risk of developing life-threatening macrovascular (e.g., CVD and stroke) and microvascular (e.g., retinopathy, neuropathy and nephropathy) complications.<sup>[5]</sup>

The strong and interdependent relationship between obesity and T2DM has led to the coining of the term 'diabesity' (also known as obesity-associated diabetes) to describe diabetes in the context of obesity.<sup>[4]</sup> It has been estimated that between 80% and 90% of all diagnoses of T2DM are secondary to overweight or obesity.<sup>[4]</sup> Both obesity and T2DM make a significant contribution to healthcare expenditure of both industrialised and semi-industrialised nations. In the US, the annual health-care cost attributable to obesity was US\$190.2 billion in 2005, representing ~21% of total US healthcare expenditure.<sup>[6]</sup> Global health expenditure on diabetes was US\$376 billion in 2010 and is expected to reach US\$490 billion by 2030.<sup>[7]</sup> According to the Australian Diabetes, Obesity and Lifestyle study, the total annual direct cost attributable to overweight and obesity for Australian adults aged ≥30 years was AUS\$21.7 billion in 2005<sup>[8]</sup>, while the amount attributed to diabetes in the same year was AUS\$10.6 - billion.<sup>[9]</sup> The significant financial burden of obesity and T2DM has led to an increasing emphasis on identifying effective strategies for preventing and treating these diseases.

# **Treatment options for diabesity**

While a wide range of strategies are used for the treatment and management of obesity and T2DM, the long-term efficacy of most of these approaches remains questionable. Pharmacological approaches for treating obesity and T2DM are available, but most of these have significant side effects, including headache, gastrointestinal discomfort, and nausea<sup>[10,11]</sup>, and are thus not suitable for long-term use. Surgical approaches, such as gastric banding, are an effective treatment option, but are costly and carry the risk of complications from the surgery, and so are typically reserved for individuals with severe obesity who have not responded to other forms of treatment.<sup>[12]</sup>

Diet and lifestyle interventions, particularly low-energy diets and increased physical activity, remain the first-line therapeutic strategies for tackling both obesity and T2DM, and have been shown to be effective in preventing the progression to T2DM in overweight and obese subjects.<sup>[13]</sup> However, a major challenge with most dietary interventions is the difficulty individuals experience in maintaining weight loss in the long term. In fact, one review paper noted that only about 20% of overweight individuals were able to successfully maintain a weight loss of  $\geq$ 10% of their initial body weight for at least 1 year.<sup>[14]</sup> Thus, while low-energy diets are often effective in achieving short-term weight loss, most individuals end up regaining any lost weight within a relatively short time-frame after the diet ends and often end up heavier than they were before dieting. In this context, it remains important to identify diets that are sustainable and can therefore assist individuals in maintaining long-term weight loss or avoiding further weight gain.

Low glycaemic index (GI) or glycaemic load (GL) diets are one dietary approach that has been widely applied to the management of obesity and T2DM, and have been shown to have beneficial effects on weight loss and insulin sensitivity. The GI of a food is determined by comparing its glycaemic response to that of the same amount of carbohydrate (CHO) from a standard food (i.e., glucose or white bread) consumed by the same subject. Low GI foods (GI values <55) are digested and absorbed more slowly than high GI foods (GI values >70), and therefore result in longer feelings of fullness after a meal, slowed gastric emptying and improved insulin sensitivity and pancreatic  $\beta$ -cell function.<sup>[15]</sup> A low GI diet has been shown to be beneficial for weight loss and insulin sensitivity, whereas chronic consumption of a high GI diet has been linked to weight gain, elevated triglyceride and reduced HDL cholesterol concentrations and insulin resistance.<sup>[16]</sup> As a result, replacing high GI CHO with low GI CHO in the diet has been suggested as a strategy to achieve metabolic benefits, including weight loss and improved insulin sensitivity. Consequently, promoting the consumption of (lower GI) whole-grains and whole-grains based foods in the place of (higher GI) refined grains represents a potential sustainable approach for the management of diabesity.

## Whole-grains

Whole-grains consist of the entire grain, including the bran and germ in their natural ratio, while refined-grains only contain endosperm. The germ contains a mixture of lipids, proteins, and some soluble CHOs while the bran is composed of mainly fermentable CHOs (cellulose, hemicellulose and arabinoxylan) and polyphenolic lignins.<sup>[17]</sup> Due to their higher nutrients content in comparison to refined grains, whole-grains are generally considered to have a greater nutritional value. A meta-analysis reported that consumption of 40 g (and ideally 50 g) of whole-grains daily is associated with beneficial health effects in human subjects, including protection against obesity and T2DM.<sup>[18]</sup> Recommendations to consume whole-grains also feature in many national dietary guidelines, including the Australian Dietary Guidelines 2013<sup>[19]</sup> and Dietary Guidelines for Americans 8th ed. 2015–2020.<sup>[20]</sup>

#### Anti-diabesity effects

There are several features of whole-grains that contribute to their greater health benefits in comparison to refined-grains. First, the GI of whole-grains is typically lower than refined-grains; therefore, as indicated above, replacing refined-grains with whole-grains effectively reduces the GI value of food. For instance, the average GI value of 100% Whole Grain<sup>®</sup> bread (51) and whole-wheat bread (~69) are lower than that of refined wheat bread (~75).<sup>[21]</sup> Whole-grains also have a higher dietary fibre content compared to refined grains. Whole-wheat flour, for example, contains ~380% more dietary fibre than refined wheat flour (13.39 g vs. 3.52 g/100 g).<sup>[22]</sup> Dietary fibre is known to have laxative effects and blood lipid and blood glucose-lowering properties.<sup>[18]</sup> In a prospective cohort study involving 176,117 adults, higher self-reported cereal fibre intake was shown to be inversely associated with T2DM risk (relative risk 0.72 [95% CI, 0.56–0.93])<sup>[23]</sup>, while in another study intake of fibre derived from whole-grains, but not fibre from other foods, was associated with 17% reduction in the risk of all-cause mortality.<sup>[24]</sup>

The bioactive nutrients present in whole-grains, including inorganic nutrients, vitamins, minerals and antioxidant compounds, also contribute to their added health benefits compared to refined grains. Whole wheat, for example, contains essential amino acids (lysine and tryptophan), vitamins (thiamine and niacin), minerals (phosphorus and iron), and abundant bioactive compounds (alkylresorcinols, benzoxazinoids, phytosterols, tocols, lignans and

phenolic acid). The levels of alkylresorcinols (1,3-dihydroxy-5-alkylbenzene derivatives) are particularly high in whole-grains; whole wheat contains 489–660 µg of these compounds per gram, compared to only 13–47 µg/g in refined wheat.<sup>[25]</sup> Wheat alkylresorcinols have been shown to promote glucose tolerance and insulin sensitivity in a mouse model of diet-induced obesity by suppressing hepatic lipid accumulation and intestinal cholesterol absorption.<sup>[26]</sup> Other individual nutrients have also been shown to have favourable metabolic effects; benzoxazinoids and their derivatives have appetite- and weight-reducing effects<sup>[27]</sup>, lignans exhibit antioxidant effects<sup>[28]</sup>, and the phenolic acids (e.g., ferulic acid and vanillic acid) exhibit antidiabetic properties.<sup>[11]</sup> The different types of bioactive compounds present in whole-wheat including their functional properties have been well described in previous reviews<sup>[29,30]</sup> and, therefore, will not be discussed in detail here.

#### **Gut health**

Whole-grains have a number of beneficial effects on gut function in comparison to refinedgrains, including prolonging gastric emptying and increasing stomach distention and small intestinal transit time.<sup>[31]</sup> These effects are largely due to the higher dietary fibre content of whole-grains compared to refined grains, since fibre is one of the most important dietary constituents involved in the regulation of these processes.<sup>[32]</sup> Dietary fibre also promotes large bowel function and increases colonic transit time, by promoting fermentation by the gut microbiota and through its bulking action.<sup>[32]</sup> As a result, increased consumption of dietary fibre has been shown to assist in weight loss and prevention of weight gain, improve glucose tolerance and lower total plasma cholesterol levels.<sup>[33]</sup> The major forms of fibre in wheat are the insoluble fibre arabinoxylan and soluble fibre  $\beta$ -glucan.<sup>[34]</sup> Both of these forms of fibre increase faecal bulk regulate intestinal movement and decrease the amount of glucose absorbed in the small intestine, and consequently reduce circulating cholesterol concentrations.<sup>[35]</sup>

The gut is the largest endocrine organ in the body, secreting more than 30 different peptide hormones. These hormones act either on vagal afferent endings to signal satiety or enter the circulation to target distant organs.<sup>[36]</sup> The gut hormones have a diverse range of physiological effects. Glucagon-like peptide (GLP)-1, for example, enhances postprandial glucose-dependent insulin release, inhibits glucagon secretion and delays gastric emptying via the vagal pathway and endocrine actions at central sites.<sup>[36]</sup> Peptide tyrosine tyrosine (PYY) also promotes satiety both via direct actions on the hypothalamus and by reducing gut motility<sup>[37]</sup>, while ghrelin is orexigenic and promotes appetite via local and systemic actions.<sup>[38]</sup>

The hormones released by the gut depend on the types and amounts of specific nutrients, including CHO, in the diet, which interact with specialised nutrient receptors on cells within the gastrointestinal tract to facilitate hormone release.<sup>[39]</sup> For example, glucose released from the digestion of starches, including wheat, binds to the sweet taste receptor heterodimer, Taste 1 Receptor Member 2 (TAS1R2)-Taste 1 Receptor Member 3 (TAS1R3). This results in increased release of GLP-1, which in turn acts to suppress gut motility and induce satiety.<sup>[39]</sup> In addition to the amount and type of wheat consumed, there is evidence that the different physical size of the wheat particles consumed can also impact on gastrointestinal responses.<sup>[40]</sup> By way of example, one small human trial (n = 9) demonstrated that consumption of 55 g of porridge made using coarse (2 mm) wheat particles resulted in significantly lower blood glucose, insulin and glucose-dependent

insulinotropic polypeptide (GIP) concentrations in comparison to consuming the same amount of porridge made with smooth (<0.2 mm) wheat particles.<sup>[40]</sup>

The human gut microbiota contains tens of trillions of microorganisms, in which at least 1000 distinct species have been identified.<sup>[41]</sup> These microbes mainly comprise of bacteria, of which more than 90% belong to either the *Firmicutes* (60–80%) or *Bacteroidetes* (20–40%) species, although archaea, viruses, fungi and protozoa are also present.<sup>[42]</sup> There is increasing recognition that shifts in the composition of the gut microbiota have significant effects on human health, including metabolic health, and may contribute to the risk of obesity, insulin resistance and T2DM.<sup>[43]</sup> Increased abundance of *Firmicutes* in the gut is generally associated with obesity while the *Bacteroidetes* are associated with weight loss in most<sup>[44,45]</sup>, though not all<sup>[46]</sup>, human studies. In addition, increasing gut *bifidobacteria* content by supplementing the diet with a prebiotic (oligofructose) has been associated with improved glucose tolerance and glucose-induced insulin secretion and anti-inflammatory effects.<sup>[47]</sup>

The composition of the gut microbiota is highly influenced by dietary intake, with dietary factors estimated to account for ~57% of the variation in gut microbiota, in comparison with only ~12% due to genetic variation.<sup>[48]</sup> The fermentable CHOs, including dietary fibre, resistant starch and oligosaccharides (stachyose, raffinose, and fructooligosaccharides), mainly present in the bran and germ parts of the whole grain, play a particularly significant role in regulating gut microbiota composition, and this may largely explain the positive influence of whole-grains on the gut microbiota. These components all appear to have prebiotic effects, which help to increase *bifidobacteria* and *lactobacilli* in the gut, and this has been demonstrated in human clinical trials as well as animal studies.<sup>[49]</sup>

The fermentation of undigested CHOs such as dietary fibres by gut microbiota results in the generation of a number of end-products, of which short-chain fatty acids (SCFAs) are one of the most well studied. SCFAs are a subset of saturated fatty acids containing six or less carbons (C). The most abundant SCFAs are acetate (C2), propionate (C3), and butyrate (C4).<sup>[50]</sup> The majority (~95%) of these SCFAs are rapidly absorbed by the colonocytes or are released into the circulation. The SCFAs are largely utilised as an energy source to fuel the intestinal epithelial cells.<sup>[51]</sup> However, some SCFAs also act as signalling molecules for intestinal orphan G protein-coupled receptors, which are involved in regulation of glucose homeostasis and lipid metabolism, with different SCFAs having different effects.<sup>[52]</sup> Thus, propionate is mainly involved in promoting hepatic gluconeogenesis, while acetate and butyrate contribute to hepatic lipogenesis and cholesterogenesis.<sup>[53]</sup> Different bacterial species give rise to different SCFAs; Bacteroidetes mainly produce acetate and propionate and Firmicutes produce predominately butyrate.<sup>[51]</sup> The polysaccharides from the wheat bran (e.g., cellulose, arabinoxylans, and  $\beta$ -glucan), which escape digestion in the small intestine, may end up being fermented by the microbiota in the large intestine, resulting in the production of individual monosaccharides and additional SCFAs.<sup>[51]</sup> Animal studies have shown that wheat bran fibre alters intestinal microbiota composition, resulting in increased Lactobacillus counts in the ileum and Bifidobacterium counts in the colon, increased caecal SCFA concentrations and reduced pH in the colon compared to a control diet without wheat bran.<sup>[54,55]</sup>

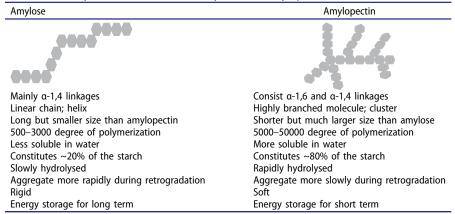


Table 1. The key differences between amylose and amylopectin in starch.

#### **High-amylose wheat (HAW)**

High-amylose wheat (HAW) is distinguished from other types of wheat by its higher amylose content. This difference has, in turn, led to suggestions that HAW may afford additional health benefits over and above those provided by other types of whole-wheat.

Starch is comprised of the glucose polymers amylose and amylopectin, which mainly differ in their branching and molecular size. The key differences between amylose and amylopectin are shown in Table 1. The total starch content in most grains, including wheat, typically comprises 72–75% amylopectin and 25–28% amylose. However, the relative proportions of these polymers can be altered either through normal selective breeding or genetic manipulation. In HAW, the amylose content of wheat can increase to up to ~50% of total starch content through normal selective breeding<sup>[56]</sup>, whereas in some mutant genotypes of wheat, the amylose content can be increased to up to 70% of total starch content.<sup>[57]</sup> Bird and Regina<sup>[58]</sup> neatly summarise how the elevation of amylose content in wheat can be attained mainly by manipulating two different mechanisms that control starch biosynthesis: (i) suppression of starch synthase IIa that reduces both glucan elongation and amylopectin synthesis and (ii) suppression of starch branching enzyme (SBE) IIa and/or SEBIIb. Similarly, the amylose content can decrease to as low as 1% (e.g., waxy wheat) through mutations in the starch synthase.

#### Potential anti-diabesity effects

To date, no published study has specifically evaluated the GI value of HAW as this type of wheat is still novel and has not yet been marketed or grown commercially. Previous studies have, however, demonstrated that the ratio of amylose to amylopectin is a major factor influencing the GI value of CHO. Consequently, the higher amylose content and amylose:amylopectin ratio of HAW in comparison to standard wheat would be expected to be associated with a lower GI value. The inverse relationship between the amylose: amylopectin ratio and GI is due to the fact that the chemically linear amylose chain forms a compact structure that limits enzyme accessibility and amylolysis, thus slowing digestion and reducing postprandial glycaemic and insulinemic response.<sup>[59]</sup> In contrast, amylopectin is highly branched and less ordered than amylose, and is thus more easily digested and

produces a higher glycaemic response. Amylose molecules also aggregate and crystallise more rapidly during retrogradation in cooked starch compared to amylopectin, and are thus resistant to enzyme hydrolysis and are more slowly digested.<sup>[60]</sup> Therefore, replacing refined-grains with HAW may be even more effective than replacement with standard whole-grains wheat in reducing the GI value of the food. Directly testing this hypothesis remains an important question to address in future studies.

In addition to the higher amylose content, HAW also has a higher dietary fibre content which contributes by the increased amount of resistant starch compared to standard wheat. Resistant starch is a form of dietary fibre and is defined as any starch that is not digested by  $\alpha$ -amylase in the small intestine and therefore passes to the large bowel to be fermented by microbiota.<sup>[61]</sup> A recent review published by Bird and Regina<sup>[58]</sup> describes the health benefits of HAW with particular emphasis on this type of wheat being a superior source of dietary fibre, in particular resistant starch, compared to standard wheat. This is supported by studies that have assessed dietary fibre content of different types of wheat, including a study that reported one specific type of HAW (of unknown amylose content) contained 2.8-3.6% of resistant starch in dry matter, compared to almost none in standard wheat.<sup>[62]</sup> Similarly, another study reported that HAW flour (~50% starch as amylose) contained 16.9% of resistant starch in dry matter compared to 1.8-7.3% in flour obtained from other wheat types.<sup>[56]</sup> The higher amount of resistant starch in HAW flour can be attributed to its higher amylose content, since a previous study identified a positive relationship between resistant starch and amylose content in rice.<sup>[63]</sup> Since resistant starch is not digested or absorbed in the small intestine, consumption of HAW would also be expected to reduce postprandial glycaemic and insulinemic response in comparison to consumption of an equivalent amount of standard wheat. In addition, HAW also contains bioactive compounds, vitamins and minerals which have beneficial effects on body weight, insulin sensitivity and/or gut health as similar to other whole-grains.<sup>[29,30,64]</sup> However, further studies are needed to determine how the levels compare to those in other commercial wheat types and whether this has the potential to confer additional health benefits.

#### Gut health

Given the significant roles of whole-grains in promoting gut function, gut hormone production and microbiota composition, it is expected that the higher levels of amylose and dietary fibres (including resistant starch) in HAW compared to standard whole-wheat will contribute to additional effects on gut. To date, however, few studies have directly tested this. In rodents, diets containing high-amylose-resistant starch have been demonstrated to reduce body fat mass via effects on gut hormone concentrations<sup>[65,66]</sup>, including increased production (in both the cecum and large intestine) and plasma concentrations of the anorexigenic gut hormones PYY and GLP-1.<sup>[65]</sup> There are also indications, however, that the effects of increased dietary intake of resistant starch may differ between lean and obese individuals. In a rodent study, consuming dietary resistant starch from high-amylose-resistant corn starch (Hi-Maize 260) resulted in decreased fat mass and improved glucose tolerance in lean, but not obese, C57BL/6J mice.<sup>[67]</sup> Thus, it will be important to evaluate the effects of HAW in both lean and obese humans and animals.

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The consumption of HAW also has the potential to favourably alter the composition of the gut microbiota and increase the production of SCFAs by providing more fuel for gut microbiota. Previous studies have demonstrated reduced Firmicutes and increased Bacteroidetes levels in rodents fed a diet containing high-amylose corn starch.<sup>[68,69]</sup> In addition, supplementing the diet of high-fat diet-fed mice with high-amylose corn starch was shown to result in an increased Bacteroidetes/Firmicutes ratio in the gut in comparison with mice fed the high-fat diet alone.<sup>[70,71]</sup> Consuming HAW (>70% amylose content) has been reported to lower the pH value (pH 5.90) of the caecal content compared with standard amylose wheat (pH 6.23).<sup>[60]</sup> This study showed that both total SCFAs and all individual SCFAs (acetate, propionate, and butyrate) in the faeces were significantly higher in rats fed with HAW than those fed with standard wheat. HAW has also been shown to preserve colonic function in rats fed Western-style moderate-fat (19%) and protein (20%) diets by reducing colonic DNA damage and increasing SCFA levels in the digesta.<sup>[72]</sup> In another study, however, HAW consumption was not associated with alterations to colon contractility, which suggests HAW does not affect gut motility and transit time.<sup>[73]</sup> The impact of HAW on the composition of gut microbiota and SCFA production especially in humans has yet to be determined and represents a critical area for future research.

Even though dietary nutrients, including dietary fibre, present in HAW may impart beneficial effects to health as discussed above there is also the possibility of adverse effects of HAW, particularly at a high level of intake. For instance, metabolic reactions occurring in the colon or distal small intestine, due to unabsorbed polysaccharides such as fructose and fructans that are also present in HAW, could potentially result in increased flatulence, abdominal discomfort/bloating and diarrhoea.<sup>[74]</sup> It is also likely, however, that these symptoms will vary between individuals. For example, a large proportion of individuals with irritable bowel syndrome have impaired gut transit time and tolerance of intestinal gas load compared with healthy subjects<sup>[75]</sup>, and therefore a HAW diet may not be advisable for this population. However, the impact of different levels of a HAW diet on gut health and whether there may be undesirable side effects associated with higher levels of consumption has yet to be directly tested either in animal models or human subjects.

#### Public health perspective and potential applications

Wheat is a versatile ingredient for many cereal-based processed products and about 20% of food calories for the world population are supplied from this grain.<sup>[60]</sup> In Australia, wheat is the largest crop produced yearly; ~21.9 million tonnes of wheat was produced in 2015–2016, which was grown over 11.1 million hectares.<sup>[76]</sup> In recent years, however, an increasing number of Australian adults are consciously avoiding the consumption of foods containing wheat due to concern about the potential negative health effects of the gluten components.<sup>[77]</sup> Since celiac disease (i.e. a medically diagnosed intolerance of gluten), affects less than 1% of the Australian population<sup>[78]</sup>, it is clear that a substantial number of adults are avoiding consumption of wheat-based products predominantly based on perceived negative health effects.<sup>[77]</sup> In this context, there is a pressing need to re-establish the confidence of Australian consumers in the health benefits that can be obtained from wheat-based products. Consequently, a systematic assessment of the effects of HAW on metabolic- and gastrointestinal health is warranted. If the superior benefits of HAW in

aiding weight loss and improving metabolic/gut health are proven, then replacement of standard wheat with HAW in staple foods, such as bread, breakfast cereals and pasta, may potentially offer an alternative approach to treat and/or prevent diabesity without changing existing dietary habits.

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