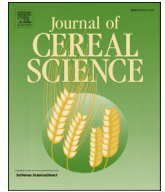


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Review

Does wheat make us fat and sick?

Fred J.P.H. Brouns^{a,*}, Vincent J. van Buul^a, Peter R. Shewry^b^a Maastricht University, Faculty of Health, Medicine and Life Sciences, Department of Human Biology, Health Food Innovation Management, P.O. Box 616, 6200 MD Maastricht, The Netherlands^b Rothamsted Research, Plant Biology and Crop Science, West Common, Harpenden, Hertfordshire AL5 2JQ, United Kingdom

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ABSTRACT

After earlier debates on the role of fat, high fructose corn syrup, and added sugar in the aetiology of obesity, it has recently been suggested that wheat consumption is involved. Suggestions have been made that wheat consumption has adverse effects on health by mechanisms related to addiction and over-eating. We discuss these arguments and conclude that they cannot be substantiated. Moreover, we conclude that assigning the cause of obesity to one specific type of food or food component, rather than overconsumption and inactive lifestyle in general, is not correct. In fact, foods containing whole-wheat, which have been prepared in customary ways (such as baked or extruded), and eaten in recommended amounts, have been associated with significant reductions in risks for type 2 diabetes, heart disease, and a more favourable long term weight management. Nevertheless, individuals that have a genetic predisposition for developing celiac disease, or who are sensitive or allergic to wheat proteins, will benefit from avoiding wheat and other cereals that contain proteins related to gluten, including primitive wheat species (einkorn, emmer, spelt) and varieties, rye and barley. It is therefore important for these individuals that the food industry should develop a much wider spectrum of foods, based on crops that do not contain proteins related to gluten, such as teff, amaranth, oat, quinoa, and chia. Based on the available evidence, we conclude that whole-wheat consumption cannot be linked to increased prevalence of obesity in the general population.

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1. Introduction

Wheat is the most widely cultivated cereal grain worldwide, being grown in temperate climates from Scandinavia in the north to Argentina in the south, including upland regions in the tropics. It is third among the cereals, behind maize and rice, in total global production, which was 704 million tons in 2011. The demand for wheat for human consumption is also increasing globally, including in countries which are climatically unsuited for wheat production, due to the adoption of western-style diets. Wheat is relatively rich in micronutrients, including minerals and B vitamins, and supplies up to 20% of the energy intake of the global population (Cummins and Roberts-Thomson, 2009).

About 95% of the wheat that is grown and consumed globally is bread wheat (*Triticum aestivum*). Bread wheat is a relatively new

species, having arisen in southeast Turkey about 9000 years ago (Feldman and Millet, 2001). It is hexaploid with three related genomes (termed A, B and D) and probably arose by spontaneous hybridization between a cultivated form of tetraploid wheat (*Triticum turgidum*) and a related wild grass species (goat grass, *Aegilops tauschii*). Most of the remaining 5% of the wheat crop is tetraploid durum wheat (also called pasta wheat) (*T. turgidum* var *durum*) which is more adapted to the dry Mediterranean climate. However, small amounts of “primitive” wheats are also grown, mainly for specialist health foods: einkorn (diploid *Triticum monococcum*), emmer (tetraploid *T. turgidum* var *dicoccon*) and spelt (hexaploid *T. aestivum* var *spelta*). The latter essentially differs from bread wheat in that the hull is not removed by threshing; resulting in a higher fibre content when consumed as whole grain.

Although wheat is a young species, it is immensely diverse, with forms adapted to a wide range of local environments and selected for different end uses. Feldman et al. (1995) estimated that at least 25,000 genetically distinct forms occur, but this is undoubtedly an underestimate with previously unreported diversity being described in recent years in countries such as China. Determination of the full genome sequence of bread wheat has been hindered by the massive genome size (17 gigabases, which is 40 times the size of

Abbreviations: ATIs, amylase-trypsin inhibitors; CD, celiac disease; GI, glycemic index; IBS, irritable bowel syndrome.

* Corresponding author. Tel.: +31 (0) 433 88 14 66; fax: +31 (0) 433 67 09 76.

E-mail addresses: fred.brouns@maastrichtuniversity.nl (F.J.P.H. Brouns), v.vanbuul@maastrichtuniversity.nl (V.J. van Buul), peter.shewry@rothamsted.ac.uk (P.R. Shewry).

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the rice genome and 5 times the size of the human genome) and the hexaploid nature. However, a recent study identified 96,000 to 98,000 genes, many of which were assigned to the three genomes (Brenchley et al., 2012). The large genome size, with a high content of mobile elements, and the hexaploid nature have, however, also resulted in high genome plasticity, which has facilitated rapid adaptation and contributed greatly to the global success of the wheat crop (Dubcovsky and Dvorak, 2007).

The wheat grain contains many hundreds of individual proteins, which may have structural, metabolic, protective or storage functions (as reviewed by Shewry (2009)). They include the gluten proteins, which are the major storage components and may account for up to 80% of the total grain protein (Wrigley et al., 1988). The protein composition of the grain is determined by the genotype, but also strongly influenced by the environment (climate and agronomy). For example, the contents of protective proteins may be greater when the plant is subjected to heat or drought stress while the total content of gluten proteins and the proportions of different gluten protein components are influenced by the availability of mineral nutrients (nitrogen and sulphur) (Shewry, 2011).

Several popular nutritional plants, such as the Paleolithic diet (CBS, 2012; Jönsson et al., 2006, 2005; Rose, 2011) and more recently the proposal of the U.S. cardiologist W.R. Davis, in his recent bestseller book, *Wheat Belly* (2011), have suggested that (whole-)wheat consumption has adverse health effects, based on different and controversial hypotheses. With this, they follow a recent trend to pinpoint the cause of obesity to one specific type of food or food component, rather than to overconsumption and inactive lifestyle in general. Hence, following discussions on the roles of fat, fructose, high fructose corn syrup and added sugar in foods, it seems that it is now the turn of wheat to take the blame for obesity. These discussions fail to take into account that obesity has a multifactorial causation (Grundy, 1998; Keith et al., 2006).

For centuries, there have been populations who consume wheat-based breads and other wheat products as the main source of their energy intake, such as in Turkey, without indices of causing weight gain. Moreover, the consumption of whole grain products, which in the U.S. and Europe are mainly based on wheat, has been shown to be associated with reduced risks of type 2 diabetes, cardiovascular disease, some types of cancer as well as a more favourable weight management (Ye et al., 2012). It is also argued that the current worldwide wheat production consists of “genetically modified” varieties, which contain new components that cause adverse health effects. In reality, the presence of such new components is not supported either by comparative studies of old and recently bred types of wheat (Ward et al., 2008) or by analyses of genomic sequences (Brenchley et al., 2012). Moreover, hard data about adverse effects of wheat, consumed in baked, extruded, and other processed foods, are not available, and there are no grounds to advise the general public not to consume this common dietary staple. Only individuals with a genetic predisposition for celiac disease, or suffering from allergy or other forms of sensitivity to gluten and other wheat proteins, will benefit from excluding wheat and related cereals from their diet.

2. Materials and methods

To ensure the quality of the research, and to obtain transparent and reproducible results, we made use of certain guidelines. In our search strategy, we used several databases of controlled scientific articles. All articles are referred to in the text and are available in English. We discuss most the relevant articles and critically evaluate the data. We also consider the scientific evidence for possible mechanisms based on recent literature.

3. Discussion

In a recent interview (CBS, 2012), the cardiologist W.R. Davis discussed his recent bestselling book: *Wheat Belly: Lose the Wheat, Lose the Weight, and Find Your Path Back to Health* (Davis, 2011). The author stated that the wheat that we eat these days is “created by genetic research in the 60s and 70s” leading to the inclusion of an unnatural protein in our “modern wheat” called gliadin. When coming to a conclusion, Davis explained that everybody is ‘susceptible’ to this gliadin protein as “gliadin binds into the opiate receptors in your brain and in most people stimulates appetite, such that we consume 440 more calories per day, 365 days per year”.

In this light, it should be noted that gliadins are present in all wheat lines and in related wild species (Goryunova et al., 2012). In addition, seeds of certain ancient types of tetraploid wheat (e.g.; Graziella Ra, Khorasan wheat/Kamut) have even greater amounts of total gliadin than modern accessions (Colomba and Gregorini, 2012). Moreover, although the genetic engineering of wheat is technically possible, it has only been used in research programs and “GM wheat” has not been marketed or grown commercially in any country. However, it could be argued that wheat has been “genetically modified” by plant breeding in the same way that other crops and livestock species have been improved by selective breeding. Because bread wheat arose in cultivation, rather than from domestication of a wild species, it has probably been subjected to selection for the whole of its 9000 year history, initially subconsciously by early farmers and later (over the past century) by the application of scientific breeding. This has exploited variation controlled by endogenous wheat genes, resulting particularly from the high genome plasticity, with the limited use of related species to transfer useful traits. The main traits selected have been high yield, good resistance to pests and pathogens and good processing properties (for bread, cookies, noodles and, in durum wheat, pasta). There is no evidence that selective breeding has resulted in detrimental effects on the nutritional properties or health benefits of the wheat grain, with the exception that the dilution of other components with starch occurs in modern high yielding lines (starch comprising about 80% of the grain dry weight) (Shewry et al., 2011). Selection for high protein content has been carried out for bread making, with modern bread making varieties generally containing about 1–2% more protein (on a grain dry weight basis) than varieties bred for livestock feed when grown under the same conditions (Monaghan et al., 2001; Snape et al., 1993). However, this genetically determined difference in protein content is less than can be achieved by application of nitrogen fertilizer (Godfrey et al., 2010).

We consider that statements made in the book of Davis, as well as in related interviews, cannot be substantiated based on published scientific studies. For the sake of brevity, we focus on four of these arguments which we consider are most relevant to the present discussion (other critical remarks are listed by Jones (2012)), while further expanding on sound nutritional and cereal science.

“The proliferation of wheat products parallels the increase in waist size”

This statement implies that a correlation between two variables can be interpreted as a true causal relationship. It is certainly true that the increase in wheat sales has a parallel with an increase in obesity. However, there are also parallel increases in the sales of cars, mobile phones, sports shoes and the average speed of winners of the Tour de France. Similarly, a correlation between the national consumption of chocolate and the number of Nobel Prize winners has been reported (Messerli, 2012).

However, it is not valid to consider these correlations as causal relationships, and in the examples listed above any such claim would be ridiculed. Moreover, the proliferation of wheat products has a much longer history than the much more recent drastic increases in occurrence of obesity, which has also occurred in populations that eat little wheat, such as several Asian countries (Yoon et al., 2006).

“The starch in wheat is different from that found in other carbohydrate-rich foods such as bananas, potatoes and vegetables. The amylopectin structure allows it to be very efficiently converted to raise blood sugar” (undesirably).

The starch present in all plant tissues (including grains and some vegetables and fruits) is a mixture of two polymers of glucose, amylopectin and amylose. Amylose has a linear chemical structure and is relatively slowly digested while amylopectin has a more branched structure and is more rapidly digested. With the exception of mutant lines, the ratio of the two polymers varies little, being about 20–25% amylose and 70–75% amylopectin (Hoover and Zhou, 2003). Mutant lines include waxy types, which comprise almost 100% amylopectin. Some waxy lines are grown commercially (notably waxy rice) but not waxy wheat. Furthermore, the ratio of amylose to amylopectin is generally not the decisive factor for an effect on the blood sugar level. It is also necessary to take into account other nutritional factors such as prior meals, the content of fat, protein and fibre in the meal as well as the matrix of the food product/meal. There are also large differences between carbohydrate-rich foods that easily fall apart in an aqueous environment, such as white bread, and therefore are readily accessible to digestive enzymes and foods that have a more solid and compact matrix, such as pasta, macaroni and spaghetti which are digested less rapidly (Juntunen et al., 2003). A study reported by Riccardi et al. (2003) tested different foods to show that composition, preparation and food matrix influence glycaemic response significantly, as depicted in Fig. 1. However, the blood glucose response after bread consumption was lower than the response after eating the same amount of potatoes or white rice (reflected in the corresponding GI values (Foster-Powell et al., 2002)), which refute the suggestion that starch from wheat generally leads to a higher glycaemic response.

“Whole-wheat bread has a Glycaemic Index (GI) of 72, which is higher than that of sugar (GI = 59)”

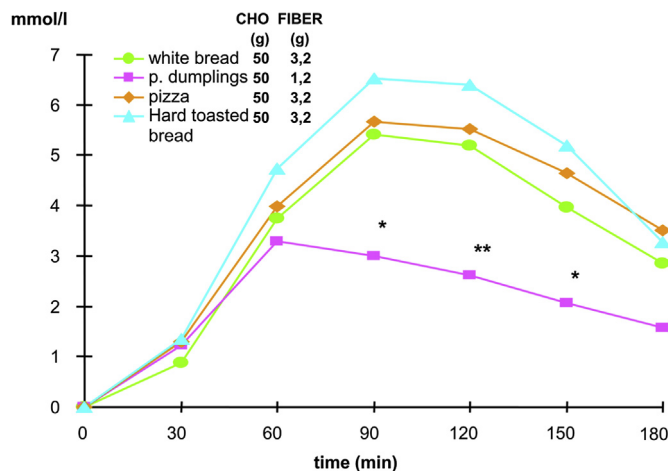


Fig. 1 Composition, preparation and food matrix influence glycaemic response significantly (as studied by Riccardi et al. (2003)).

This statement may lead to the perception that, based on GI, consuming sugar is better for your health than eating wheat. For clarification, the GI is a measure of blood glucose response and is expressed as an index comparing the consumption of a particular food to the blood glucose response after intake of 50 g of glucose. Since sugar (sucrose) consists of 50% glucose (GI = 100) and 50% fructose (GI = 27), the GI of sugar, contrary to what many people think, is relatively low. The internationally accepted average GI of sucrose is not 59, as Davis indicates, but 67 (Foster-Powell et al., 2002). This value is very close to the GI of white wheat bread, which has a range of 69–73, with a mean of 70 (mean of 7 studies (Foster-Powell et al., 2002)). Furthermore, whole-wheat bread has a slightly lower GI of 65.9 (mean of 8 Canadian studies (Foster-Powell et al., 2002)). In fact, the amount of a particular carbohydrate eaten x the GI, expressed as the glycaemic load, is much more meaningful than the GI value alone. The statement above therefore misinterprets the background to the GI methodology (Brouns et al., 2005) as well as the related digestive and metabolic mechanisms.

“Wheat opioids are so addictive that they cause people to be unable to control their eating, and removal of wheat from the diet causes withdrawal”.

There are no data available to substantiate this suggestion. The gluten storage proteins of wheat belong to a broader class of proteins with closely related forms being present in closely related species (rye and barley) and less closely related forms in other cereals (oats, millets, sorghum, corn and rice). Gluten proteins are also present in the “primitive” wheat species discussed above: einkorn, emmer and spelt. Gluten proteins are classically divided into two fractions, the gliadins which are present as monomers and the glutenins which are polymeric. Incomplete digestion of gliadin has been shown to release a peptide, called gliadorphin, that can induce opiate like effects, as demonstrated in laboratory tests in rats that were infused with the intact peptide (Sun and Cade, 2003). However, gliadorphin consists of seven amino acids (Tyr-Pro-Gln-Pro-Gln-Pro-Phe) and, as such, cannot be absorbed by the intestine. This is because the intestine peptide transporter PepT1 transports only di- and triptides (Gilbert et al., 2008) and transporters for larger peptides have not been identified. Gliadorphin is therefore not present in intact form in the human circulatory system and cannot reach and have an effect on the cells of the central nervous system. In this respect, Davis extrapolates effects observed on cells in a laboratory setting to the *in vivo* situation in humans. There are no studies in which gliadorphin has been shown to be absorbed in intact form by the intestine and no evidence that gliadin either stimulates appetite or induces addiction-like withdrawal effects. The author references a study to support his argument in this respect, but the study referred to did not include actual feeding of any food (Jones, 2012). By contrast, Giacco, et al. (2011) and Koh-Banerjee et al. (2004) concluded that regular consumption of whole grains was negatively correlated with weight gain. These authors described 14 cross sectional studies, most of which were performed in the USA, in which higher intake of whole grains was correlated with a lower body mass index (BMI). In addition, they presented three studies in which a significantly lower waist circumference was noted. The argument that refraining from consumption of wheat in the daily diet induces weight loss should also be interpreted in the light of the fact that a very limited number of foods available in the market do not contain wheat. This limited availability of wheat-free foods may itself cause consumption monotony, leading to reduced overall intake of food and energy. The latter will result in weight loss, which will improve (type 2) insulin sensitivity and diabetic state, a dieting-related phenomenon which occurs during virtually all popular diet interventions.

4. Gluten sensitivity

Very recently, Soares et al. (2013) fed mice an *ad libitum* high-fat diet to induce obesity. The mice were divided into a control group, containing no gluten, and a group receiving 4.5% wheat gluten, for 8 weeks. The high-fat diet was composed of 25%, 61% and 15% of the total energy from carbohydrate, fat and protein, respectively. As the diet composition (excessive fat and low carbohydrate) was not representative for the human diet, and there was no control group in which the added gluten was exchanged for another isolated protein type, to assure out that the effects observed were gluten specific effect rather than a general protein content effect, we feel that it is premature to follow the authors conclusion that gluten exclusion helps in reducing body weight and that it can be a new dietary approach to prevent the development of obesity and related sickness in the general human population. Such statements on the adverse effects of gluten-containing (whole-)wheat are diametrically opposite to the observations that the consumption of whole grain and whole grain fibre significantly improves blood glucose control, improves cholesterol levels, reduces blood pressure and lowers the serum concentration of high sensitivity C-reactive protein, a marker of low grade inflammation (Gaskins et al., 2010; Jenkins et al., 2007; Masters et al., 2010; Qi et al., 2006; Raninen et al., 2011) These observations all indicate improvement in overweight related metabolic dysregulation (syndrome X) and have been attributed largely to the fibre (β -glucan and arabinoxylan) and phytochemicals (phenolics, sterols, tocopherols and vitamins) that are concentrated in the aleurone layer of the bran (Brouns et al., 2011) as well as present in the wheat germ fraction. These compounds, as depicted in Fig. 2 (adapted from Barron et al. (2007), are thought to exert synergistic effects on specific health-related metabolic processes (Fardet, 2010).

Recently, Björck, et al. (2011) summarized the findings of the HEALTHGRAIN project supported by the European Commission which included 26 academic research centres. They concluded that in well-controlled studies a negative correlation was observed between the circulating levels of short-chain fatty acids (SCFA) resulting from grain fibre fermentation in the colon and improved insulin sensitivity and glucose homeostasis. As a consequence, insulin production at a certain carbohydrate load was favourably reduced. This points to important effects of components that are either not present, or only present in insignificant amounts in white

wheat flour, but are present in whole wheat and whole grain flour. In this respect, it is also noteworthy that the digestion and metabolism of whole grain goods induces significantly different effects on insulin-, incretin- and satiety hormone responses compared to the consumption of refined (white flour based) wheat bread (Juntunen et al., 2003).

Hauner et al. (2012), summarized the evidence on carbohydrate intake and focused on the relation between wheat and nutrition-related diseases. The authors conclude that the evidence regarding the relevance of refined grain and whole-grain product intake for the risk of obesity is judged as insufficient. Moreover, they conclude that existing cohort studies show a possible relationship between whole-grain product intake and a reduced risk of obesity, a probable relationship with a lower risk of diabetes (see also: de Munter et al., 2007) and coronary heart disease, and a convincing relationship with a reduced level of LDL cholesterol. In addition, Aune, et al. (2011) concluded that the intake of dietary fibre from cereals and other whole grains is associated with a reduced risk of colorectal cancer.

Although the studies discussed above indicate that whole grain consumption has health benefits, it should also be noted that part of the population cannot tolerate wheat or other cereals containing related proteins, particularly those suffering from celiac disease. CD is a genetically predisposed condition (Catassi and Fasano, 2008; Fasano and Catassi, 2001) and results from an autoimmune response initiated by the binding of modified gluten peptides to T-cells of the immune system. The presented peptides are then recognized by specific CD4+ T cells which release inflammatory cytokines leading to damage of the gut villi. Individuals carrying HLA-DQ2 or HLA-DQ8 as major genetic predisposition are affected, representing ~1% of the population. Rubio-Tapia et al. (2009) concluded that the prevalence of CD in the United States was 0.71% (1 in 141), similar to that found in several European countries (Mustalahti et al., 2010).

Very recently, gluten sensitivity has been defined as a new etiologically heterogeneous syndrome in which environmental factors may play a role in addition to that of food (Biesiekierski et al., 2011; Carroccio et al., 2012a; Di Sabatino et al., 2012; Pietzak, 2012). Other data shows that gluten sensitivity occurs in approximately 30% of the people suffering from irritable bowel syndrome (IBS). Given the prevalence of IBS in most countries, 10–15% (in some countries >30%) (Carroccio et al., 2012b; Verdu et al.,

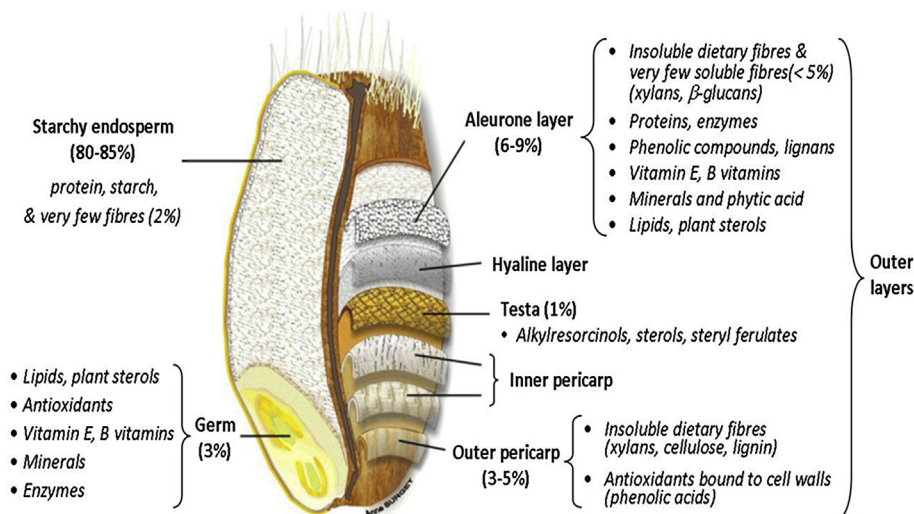


Fig. 2. Histological structure of wheat grain. Adapted from Barron et al. (2007) showing bioactive components which are related to the fiber fraction of wheat and are present in whole wheat meal but absent in refined "white" flour.

2009), and this number is probably an underestimate because many sufferers are not diagnosed, our conservative estimate is that gluten sensitivity affect at least 5–10% of the population.

It should be noted in this respect that gluten sensitivity is not the same as wheat allergy (Battais et al., 2008), which occurs in about 0.3–3.0% in adults and children. Wheat grain proteins are involved in the three routes of sensitization: inhalation, contact and ingestion. Depending on the route of allergen exposure and the underlying immunologic mechanisms, wheat grain allergy can appear as occupational asthma and rhinitis, contact urticaria or classic food allergy affecting the skin, gut and/or respiratory tract. Allergy may also appear as exercise-induced anaphylaxis. Apart from gliadin and glutenin protein fractions, wheat allergy can be caused by a large number of other wheat components (such as α -amylase inhibitors, serpin (serine proteinase inhibitor), acyl-coenzyme A oxidase, fructose-biphosphate aldolase and wheat flour peroxidase) (Battais et al., 2008; Tatham and Shewry, 2008).

A recent study (Sapone et al., 2011) evaluated possible mechanisms underlying gluten sensitivity. Patients who were not suffering from coeliac disease (proved by gut tissue biopsy analysis) but were sensitive to gluten were exposed to a supervised 4-month gluten or non-gluten diet. The main gastrointestinal symptoms of the gluten-sensitive individuals were gas production, diarrhoea, weight loss, and abdominal pain. In this study, the gluten-sensitive individuals did, however, show decreased intestinal permeability (as measured by urinary lactulose/mannitol test). In the only available double-blind, randomized, placebo-controlled study addressing wheat gluten sensitivity (Biesiekierski et al., 2010), a re-challenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a gluten-free diet. Participants received either gluten or placebo in the form of two bread slices plus one muffin per day with a gluten-free diet for up to 6 weeks. Symptoms were evaluated using a visual analogue scale and markers of intestinal inflammation, injury, and immune-activation were monitored. Although more intestinal distress symptoms were reported in those consuming wheat gluten, there were no changes in faecal lactoferrin, levels of celiac antibodies, high sensitive C-reactive protein, or intestinal permeability. This highly controlled study (Biesiekierski et al., 2010) clearly disproves the suggestion that gluten protein in wheat and/or wheat germ agglutinin cause adverse effects in *individuals without celiac disease*, thus giving no reason to discourage the general population to consume wheat containing products.

However, some gluten-containing products also contain relatively rapidly fermentable carbohydrates, such as oligofructose and arabinoxylan. Exclusion of these and other fermentable oligo-, di- and monosaccharides as well as polyols; (also referred to as “FODMAPs”) from the diet has been reported to reduce intestinal distress to similar extents as gluten free diets (Barrett and Gibson, 2012). It is therefore still unclear whether gluten proteins or other factors are involved in the aetiology of gluten sensitivity in non-celiac patients (Biesiekierski et al., 2011).

The very recent studies of Schuppan et al. (2012) and Junker et al. (2012) on “cereal triggers of innate immune activation” describe the role of wheat amylase-trypsin inhibitors (ATIs), which probably confer defence against pests and parasites by inhibiting their digestive enzymes. The authors state that, based on the review of Ryan (1990), the breeding of high yielding and highly pest-resistant varieties of wheat has automatically lead to the selection of types that have a high content of ATIs. According to Altenbach et al. (2011), the ATIs are accumulated to sufficiently high levels in the grain to also function as storage proteins. These ATIs appear to largely resist intestinal degradation in humans and stimulate mucosal cytokine release after feeding *in vivo*.

Preliminary studies showed that neither gliadin which had been digested *in vitro* with trypsin and pepsin nor the celiac-active peptide 31–43 from α -gliadin elicited innate immune responses in intestinal epithelial cells. The pepsin-trypsin digested gliadin (but not p31–43) did strongly activate inflammatory responses but this activity was due to the presence of contaminating ATIs.

These findings identify cereal ATIs as novel contributors to celiac disease. Moreover, the authors suggest that ATIs may fuel inflammation and immune reactions in other intestinal and even non-intestinal immune disorders (Junker et al., 2012). This clearly warrants further research to unravel oral tolerance and gut disease related mechanisms. However, the existence of many anecdotal patient reports should not be ignored due to lack of scientific data and evidence, but used as a basis for well-designed studies and with more specific biomarkers.

In this respect, some medical doctors advise those who suffer from physical complaints that cannot be explained on the basis of routine medical testing (*no physical cause can be established*) to request a gluten sensitivity test and/or to refrain for several weeks from consuming gluten-containing foods to see whether their symptoms (such as sensitive intestinal system, gastrointestinal distress, bloating, rumbling, colic, chronic fatigue, poor concentration, ADHD, frequent headache, migraine, repeating episodes of loose stools of diarrhoea and arthritis) disappear.

5. Conclusion

Although the adverse effects of wheat on some individuals should not be ignored, five major recent scientific reviews addressing the impact of cereal consumption on health and disease concluded that the consumption of whole grains, of which globally most widely consumed is wheat, generally exerts positive effects on health, thus recommending increased intake of whole grain for the general public, in exchange for refined foods (Björck et al., 2011; Fardet, 2010; Hauner et al., 2012; Jonnalagadda et al., 2011).

Wheat-containing foods prepared in customary ways and eaten in recommended amounts have been associated with numerous health benefits. In particular, the regular consumption of whole-grain products has been shown to be associated with significant reductions in risks for type 2 diabetes and heart disease and more favourable long term weight management. These findings are supported by the outcome of a recent cohort, where it was observed that individuals who consumed recommended amounts of (whole)-wheat had the least amount of visceral fat accumulation (Molenaar et al., 2009). Arguments that the currently consumed wheat has been genetically modified resulting in adverse effects on body weight and illnesses cannot be substantiated. In particular, populations in some countries have obtained the major part of their daily energy intake from wheat-based foods for many years, such as Turkey, without reporting any detrimental effects on body weight or chronic disease. In line with this is the evidence that grains and grasses have already been consumed and processed throughout Europe during the Mid-Upper Palaeolithic era (Revedin et al., 2010). However, individuals who have a genetic predisposition for developing celiac disease or who are sensitive to gluten and/or allergic to wheat will benefit from avoiding wheat and other cereals containing related proteins, including primitive wheats (einkorn, emma, spelt), rye and barley. It is important that the food industry should be developing a much wider spectrum of foods for this section of the population, based on crops that do not contain proteins related to gluten, such as teff, amaranth, oat, quinoa, chia. The recent development of commercial high yielding varieties of oats (which are considered safe for those suffering from intolerance to gluten) is an important step in this respect. Further research and development on allergy and intolerance to wheat is also warranted,

with various strategies being proposed to reduce exposure to gluten (Gilissen et al., 2012; Shewry et al., 2012). These include the reduction of (celiac) immunogenic epitopes in existing foods/grains that contain gluten, the production of guaranteed safe, gluten-free foods for patients with celiac disease and gluten intolerance and increasing the production of foods based on crops that do not contain proteins related to gluten. Since about 1% of the current population of Europe and the U.S. population suffers from celiac disease and probably 5–10% from gluten sensitivity (due to difficulties to diagnose this condition, the real number may even be higher), these strategies will have both global economic and public health impacts.

Conflict of interest

The authors declare to have no conflict of interest.

References

- Altenbach, S.B., Vensel, W.H., Dupont, F.M., 2011. The spectrum of low molecular weight alpha-amylase/protease inhibitor genes expressed in the US bread wheat cultivar butte 86. *BMC Research Notes* 4, 242.
- Aune, D., Chan, D.S., Lau, R., Vieira, R., Greenwood, D.C., Kampman, E., Norat, T., 2011. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ: British Medical Journal* 343.
- Barrett, J.S., Gibson, P.R., 2012. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (fodmaps) and nonallergic food intolerance: fodmaps or food chemicals? *Therapeutic Advances in Gastroenterology* 5, 261–268.
- Barron, C., Surget, A., Rouau, X., 2007. Relative amounts of tissues in mature wheat (*Triticum aestivum* L.) grain and their carbohydrate and phenolic acid composition. *Journal of Cereal Science* 45, 88–96.
- Battais, F., Richard, C., Jacquenet, S., 2008. Wheat grain allergies: an update on wheat allergens. *European Annals of Allergy and Clinical Immunology* 40, 67–76.
- Biesiekierski, Newnham, E.D., Irving, P.M., Barrett, J.S., Haines, M., Doecke, J.D., Shepherd, S.J., Muir, J.G., Gibson, P.R., 2010. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *American Journal of Gastroenterology* 106, 508–514.
- Biesiekierski, Rosella, O., Rose, R., Liels, K., Barrett, J., Shepherd, S., Gibson, P., Muir, J., 2011. Quantification of fructans, galactooligosaccharides and other shortchain carbohydrates in processed grains and cereals. *Journal of Human Nutrition and Dietetics* 24, 154–176.
- Björck, I., Östman, E., Kristensen, M., Anson, N.M., Price, R.K., Haenen, G.R.M.M., Havenaar, R., Bach Knudsen, K.E., Frid, A., Mykkänen, H., 2011. Cereal grains for nutrition and health benefits: overview of results from in vitro, animal and human studies in the healthgrain project. *Trends in Food Science and Technology* 25.
- Brenchley, R., Spannagl, M., Pfeifer, M., Barker, G.L.A., D'Amore, R., Allen, A.M., McKenzie, N., Kramer, M., Kerhornou, A., Bolser, D., Kay, S., Waite, D., Trick, M., Bancroft, I., Gu, Y., Huo, N., Luo, M.-C., Sehgal, S., Gill, B., Kianian, S., Anderson, O., Kersey, P., Dvorak, J., McCombie, W.R., Hall, A., Mayer, K.F.X., Edwards, K.J., Bevan, M.W., Hall, N., 2012. Analysis of the bread wheat genome using whole-genome shotgun sequencing. *Nature* 491, 705–710.
- Brouns, F., Björck, I., Frayn, K., Gibbs, A., Lang, V., Slama, G., Wolever, T., 2005. Glycaemic index methodology. *Nutrition Research Reviews* 18, 145.
- Brouns, F., Hemery, Y., Price, R., Anson, N.M., 2011. Wheat aleurone: separation, composition, health aspects, and potential food use. *Critical Reviews in Food Science and Nutrition* 52, 553–568.
- Carroccio, A., Mansueto, P., Iacono, G., Soresi, M., D'Alcamo, A., Cavataio, F., Brusca, I., Florena, A.M., Ambrosiano, G., Seidita, A., 2012a. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *American Journal of Gastroenterology*.
- Carroccio, A., Mansueto, P., Iacono, G., Soresi, M., D'Alcamo, A., Cavataio, F., Brusca, I., Florena, A.M., Ambrosiano, G., Seidita, A., 2012b. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *American Journal of Gastroenterology*.
- Catassi, C., Fasano, A., 2008. Celiac disease. *Current Opinion in Gastroenterology* 24, 687–691.
- CBS, 2012. Modern wheat a “perfect, chronic poison,” doctor says. In: Farber, D. (Ed.), *CBS News*. CBS This Morning, New York.
- Colomba, M.S., Gregorini, A., 2012. Are ancient durum wheats less toxic to celiac patients? A study of α -gliadin from graziella ra and kamut. *The Scientific World Journal* 2012.
- Cummins, A.G., Roberts-Thomson, I.C., 2009. Prevalence of celiac disease in the asia-pacific region. *Journal of Gastroenterology and Hepatology* 24, 1347–1351.
- Davis, W.R., 2011. *Wheat Belly: Lose the Wheat, Lose the Weight, and Find Your Path Back to Health*. Rodale Books.
- de Munter, J.S., Hu, F.B., Spiegelman, D., Franz, M., van Dam, R.M., 2007. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Medicine* 4, e261.
- Di Sabatino, A., Vanoli, A., Giuffrida, P., Luinetti, O., Solcia, E., Corazza, G.R., 2012. The function of tissue transglutaminase in celiac disease. *Autoimmunity Reviews*.
- Dubcovsky, J., Dvorak, J., 2007. Genome plasticity a key factor in the success of polyploid wheat under domestication. *Science* 316, 1862–1866.
- Fardet, A., 2010. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutrition Research Reviews* 23, 65–134.
- Fasano, A., Catassi, C., 2001. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 120, 636–651.
- Feldman, M., Millet, E., 2001. The contribution of the discovery of wild emmer to an understanding of wheat evolution and domestication and to wheat improvement. *Israel Journal of Plant Sciences* 49, 25.
- Feldman, N., Norenberg, C., Voet, H., Manor, E., Berner, Y., Madar, Z., 1995. Enrichment of an Israeli ethnic food with fibres and their effects on the glycaemic and insulinaemic responses in subjects with non-insulin-dependent diabetes mellitus. *British Journal of Nutrition* 74, 681–688.
- Foster-Powell, K., Holt, S.H.A., Brand-Miller, J.C., 2002. International table of glycaemic index and glycaemic load values: 2002. *American Journal of Clinical Nutrition* 76, 5–56.
- Gaskins, A.J., Mumford, S.L., Rovner, A.J., Zhang, C., Chen, L., Wactawski-Wende, J., Perkins, N.J., Schisterman, E.F., 2010. Whole grains are associated with serum concentrations of high sensitivity c-reactive protein among premenopausal women. *Journal of Nutrition* 140, 1669–1676.
- Giacco, R., Della Pepa, G., Luongo, D., Riccardi, G., 2011. Whole grain intake in relation to body weight: from epidemiological evidence to clinical trials. *Nutrition, Metabolism and Cardiovascular Diseases*.
- Gilbert, E., Wong, E., Webb, K., 2008. Board-invited review: peptide absorption and utilization: implications for animal nutrition and health. *Journal of Animal Science* 86, 2135–2155.
- Gilissen, L.J.W.J., Van den Broeck, H.C., Londono, D.M., Salentijn, E.M.J., Koning, F., van der Meer, I.M., Smulders, M.J.M., 2012. Food-related strategies towards reduction of gluten intolerance and gluten sensitivity. In: Koehler, P. (Ed.), 25th Meeting Working Group on Prolamin Analysis and Toxicity. German Research Centre for Food Chemistry, Freising, Germany, pp. 93–96.
- Godfrey, D., Hawkesford, M.J., Powers, S.J., Millar, S., Shewry, P.R., 2010. Effects of crop nutrition on wheat grain composition and end use quality. *Journal of Agricultural and Food Chemistry* 58, 3012–3021.
- Goryunova, S.V., Salentijn, E.M., Chikida, N.N., Kochieva, E.Z., van der Meer, I.M., Gilissen, L.J., Smulders, M.J., 2012. Expansion of the gamma-gliadin gene family in *aegeolus* and *tritium*. *BMC Evolutionary Biology* 12, 215.
- Grundy, S.M., 1998. Multifactorial causation of obesity: Implications for prevention. *The American Journal of Clinical Nutrition* 67, 563S–572S.
- Hauner, H., Bechthold, A., Boeing, H., Brönstrup, A., Buyken, A., Leschik-Bonnet, E., Linseisen, J., Schulze, M., Strohm, D., Wolfram, G., 2012. Evidence-based guideline of the German nutrition society: carbohydrate intake and prevention of nutrition-related diseases. *Annals of Nutrition and Metabolism* 60, 1–58.
- Hoover, R., Zhou, Y., 2003. In vitro and in vivo hydrolysis of legume starches by α -amylase and resistant starch formation in legumes—a review. *Carbohydrate Polymers* 54, 401–417.
- Jenkins, D., Kendall, C., Faulkner, D., Kemp, T., Marchie, A., Nguyen, T., Wong, J., De Souza, R., Emam, A., Vidgen, E., 2007. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *European Journal of Clinical Nutrition* 62, 781–788.
- Jones, J.M., 2012. *Wheat belly—an analysis of selected statements and basic theses from the book*. *Cereal Foods World* 57, 177–189.
- Jonnalagadda, S.S., Harnack, L., Liu, R.H., McKeown, N., Seal, C., Liu, S., Fahey, G.C., 2011. Putting the whole grain puzzle together: health benefits associated with whole grains—summary of american society for nutrition 2010 satellite symposium. *Journal of Nutrition* 141, 1011S–1022S.
- Jönsson, T., Åhrén, B., Pacini, G., Sundler, F., Wierup, N., Steen, S., Sjöberg, T., Ugander, M., Frostegard, J., Goransson Lindeberg, S., 2006. A paleolithic diet confers higher insulin sensitivity, lower c-reactive protein and lower blood pressure than a cereal-based diet in domestic pigs. *Nutrition and Metabolism* 3, 39.
- Jönsson, T., Olsson, S., Åhrén, B., Bøg-Hansen, T.C., Dole, A., Lindeberg, S., 2005. Agrarian diet and diseases of affluence—do evolutionary novel dietary lectins cause leptin resistance? *BMC Endocrine Disorders* 5, 10.
- Junker, Y., Zeissig, S., Kim, S.J., Barisani, D., Wieser, H., Leffler, D.A., Zevallos, V., Libermann, T.A., Dillon, S., Freitag, T.L., 2012. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *Journal of Experimental Medicine* 209, 2395–2408.
- Juntunen, K.S., Laaksonen, D.E., Autio, K., Niskanen, L.K., Holst, J.J., Savolainen, K.E., Liukkonen, K.H., Poutanen, K.S., Mykkänen, H.M., 2003. Structural differences between rye and wheat breads but not total fiber content may explain the lower postprandial insulin response to rye bread. *American Journal of Clinical Nutrition* 78, 957–964.
- Keith, S.W., Redden, D.T., Katzmarzyk, P., Boggiano, M.M., Hanlon, E.C., Benca, R.M., Ruden, D., Pietrobelli, A., Barger, J., Fontaine, K., 2006. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *International Journal of Obesity* 30, 1585–1594.
- Koh-Banerjee, P., Franz, M., Sampson, L., Liu, S., Jacobs, D.R., Spiegelman, D., Willett, W., Rimm, E., 2004. Changes in whole-grain, bran, and cereal fiber

- consumption in relation to 8-y weight gain among men. *American Journal of Clinical Nutrition* 80, 1237–1245.
- Masters, R.C., Liese, A.D., Haffner, S.M., Wagenknecht, L.E., Hanley, A.J., 2010. Whole and refined grain intakes are related to inflammatory protein concentrations in human plasma. *Journal of Nutrition* 140, 587–594.
- Messerli, F.H., 2012. Chocolate consumption, cognitive function, and nobel laureates. *New England Journal of Medicine* 367, 1562–1564.
- Molenaar, E.A., Massaro, J.M., Jacques, P.F., Pou, K.M., Ellison, R.C., Hoffmann, U., Pencina, K., Shadwick, S.D., Vasan, R.S., O'Donnell, C.J., 2009. Association of lifestyle factors with abdominal subcutaneous and visceral adiposity the framingham heart study. *Diabetes Care* 32, 505–510.
- Monaghan, J.M., Snape, J.W., Chojecki, A.J.S., Kettlewell, P.S., 2001. The use of grain protein deviation for identifying wheat cultivars with high grain protein concentration and yield. *Euphytica* 122, 309–317.
- Mustalhti, K., Catassi, C., Reunanen, A., Fabiani, E., Heier, M., McMillan, S., Murray, L., Metzger, M.H., Gasparin, M., Bravi, E., 2010. The prevalence of celiac disease in europe: results of a centralized, international mass screening project. *Annals of Medicine* 42, 587–595.
- Pietzak, M., 2012. Celiac disease, wheat allergy, and gluten sensitivity. *Journal of Parenteral and Enteral Nutrition* 36, 685–755.
- Qi, L., van Dam, R.M., Liu, S., Franz, M., Mantzoros, C., Hu, F.B., 2006. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care* 29, 207–211.
- Raninen, K., Lappi, J., Mykkänen, H., Poutanen, K., 2011. Dietary fiber type reflects physiological functionality: comparison of grain fiber, inulin, and polydextrose. *Nutrition Reviews* 69, 9–21.
- Revedin, A., Aranguren, B., Becattini, R., Longo, L., Marconi, E., Lippi, M.M., Skakun, N., Sinitsyn, A., Spiridonova, E., Svoboda, J., 2010. Thirty thousand-year-old evidence of plant food processing. *Proceedings of the National Academy of Sciences* 107, 18815–18819.
- Riccardi, G., Clemente, G., Giacco, R., 2003. Glycemic index of local foods and diets: the mediterranean experience. *Nutrition Reviews* 61, S56–S60.
- Rose, M., 2011. #gluten, #depression and Brain/neuro Problems. *TrulyGlutenFree*, Manchester, UK.
- Rubio-Tapia, A., Kyle, R.A., Kaplan, E.L., Johnson, D.R., Page, W., Erdtmann, F., Brantner, T.L., Kim, W., Phelps, T.K., Lahr, B.D., 2009. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* 137, 88–93.
- Ryan, C.A., 1990. Protease inhibitors in plants: genes for improving defenses against insects and pathogens. *Annual Review of Phytopathology* 28, 425–449.
- Sapone, A., Lammers, K.M., Casolaro, V., Cammarota, M., Giuliano, M.T., De Rosa, M., Stefanile, R., Mazzarella, G., Tolone, C., Russo, M.I., 2011. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Medicine* 9, 23.
- Schupann, D., Junker, Y., Zevallos, V., Wieser, H., 2012. Cereal triggers of innate immune activation. In: Koehler, P. (Ed.), 25th Meeting Working Group on Pro-lamin Analysis and Toxicity. German Research Centre for Food Chemistry, Germany, pp. 93–96.
- Shewry, P., 2009. Wheat. *Journal of Experimental Botany* 60, 1537–1553.
- Shewry, P.R., 2011. Effects of nitrogen and sulfur nutrition on grain composition and properties of wheat and related cereals. *The Molecular and Physiological Basis of Nutrient Use Efficiency in Crops*, 103–120.
- Shewry, P.R., Charmet, G., Branlard, G., Lafandra, D., Gergely, S., Salgó, A., Saulnier, L., Bedó, Z., Mills, E., Ward, J.L., 2012. Developing new types of wheat with enhanced health benefits. *Trends in Food Science and Technology*.
- Shewry, P.R., Gebruers, K., Andersson, A.A.M., Aman, P., Piironen, V., Lampi, A.M., Boros, D., Rakszegi, M., Bedo, Z., Ward, J.L., 2011. Relationship between the contents of bioactive components in grain and the release dates of wheat lines in the healthgrain diversity screen. *Journal of Agricultural and Food Chemistry* 59, 928–933.
- Snape, J., Hyne, V., Aitken, K., 1993. Targeting genes in wheat using marker-mediated approaches. In: *Proceedings of the Eighth International Wheat Genetics Symposium*, pp. 749–759.
- Soares, F.L.P., de Oliveira Matoso, R., Teixeira, L.G., Menezes, Z., Pereira, S.S., Alves, A.C., Batista, N.V., de Faria, A.M.C., Cara, D.C., Ferreira, A.V.M., 2013. Gluten-free diet reduces adiposity, inflammation and insulin resistance associated with the induction of PPAR-alpha and PPAR-gamma expression. *Journal of nutritional biochemistry* 24, 1105–1111.
- Sun, Z., Cade, R., 2003. Findings in normal rats following administration of gliadorphin-7 (gd-7). *Peptides* 24, 321–323.
- Tatham, A., Shewry, P., 2008. Allergens to wheat and related cereals. *Clinical and Experimental Allergy* 38, 1712–1726.
- Verdu, E.F., Armstrong, D., Murray, J.A., 2009. Between celiac disease and irritable bowel syndrome: the “no man's land” of gluten sensitivity. *American Journal of Gastroenterology* 104, 1587–1594.
- Ward, J.L., Poutanen, K., Gebruers, K., Piironen, V., Lampi, A.-M., Nystrom, L., Andersson, A.A., Boros, D., Rakszegi, M., Bedo, Z., 2008. The healthgrain cereal diversity screen: concept, results, and prospects. *Journal of Agricultural and Food Chemistry* 56, 9699–9709.
- Wrigley, C., Bietz, J., Pomeranz, Y., 1988. Proteins and amino acids. *Wheat: Chemistry and Technology* 1, 159–275.
- Ye, E.Q., Chacko, S.A., Chou, E.L., Kugizaki, M., Liu, S., 2012. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *Journal of Nutrition* 142, 1304–1313.
- Yoon, K.H., Lee, J.H., Kim, J.W., Cho, J.H., Choi, Y.H., Ko, S.H., Zimmet, P., Son, H.Y., 2006. Epidemic obesity and type 2 diabetes in asia. *Lancet* 368, 1681–1688.