



The wheat and nutrition series

A compilation of studies on wheat and health

Papers published by CIMMYT and as part of a special series
in *Cereal Foods World*, during 2014-17

Contributing authors:

Julie Miller Jones, Distinguished Scholar and Professor Emerita at
St. Catherine University, U.S.A.; and Roberto J. Peña,
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CIMMYT - The International Maize and Wheat Improvement Center (www.cimmyt.org) - is the global leader in publicly-funded maize and wheat research and related farming systems. Headquartered near Mexico City, CIMMYT works with hundreds of partners throughout the developing world to sustainably increase the productivity of maize and wheat cropping systems, thus improving global food security and reducing poverty. CIMMYT is a member of the CGIAR System and leads the CGIAR Research Programs on Maize and Wheat and the Excellence in Breeding Platform. The Center receives support from national governments, foundations, development banks and other public and private agencies.

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Abstract: Including papers about wheat and health published during 2014-17 by CIMMYT, in partnership with Bimbo, a Mexican multinational bakery product company and, with permission of AACC International, from a special series in Cereal Foods World, the detailed reviews cite the best scientific knowledge to show that consumption of whole grains is associated with a lower risk of coronary disease, diabetes, hypertension, obesity and overall mortality and that that eating whole and refined grains is beneficial for brain health and associated with reduced risk for diverse types of cancer. Finally, the evidence shows that, for the general populace that suffers no food allergies or special sensitivities, gluten- or wheat-free diets are not inherently healthier and may actually put individuals at risk of dietary deficiencies.

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Summary: The wheat and nutrition series

In mid-2015 the CIMMYT Global Wheat Program partnered with Bimbo, a Mexican multinational bakery product manufacturing company, to develop a series of literature reviews about grains and health, specifically looking at what is known or not known. The papers published so far appear in this compilation; here is a brief summary of what we have learned.

Carbohydrate-rich staples, especially of wheat and other grains, provide macronutrients and inexpensive sources of energy, protein, minerals, vitamins, and other beneficial phytochemicals. The carbohydrates in the bran and germ and the endosperm cell wall contribute dietary fiber that helps to modulate the amount and type of gut bacteria, as well as to promote the growth of beneficial bacteria. Consumption of whole grains is associated with lower risk of coronary disease, diabetes, hypertension, obesity and even overall mortality. Diets rich in dietary fiber, especially cereal fiber, appear to reduce Type 2 diabetes mellitus. Additionally, the antioxidant and anti-inflammatory agents, bioactive compounds, vitamins, and minerals in whole and enriched grains are beneficial for brain health, helping to prevent damage to brain tissue and maintain optimal cognitive functioning.

Moreover, clear data show that eating whole and refined grains as part of a balanced diet is associated with decreased risk for a wide variety of cancers and that there is an inverse relationship between dietary fiber and colon cancer. For breast cancer, there was no association or an inverse association with dietary fiber intake, whereas low consumption of bread was associated with an increased risk. Control studies show that refined grain intake was associated with increased risk, but the increase was slight. Most of the studies indicate that total carbohydrate intake is not related to lung, prostate or stomach cancers.

On the other hand, all proteins, including those found in grains, can cause allergies. Among grains, wheat ranks as one of the big-eight food allergens, but wheat allergy affects less than 1% of the population in the USA. Only 1% of the US population has celiac disease, less than 1% has grain allergies, and an estimated 0.6-6% has non-celiac gluten sensitivity. Elimination of any specific grain, such as wheat, or a dietary component, such as gluten, should be done only when medically necessary.

Still, imbalances can be problematic. The consumption of fat and refined carbohydrates, combined with a lack of dietary fiber, bran and whole grains, can decrease microbiome diversity in the digestive tract, change fermentation patterns, elevate glycemic response, increase the risk of insulin resistance and increase levels of inflammation. Unfortunately, the consumption of dietary fiber and whole grains is far below recommended levels in nearly every country around the globe.

Finally, elimination diets are not inherently healthier and may actually put individuals at risk of dietary deficiencies, so care must be taken when considering gluten-free or other such diets. The exclusion of cereal grains, for example, would reduce fiber intake far below the recommended amounts for a healthy digestive system; in that regard, wheat- and gluten-free diets can in fact harm human health. Moreover, it is inaccurate to label wheat and gluten as wholesale dangers for humans, particularly for the billions of people who need wheat to survive or as a key source of basic nutrients.

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Anti-Wheat Fad Diets Undermine Global Food Security Efforts

Wheat consumption healthy despite claims in self-help publications



Roberto J. Peña, Hans J. Braun and Julie Mollins
Global Wheat Program, CIMMYT

WHEAT DISCUSSION PAPER

Anti-Wheat Fad Diets Undermine Global Food Security Efforts

Wheat consumption healthy despite claims in self-help publications

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1. Introduction

A recent review paper released by Britain's University of Warwick (Lillywhite and Sarrouy 2014) addresses two fundamental questions regarding wheat: "Are whole grain products good for health?"; and "What is behind the rise in popularity of gluten- and wheat-free diets?"

The paper was commissioned by cereal-maker Weetabix to address reports in the news media that wheat products are the cause of health problems, resulting in an increasing number of consumers switching to low-carbohydrate grain- and wheat- free diets. For many health professionals this is a worrying trend because wheat not only supplies 20 percent of the world's food calories and protein, but has important benefits beyond nutrition, the authors state.

The Warwick paper provides a scientific assessment of the benefits of whole grain consumption, information that the authors note seems to have been lost in media headlines and the reporting of "pseudo-science."

The paper concludes that whole grain products are good for human health, apart from the 1 percent of the population who suffer from celiac disease and another 1 percent who suffer from sensitivity to wheat (Lillywhite and Sarrouy 2014). Eating whole-grain wheat products is positive, improves health and can help maintain a healthy body weight, the authors report.

Scientific evidence regarding wheat- and carbohydrate-free diets is thin and selectively used, they state, and a low cereal and carbohydrate diet "may cost more but deliver less."

Additionally, an economically viable industry has developed around so-called "free-from" diets and may be persuading consumers to switch from staple foods to specialist foods created especially for those who need to avoid gluten, a protein found in wheat and other grains, they add.

This Wheat Discussion Paper serves as a foundation upon which the authors hope further conversation will develop. It aims to highlight unsubstantiated nutritional claims about wheat and shine a spotlight on the important role of wheat and fiber in human

diets. It also seeks to encourage discussion about how non-scientific claims about wheat could affect poor consumers and global food security.

2. About CIMMYT

The International Maize and Wheat Improvement Center (CIMMYT) is an intergovernmental research institute working with an international community of public and private partners to reduce worldwide poverty and hunger by sustainably increasing the productivity of maize and wheat.

CIMMYT, a non-profit organization, plays a key role in providing wheat germplasm – genetic material from wheat – to be tested and improved by government-run national agricultural research systems before its potential release to farmers. Additionally, CIMMYT provides smallholder farmer training and skills development on such topics as crop management and agricultural practices.

Under the direction of Norman Borlaug in the 20th century, CIMMYT led efforts to develop semi-dwarf wheat varieties that are estimated to have helped save more than 1 billion lives in Pakistan, India and other areas of the developing world as global population expanded and arable land became more scarce.

Borlaug started work on wheat improvement in the mid-1940s in Mexico where CIMMYT is headquartered near Mexico City. The country became self-sufficient in wheat production in the early 1960s due to the high-yielding, disease-resistant, semi-dwarf wheat varieties developed by Borlaug and his colleagues.

Borlaug was awarded the Nobel Peace Prize in 1970 for his innovative, life-saving work, which became widely known as the Green Revolution. He used traditional plant-breeding techniques, still used worldwide for producing wheat and other food crops. Farmers prefer short-stalk wheat because it doesn't fall over – or lodge – as easily as taller varieties, which means less grain is lost and harvests are bigger.

As the global population grows from more than 7 billion today to a projected 9.6 billion by 2050, wheat farmers continue to play a crucial role in food security.

Already, U.N. food agencies and the World Health Organization (WHO) estimate that at least 800 million people (WFP) do not get enough food and that more than 2 billion (FAO) suffer from micronutrient deficiency, or “hidden hunger.” Stunting affects more than 160 million children under age 5 and wasting affects more than 50 million children under age 5. Under-nutrition is linked to almost half of all child deaths under age 5, almost 3 million per year. On the other hand, about half a billion people are obese and three times as many are overweight (WHO).

3. Healthy diets

A healthy diet helps prevent malnutrition as well as non-communicable diseases (NCDs) and conditions (FAO). However, increasing production of processed food, rapid urbanization and lifestyles have shifted dietary patterns (WHO). A healthy diet for adults includes fruit, vegetables, legumes, nuts and whole grains. Adults should eat at least 400 grams (14 ounces), or five portions, of fruit and vegetables daily, while less than 10 percent of total energy should come from free sugars and less than 30 percent of total energy from fat, according to the WHO. Unsaturated fats are better than saturated fats, and trans fats should be avoided, the U.N. health agency reports.

Whole grains make up an important part of healthy diets. The 2005 Dietary Guidelines for Americans recommend eating at least three 1-ounce servings of whole grains to reduce the risk of diabetes and coronary heart disease and to maintain a healthy weight. Whole grains are especially important for their fiber content.

Refined grains have benefits in the diet as well, namely, added nutrients, such as B vitamins (thiamin, riboflavin, niacin) and iron. Additionally, important nutrients like copper and iron are more easily absorbed when eaten with refined grains.

For children in particular, good nutrition is vital to prevent the risk of death or developing non-communicable diseases and to ensure healthy growth and development. As well as taking into consideration the guidelines for adults, breastfeeding plays an important role in ensuring a nutritional beginning to life.

The WHO and FAO recommend that governments, public and private sector stakeholders must collaborate to help promote a healthy food environment, which allows people to adopt healthy dietary practices.

In practice, such activities include coordinating trade, food and agricultural policies with the protection and promotion of public health, encouraging consumer demand for healthy food and promoting nutrition in infants and young people.

4. Health benefits of wheat

Wheat grain possesses several components that contribute to good nutrition (Bjork et al. 2012; Fardet et al. 2012; Flight and Clifton 2006; Shewry 2009). The dietary fiber it contains – comprised of polysaccharides, which pass undigested from the small intestine into the large intestine and colon – is a highly beneficial, fermentable prebiotic agent that promotes the growth of beneficial probiotic bacteria in the bowel.

Wheat grain and flour are also sources of complex carbohydrates, which are important in the diet. Most whole grains are abundant sources of dietary fiber and other nutrients, such as minerals and antioxidants, which have shown beneficial effects on human health including improvement of weight loss, insulin sensitivity, and lipid profile, as well as inhibition of systemic inflammation (Huang et al. 2015; Bjork et al. 2012; Gibson et al. 2014). Evidence from myriad epidemiological studies show that consumption of whole grain products or their effective components, especially dietary fiber found in the grain, i.e., cereal fiber, may reduce the risk of chronic disease, cardiovascular disease and Type 2 diabetes (Huang et al. 2015 and Bjork et al. 2012).

In about 35 percent of countries fortification of milling flours with minerals and vitamins is mandatory. In these cases, the consumption of wheat-based foods helps reduce micronutrient deficiency, particularly in relation to iron, zinc, folic acid and vitamin A. Additionally, many wheat-based foods – bread used for sandwiches or wraps, for example – serve as “vehicles” for the consumption of complementary animal- and vegetable-based foods, contributing to balanced and healthy diets.

5. Wheat and food security

For more than 10,000 years, wheat production and consumption has contributed to the socio-economic development of humankind (Salamini et al. 2002). Wheat is readily adaptable to a range of diverse environments, including marginal and extreme ecosystems. It is cultivated on about 220 million hectares (539 million acres) worldwide, which produce roughly 700 million metric tons a year. The grain provides on average a vital 20 percent of calories and protein for more than 4.5 billion people in 94 developing countries (Braun et al. 2010).

Over the next 35 years, wheat production must grow 60 percent to keep pace with demand as the population grows, according to FAO. However, climate change will have a profound impact on wheat production, affecting crops through such risk factors as increased levels of pests and disease, water shortages and nutrient depletion in soil, jeopardizing production levels. A short supply of wheat, particularly in developing countries, will result in serious nutritional problems and could lead to social unrest (CIMMYT 2011). Therefore, it is vital that the international community accelerate efforts to bolster the production of high-yielding wheat varieties to meet nutritional demands.

6. Wheat and fad diets

It is generally accepted among nutritionists that low-carbohydrate fad diets, which often vilify wheat, can lead to rapid but temporary weight loss.

Although low-carbohydrate diets show more rapid weight loss than other diet types in the first six months, they do not result in greater weight loss over time and lead to more dropouts than more balanced diets, which do not eliminate entire food groups, writes Julie Miller Jones, a nutritionist and professor emeritus of food and nutrition at St. Catherine University in St. Paul, Minnesota (Miller Jones 2012).

Not only do the proponents of anti-wheat fad diets cast aside well-established medical and nutritional advice, they also disregard dietary guidelines and recommendations established by such reputable institutions as the World Health Organization, the U.N. Food and Agriculture Organization, the

U.S. Department of Agriculture, the Whole Grains Council, the Academy of Nutrition and Dietetics, the American Diabetes Association and the American Heart Association.

To a large degree, their arguments are based on a view that imagines what dietary practices were like for early human hunter-gatherers before farmers began to domesticate wild grasses, creating wheat, which led to a more secure food supply and the capacity to develop sedentary societies.

Some authors of anti-wheat diet books claim that wheat varieties grown today are unsuitable for human consumption because they haven't been tested for safety. They take aim at the efforts of wheat breeders at the International Maize and Wheat Improvement Center (CIMMYT), claiming that the conventional breeding methods they use result in wheat that is a drastic departure from what our ancestors consumed as wheat.

Arguments posed in literature and the popular press regarding the dangers of consuming wheat and gluten overlook the key role that wheat plays in nutrition and ensuring global food security. In an effort to mitigate the impact of population growth, land scarcity and climate change, scientists at CIMMYT are developing wheat varieties with higher micronutrient content and reinforcing the capacity of wheat to withstand heat and drought caused by global warming.

Zinc supplementation can help reduce the duration and impact of diarrhea in children, and iron and vitamin A supplements can reduce the risk of anemia and blindness.

Fad-diet hyperbole over the supposed dangers of wheat consumption might cause worry and unnecessary health fears among all sectors of society, but it is the poor and low-waged that may suffer the most from these campaigns. Many families cannot afford such nutrient-rich foods as fresh fruit, vegetables, beans, meat and milk, and rely on bread, rice or maize and legumes – food staples – to supplement their diets.

Socioeconomic factors can make it impossible for many people to afford or in some cases even access specialty food items.

In November, at the Second International Conference on Nutrition (ICN2) in Rome, the WHO, the FAO and 170 governments committed to fight malnutrition in all its forms, including hunger, micronutrient deficiencies and obesity. They laid out a framework for ending hunger, achieving food security and improving nutrition by 2025 (FAO/WHO).

Governments who signed onto the framework are tasked with encouraging a reduction in trans fats, saturated fats, sugar and salt, and to improve the nutrient content of foods through regulatory and voluntary instruments.

7. Anti-wheat books

Grouping the key arguments of anti-wheat books, which link wheat, gluten and carbohydrate consumption with chronic diseases allows the following analysis:

7.1 Wheat and chronic disease

Only 1 percent of people have celiac disease and 1 percent suffer from sensitivity to wheat (Lillywhite and Sarrouy 2014). People with celiac disease have a digestive condition which causes an adverse reaction to gluten resulting in diarrhea, bloating, flatulence, abdominal pain, weight loss and fatigue due to malnutrition. Celiac disease is an autoimmune condition, which means the immune system attacks healthy tissue, damaging the surface of the small bowel and preventing proper nutrient absorption.

Recently, some anti-wheat books have emphasized that cereal – in particular wheat – consumption contributes to degenerative diseases and such autoimmune neurological diseases as Alzheimer’s and Parkinson’s. The authors emphasize that they are writing for a U.S. audience – they claim all U.S. consumers will benefit from diets without cereals and cereal products. They state that cereals in general are unhealthy due to their high carbohydrate content, and that wheat is particularly dangerous because of gluten.

Maize, wheat, and rice-based foods are inexpensive, satisfying culinary preferences as well as caloric and essential nutrient needs for billions of people on all continents who consume them as a major food staple. If it were correct that cereals were the cause of Alzheimer’s, arteriosclerosis, Parkinson’s, autism and

loss of cognitive capacity and neurodevelopmental disorders, civilization would have been incapacitated and come to a halt many years ago.

Alarming, anti-wheat and cereals activism continues to gain momentum among consumers who hope to improve their health. However, wheat- and gluten-free diets can in fact be damaging to human health because they may not provide enough fiber and essential micronutrients (Biesiekierski et al. 2014; Lee et al. 2009). The recommended daily intake of dietary fiber is 38 grams (1.34 ounces) and 25 grams for adult men and women respectively, which is achievable by consuming a few servings of wheat foods or other cereals grains (Miller Jones 2012). In contrast, fruits and vegetables supply only 2 to 4 grams per serving, which means an adult male on a wheat-free diet would have to consume approximately 12 to 13 servings of fruit and vegetables a day to get the same amount of dietary fiber (Miller Jones 2012). The exclusion of cereal grains would result in a fiber-intake deficit far below the recommended amount needed to maintain a healthy digestive system.

7.1.1 Autoimmune disorders

Diverse gluten-induced conditions trigger the immune system in a range of ways via gliadin, which is one of two main protein fractions of the gluten protein complex. Sapone et al. (2012) propose a diagram and nomenclature for the spectrum of gluten related disorders (Figure 1).

As can be seen in Figure 1, gluten sensitivity is not an autoimmune condition as claimed by some anti-wheat literacy; it is believed to be innate or congenital.

7.1.1.1 Gluten Intolerance or Celiac Disease. The U.S. Celiac Disease Foundation estimates that 1 in 100 people suffer from the chronic condition of intolerance to gluten. This intolerance manifests itself as celiac disease, a genetic condition mediated by an immune response triggered mainly by small gliadin undigested peptides; among these, a unique 33-mer gliadin fragment is more immunogenic. This peptide is resistant to degradation by gastric, pancreatic and brush border peptidases (Sapone et al. 2012). On the surface of the small intestine, it is the main trigger of bowel inflammation intestinal damage, up regulation of the 47-K Zinulin peptide, responsible for the opening of the intestine wall and entrance of the gliadin protein. The reaction (deamidation) of this gliadin peptide with tissue transglutaminase (tTG) promotes recognition by HLA-DQ2/HLADQ8

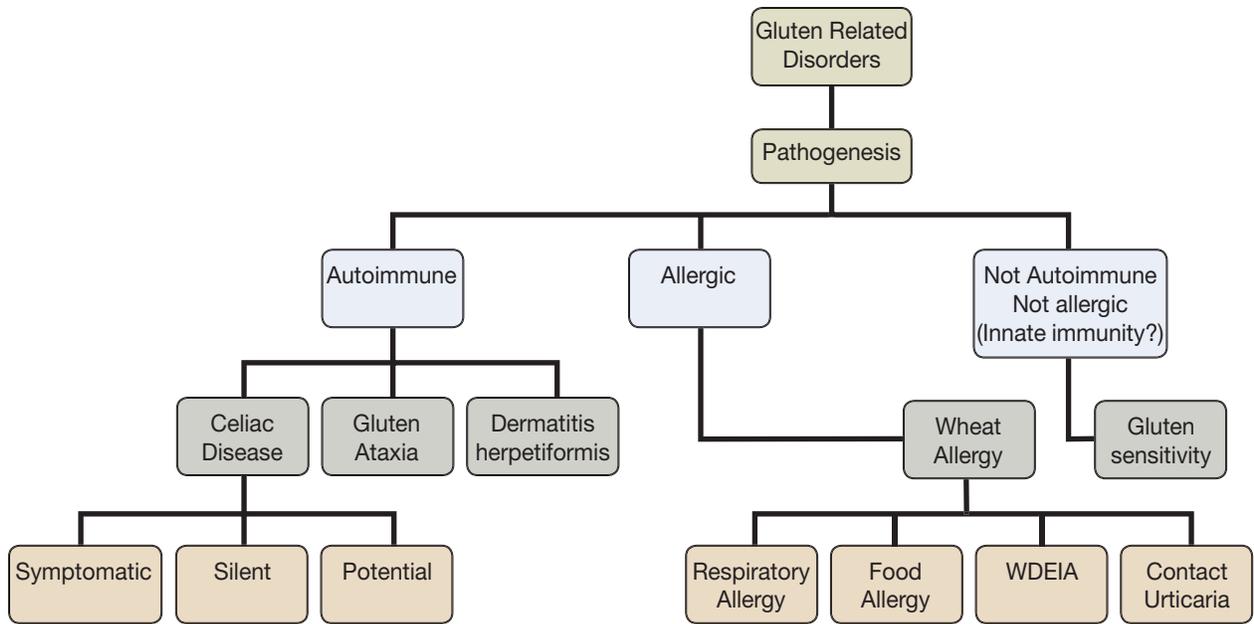


Figure 1. Proposed new nomenclature and classification of gluten related disorders adopted from Sapone et. al. (2012)

antigen presenting cells and triggering the onset of celiac disease and related immune disorders (Fasano 2011; Jackson et al 2012; Lundin 2014; Sapone 2012; Setty et al. 2008; Shan et al. 2002). This chronic enteropathy shows a wide range of manifestations of variable severity.

At present there is no cure or therapeutic action that can be taken against celiac disease. Therefore, those suffering from the disease must eliminate gluten from their diets (Cummins and Roberts-Thomson 2009).

Some anti-wheat books indicate it is possible that some of the inflammatory processes provoked by the consumption of gluten may in some cases trigger the increase of inflammatory cytokines levels, which by attacking the brain could contribute to the onset of Alzheimer's, Parkinson's, multiple sclerosis and autism. In addition, these authors speculate that the anti gliadin antibodies (AGA) could combine with similar gliadin-like proteins in the brain, promoting even more production of cytokines, provoking more neuropathies. However, Sofi et al. (2014) indicate that pre-inflammatory cytokines are more related to irritable bowel syndrome (IBS).

These arguments could hypothetically be possible metabolically. However, the authors do not present studies that demonstrate these processes actually occur. Fasano (YouTube, 21 January 2014) indicates that the potential relationship of gluten sensitivity to autism and schizophrenia is still very controversial.

Hadjivassiliou et al. (2010) reported a certain relationship between neuropathies and mainly celiac disease. But these authors actually show that only a small proportion (10 to 22.5 percent) of celiac disease patients have a neurological condition. They also indicate that there are differences in disease etiology in patients whose main manifestation occurs in the nervous system and those whose primary manifestation resides in the gastrointestinal system. At the same time, they indicate that it is unclear whether the central nervous system (CNS) pathology associated with gluten sensitivity (as they refer mainly to celiac disease) results from access of circulating antibodies that react with brain antigens after compromising the blood-brain barrier, or if it relates to a specific T-cell subset that is involved in immune surveillance of the brain. Why gluten presentation should specifically occur at a site distant to the digestive system (CNS, skin) is unclear. Finally (Hadjivassiliou et al. 2010) indicate that not all patients presenting certain neuropathies claimed to be caused or related by celiac disease got better when excluding gluten from their diet.

7.1.1.2 Wheat allergic response. Wheat allergy is an adverse immunologic reaction where IgE antibodies intervene when there is exposure to wheat proteins (gluten but also other proteins), affecting the skin, gastrointestinal tract or respiratory tract, depending on the exposure and the site the immune response resides. Wheat allergy is a classic food allergy, which is wheat-dependent, producing exercise-induced anaphylaxis (WDEIA); baker's asthma and rhinitis; and contact urticaria (Sapone et al. 2012). The incidence of people affected by WA is lower than that affected by celiac disease (Sapone et al. 2012).

7.1.1.3 Non-Celiac Gluten Sensitivity. It is now well known that besides celiac disease and wheat allergies, there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms can be identified. However, gluten sensitivity is still an undefined syndrome, with several unsettled issues despite the increasing awareness of its existence. Only a few double blind, randomized placebo control (DBPC) studies have been performed, showing that in a variable proportion of patients classified as having gluten sensitivity, their symptoms could have been caused by a nocebo (a detrimental effect on health produced by psychological or psychosomatic factors such as negative expectations of treatment or prognosis effect) (Lundin 2014; van Buul and Brouns 2013; Volta et al. 2014).

Gluten sensitivity is an adverse reaction to gluten. Both gluten sensitivity and celiac disease involve an immune system response and may have similar symptoms, but the type of immune response is different (Sapone et al. 2012). People with gluten sensitivity do not develop severe intestinal damage like that seen in patients with celiac disease. These are generally defined as non-celiac gluten sensitivities (NCGS). The symptoms of NCGS are similar to those of patients with irritable bowel syndrome, including abdominal pain, bloating, gas, diarrhea, and constipation (Lundin 2014). Sapone et al. (2012) define NCGS patients as those patients in which celiac disease, wheat allergy and other clinically overlapping diseases (e.g., Type-1 diabetes, inflammatory bowel diseases and *Helicobacter pylori* infection) have been ruled out. In NCGS patients, and in those suffering celiac disease, their symptoms are caused by gluten exposure and eased by gluten withdrawal.

NCGS is not accompanied by the concurrence of anti-tTG autoantibodies or other autoimmune comorbidities. The small intestine of gluten sensitive patients is usually normal (Sapone et al. 2012).

Objective biomarkers to diagnose gluten sensitive condition are not available and may be difficult to develop. Gluten sensitivity may be caused by improper immune responses, intolerance to poorly digestible and fermentable substances in the wheat, or a combination of these.

Although the number of people suffering from NCGS has been estimated much higher than those suffering from celiac disease, some studies have demonstrated that the sensitivity of some of the patients who have been diagnosed with NCGS with inflammation and other gastrointestinal symptoms, were rather affected by the presence of fermentable, poorly absorbed oligo-, di-, monosaccharides and polyols (FODMAPS) or other foods (Biesiekierski et al. 2013b; Biesiekierski et al. 2014; Carroccio et al. 2012; Lundin 2014; Halmos et al. 2014). Future research in the NCGS area should address how much gluten really is involved, using manageable, clinically acceptable, placebo-controlled investigation procedures.

For example, the study of Carroccio et al. (2012) shows a diagram of their clinical design and the response of 920 patients showing irritable bowel syndrome (IBS symptoms and fulfilling the criteria for NCGS (Figure 2). Two groups of patients were identified. One group with 70 patients was suffering from no celiac wheat sensitivity alone and a second group with 206 patients suffering from multiple food hypersensitivity, including wheat sensitivity. Out of the total 920 patients, 644 did not suffer from wheat sensitivity and were excluded from the study (Carroccio et al. 2012).

A major limitation in studying NCGS is diagnosis, which remains highly presumptive. Therefore, at present a proportion of patients classified as suspected NCGS might improve after commencing a gluten free diet (GFD) because of elimination of gluten or simply by a placebo effect (Volta et al. 2014). Although, according to Lundin (2014) there are no conclusive studies demonstrating the benefits of a GFD in NCGS patients.

7.1.1.4 Wheat toxicity. Fasano, in a seminar transmitted on YouTube (21 January 2014) based mainly on a review article by Sapone et al. (2012) and by results and new findings reported during the second Meeting of Experts on Gluten Sensitivity (Catassi et al. 2013), explained his research group's work of more than 15 years. Fasano indicated that three major elements are involved in celiac disease and NCGS. Genetic factors (an individual's genes), environmental factors (food or intruder), and gut

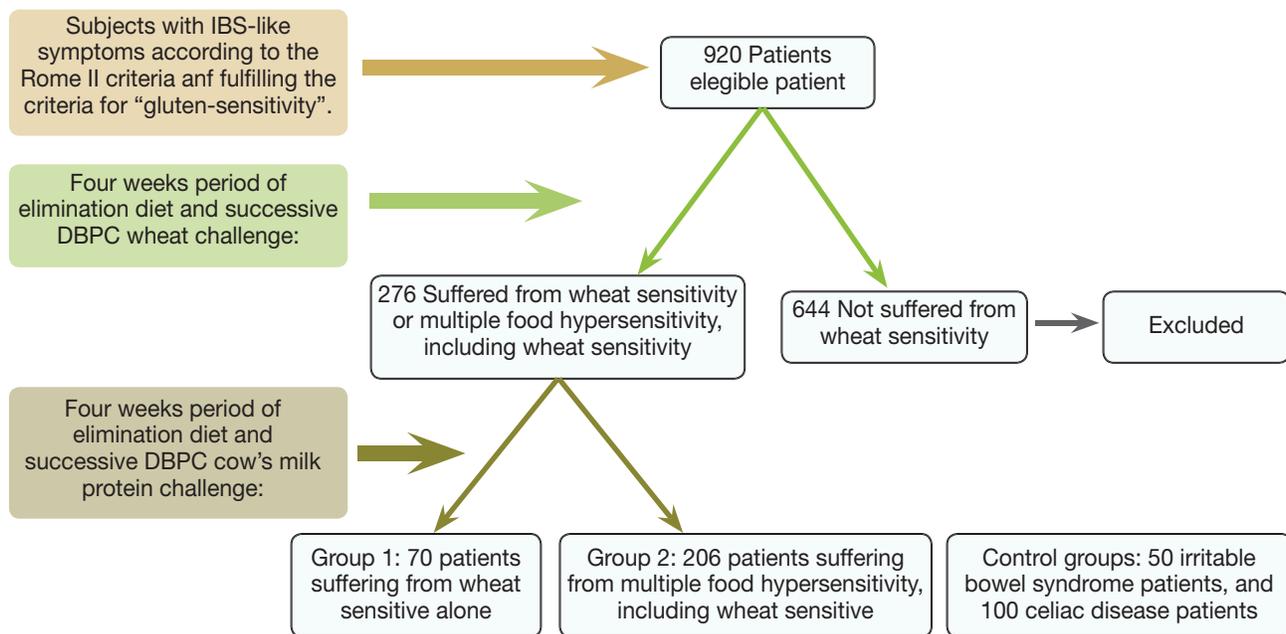


Figure 2. Clinical study design and results from the study (Adopted from Carroccio et. al. 2012)

permeability. In his discussion of the food factor, Fasano indicated rightly that humankind was not meant to eat wheat or gluten. During 2.5 million years of evolution humankind has been 99.99 percent gluten-free. Humankind started eating wheat only about 10,000 years ago. Therefore, gluten is toxic for everybody, but not everybody gets sick. Don't get confused, he said, explaining that "the vast majority of people will clean up the fragments of gliadin and nothing happens. Only a very small percent of people lose this battle and the gluten fractions crossing the intestine will cause problems. The gluten fragments are taken as bacteria that can harm us. Some of the ones that lose the battle bear at least some of the factors that make them prone to acquire the disease."

It is inaccurate and dangerous to label wheat and gluten a wholesale danger for the human population—especially for the billions of people that need wheat to survive or for basic nutrients. The small numbers of people that cannot tolerate gluten should embrace a gluten-free diet, and that will solve most of their health conditions and discomfort.

7.1.1.5 Inflammation, Zonulin and Tight Junction (TJ). Gliadin peptides in the gut promote production of the protein zonulin, which opens the gut and increases permeability allowing the entry of undesirable peptides and other unwanted simple components. Hence gliadin is the trigger that

activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability and unwanted macromolecules (Drago et al. 2006). Fasano (2001) developed an illustrative diagram showing the pathological and therapeutic implications of the passage of macromolecules through the tight junction (Figure 3). The diagram shows how many different conditions can occur if a person has a "leaky gut," a proposed condition some health practitioners say causes a range of long-term health problems, including chronic fatigue syndrome and multiple sclerosis. The human gut must be protected and for that it needs gut microbiota, which can protect against infectious bacteria, inflammation and gut permeability (Frazier et al. 2011) and contribute enzymatic complexes that help to completely digest food. Additionally, a Zonulin blocker drug has been developed to reduce or prevent gut permeability (Fasano, YouTube, 21 January 2014). The drug Larazotide Acetate consistently reduced gastrointestinal symptoms in three gluten challenge clinical trials by preventing leaky gut.

Inflammatory processes and gut permeability are the two major elements for the initiation of immune and autoimmune events. Triggers could involve such factors as peptides from wheat and other food, short chain carbohydrates, sugars, good and bad bacteria and a lack of certain hydrolyzing enzymes. They could also be due to innate predisposition or to variations during childbirth, diet in the early months, childhood and adulthood. Antibiotics and other medical drugs

may also lead to a favorable predisposition for triggers resulting in a permeable gut. These factors may act on an individual or complementary basis to cause the problem (Fasano 2011; Halmos et al. 2014). Arthur Agatston and Natalie Geary, in their book. “The South Beach Diet Gluten Solution” (2013) explain in detail the signs of non-celiac gluten sensitivity and whether inherited or external factors made the person NCGS. They also emphasize that being NCGS does not necessarily mean you cannot eat gluten. They explain that it is important to determine tolerance levels to gluten-containing foods.

7.1.1.6 Microbiome. Fasano queries: “What happened to these people that suddenly lose their capability to eat gluten?” What other factors must be considered? (Fasano, YouTube, 21 January 2014). Perhaps, he suggests, the age at which a baby was introduced to gluten and, or, the changes of the microbiome composition as we age, or changes in our dietary habits, environment and lifestyle could affect the human ability to properly digest gluten.

It is important to consider that bacteria within the human body express 100 times more genes than we, as humans, do. Human beings are made up of genomes as well as microbiomes. The microbiome is inherited from the mother, which means babies delivered through the birth canal receive her microbiomes. Some have suggested that babies born

by caesarean might have a higher risk of developing celiac disease or other diseases because they did not get all the microbiomes and microbiome-related enzymes present in the mother, which contribute to digestion of food in the small intestine.

Agatston and Geary (2013) also ask why those who are NCGS do not have the ability to digest gluten at a manageable level. There are other factors that could be related to the microbiome and immune system affecting the capacity to perform better in the presence of gliadin or other protein or even bacteria. To list some:

- Not enough enzymes to digest excessive amounts of ingested food.
- Excessive concentration of gluten in our food (gluten is added to some baking products, soups, dressings, sausages, etc.).
- Digestive track congestion with resulting inflammation from very low traffic and gut damage (and permeability).
- Abuse of pain relievers and anti-inflammatory drugs such as non-steroidal anti-inflammatory medications (NSAID), including aspirin, naproxen, indomethacin and ibuprofen (30 billion doses of NSAIDs are taken in the United States each year). These drugs can damage both the stomach and small intestine, contributing to the capacity of gliadin peptides to leak through the intestinal lining causing diverse immune reactions.

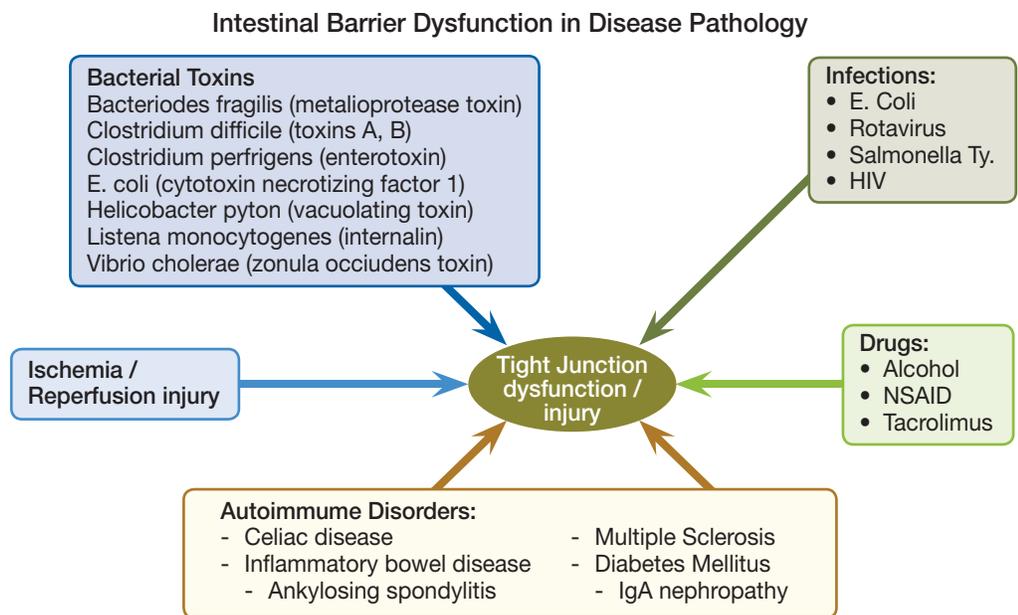


Figure 3. Pathological and therapeutic implications of macromolecules passage through the tight junction (adopted from Fasano, 2001)

- Abuse of antibiotics may also contribute to our gluten-related problems.
- Overuse and over-prescription of antibiotics is very high in the United States today. Medical doctors often unnecessarily prescribe antibiotics for bronchitis and flu, starting in childhood. Antibiotics kill both bad and good bacteria (microbiome) in the intestine, reducing their ability to aid the digestion of gluten.
- The human body needs good bacteria. Throughout life good bacteria is affected by medications, diet, lifestyle and environment. A study (De Filippo et al. 2010) has shown that eating a high-fiber diet in rural Africa generates different gut flora than that found in Western children who eat a low-fiber diet heavy in meat and starch. The gut flora of African children is protective against diarrhea and inflammatory disease, while the gut flora of Western children from industrialized countries is associated with a higher incidence of Western diseases such as diabetes, allergies, inflammatory bowel disorder, and obesity (De Filippo et al. 2010).

7.1.2 Carbohydrates, obesity, diabetes and neuropathy

Most of these books do not present any nutritional information that is not already well known with regard to general causes of weight gain, obesity and related health problems. It is generally accepted by nutritionists that lowering daily caloric intake from more than 3,000 kilocalories to recommended levels of below 2,500 kilocalories will result in weight loss.

Most of the arguments that relate to wheat and obesity have already been analyzed, discussed and often refuted on scientific grounds (Miller Jones 2012, the National Wheat Improvement Committee of the United States in collaboration with several universities and research institutes from the United States and Europe, CIMMYT and by several other scientific studies [Biesiekierski et al. 2013a; Brouns et al. 2013; Kasarda 2011; Shewry 2009]).

Other arguments indicate that high carbohydrate foods are the main cause of brain dysfunction and diseases or conditions such as depression, epilepsy or anxiety, among others. Sugar levels close to the high limit tend to make the brain shrink, one author argues. High glycemic index, refined flours, glucose, and fructose, all cause diabetes and inflammatory reactions affecting the brain and natural antioxidants promote Alzheimer's, atherosclerosis, dementia and reduce cognitive capacity.

These arguments are taken beyond the caloric load of wheat and include all cereal grains as well as fruit with high starch and glucose concentration. In general, the recommendation is to consume low carbohydrate foods, and the elimination from our diet of wheat, rye and barley because these contain gluten.

There is no doubt the scientific and therapeutic communities agree that excessive caloric intake is related with high glucose in blood, promoting Type 2 diabetes and obesity and cardiovascular diseases. We also know that it affects hormones and the capacity for the metabolism to operate normally.

Researchers at Australia's Monash University have proven that a diet low in FODMAPS is an effective strategy for managing symptoms (diarrhea, bloating, abdominal pain, and flatus) of Irritable Bowel Syndrome caused by poor absorption, osmotic activity, and rapid fermentation of short chain and simple sugars (Barrett 2013). Up to 86 percent of patients with IBS have achieved relief of overall gastrointestinal symptoms and, more specifically, bloating, flatus, abdominal pain, and altered bowel habit from the approach (Barrett 2013).

Although wheat is high in FODMAPS, hundreds of other foods are also high in FODMAPS. Therefore, a high FODMAPS diet does not exclude wheat. A balanced diet can regulate the amount of FODMAPS, avoiding inflammation and loss of cognitive capacity (Gómez-Pinilla 2008).

Excessive eating causes people to become overweight and even morbidly obese, which is associated with Type 2 diabetes and cardiovascular diseases. The solution to these problems is in the reduced caloric intake of a balanced diet with sufficient dietary fiber and good amount of antioxidants accompanied by physical exercise.

It is also known that changes in microbiota may also be a factor in becoming obese. Round and Mazmanian (2009) showed that the microbiome (gut flora) of overweight individuals was different from the microbiome of thin individuals.

On the other hand, Cho and Blaser (2012) in an experiment with mice, showed that excessive use of antibiotics affects our good microbiome, causing metabolic changes, possibly affecting the metabolism of fatty acids, increasing digestion of fat, enhancing caloric intake and an increase in accumulated fat

of approximately 10-15 percent higher than the control mice. Trasande et al. (2013) postulated that microbes in our intestines may play a critical role in caloric intake from food. Exposure to antibiotics early in life may kill off healthy bacteria that influence the absorption of nutrients. In a study, Trasande et al. (2013) found that administering babies antibiotics before the age of six months increased the chance of being overweight by age 3 by 22 percent. These studies contribute to evidence of the effect of antibiotics on gut bacteria, contributing to obesity.

Contrary to what anti-wheat books claim, people consuming three servings of whole grains throughout the day are less likely to acquire Type 2 diabetes (Venn and Mann, 2004) than those that consuming a smaller number of servings. In a survey of children and adolescents, those who ate breakfast, which included wheat, maize, oats or rice, were associated with low saturated fat or cholesterol intake and high intake of carbohydrates, dietary fiber and various micronutrients, had a lower prevalence of obesity than those that did not eat cereal at breakfast or that skipped the meal altogether. Those who skipped breakfast showed higher body mass than those that had any of the two types of breakfast: ready-to-eat cereal (RTEC) and non RTEC breakfasts (Deshmukh-Taskar et al. 2010). Additionally, Rampersaud et al. (2005) in a similar study found that those children and adolescents that had breakfast including regular milk and cereal-based food showed better scholastic performance than those skipping breakfast.

Thus, a balanced breakfast should have a good, but balanced, load of cereal grains including wheat, milk and some polyunsaturated fat.

In an essay published in April 2014 on the CIMMYT website¹, nutritionist Miller Jones refers to statements indicating that the increase in obesity and diabetes in the United States directly correlates with the increase in the sales of wheat-based products. But wheat is not the real culprit.

“Food available for consumption increased in all major food categories from 1970 to 2008. The number of average daily calories consumed per person increased approximately 600 calories during that period,” Miller Jones reported, referring to data from the President’s Council on Fitness, Sports and Nutrition and statistics from the U.S. Census Bureau.

Weight-loss diets that advocate the elimination of an entire food group such as wheat may cause initial weight loss, but, like many fad diets, rarely show long-term maintenance of weight loss.

In fact, studies confirm that the easiest diets to maintain are those that deviate least from normal eating patterns. They are also much more likely to be associated with long-term weight loss and maintenance of the loss. Further, diets that include a balance of foods and do not have “forbidden” or excluded foods are associated with the greatest success in sustaining the weight loss.

Elimination of wheat and gluten can result in problems because wheat is a major contributor to dietary fiber, B vitamins and other nutrients.

7.2 Modern wheat vs old wheat and health

People first began eating grains about 75,000 years ago in western Asia (National Geographic 2014). These grains, including *T. boeoticum* (an ancestor of einkorn) and wild emmer (*diccocooides*), were ancestors of today’s wheat. People harvested the grasses that grew naturally near their communities. They began cultivating, or growing, grain more recently and ancient people ate grains in much the same way we do today. Wheat grains were made into flour and used in breads.

Modern bread wheat is the most widely cultivated type of wheat today, making up more than 90 percent of global production. It is the product of natural hybridization among several grasses (Figure 4). One parent is *Triticum urartu*, a wild grass that still grows in the Middle East. *Triticum urartu* spontaneously hybridized with *Aegilops speltoides* and formed wild Emmer (*Triticum dicoccocoides*). The cultivated form (*T.dicocum*) was consumed by the ancient Egyptians and Romans and is still consumed today in India. Durum wheat, derived from emmer (*Triticum durum*), is used today for pasta and semolina products. Around 10,000 years ago, emmer crossed naturally with goat grass (*Aegilops tauschii* (Peng et al. 2011) and formed the ancestor of modern bread wheat (*T. aestivum*). Wheat was wild at the outset until our ancestors started to cultivate and domesticate it.

¹ www.cimmyt.org/en/wheat-matters/item/of-wheat-weight-gluten-and-food-intolerances

Modern wheat (*Triticum aestivum*, or bread wheat, and *Triticum durum*, or pasta wheat), and other varieties such as *Triticum spelt* (spelt wheat) and *Triticum turgidum* subsp. *Turanicum*, commercially known as Kamut wheat, has not changed in its fundamental genetic composition.

The nutritional and protein composition of durum and bread wheat eaten today varies very little from the wheat consumed 8,000 to 9,000 years ago. Ancient wheat had the same genetic base that wheat breeders still use today to generate improved wheat cultivars. The genes are the same, although recombined in diverse ways through cross-breeding (Cavanagh et al. 2013).

Alessio Fasano, an internationally recognized researcher of celiac disease pathology, immunology and related disorders at Massachusetts General Hospital, asserted in a seminar that modern wheat is no different from old wheat in its constitutional make up and grain composition (YouTube, 21 January 2014). In support of this, several biochemical genetic, and genomic studies (Akhunov et al. 2010; Cavanagh et al. 2013; Kasarda 2011; Naghavi et al. 2013;

Peng et al. 2011; Shewry 2009) have shown that the cultivars of different varieties consumed today – including bread and durum wheat, emmer, spelt and kamut have their origin in the diploid and tetraploid ancestors (*T. Urartu*, *Ae. tauschii*, and wild emmer, among others.).

In addition, the gluten proteins found in modern wheat have their origin in the diploid species *T. urartu*, *Ae. speltooides*; and *Ae. tauschii*, i.e. also the diploid ancient wheats contain gluten (Dhanapal et al. 2010; Gutierrez et al. 2010; Molberg et al. 2005; NWIC, 2013; Salentijn et al. 2012). The protein content of wheat we eat today is similar to that consumed at least 100 years ago (Kasarda 2011). Some studies have found that the species *T. monococcum* (cultivated einkorn), and other landraces, or “old modern wheat”, of *T. aestivum*, *T. compactum* and *T. spelta* in which the wheat we eat today originated also contain gliadins (gluten proteins) similar to those in modern wheat that generate the gliadin peptides (epitopes) that provoke celiac disease (Colomba and Gregorini 2012; Molberg et al. 2005; van den Broek et al. 2010; Salentijn et al. 2012; Suligoj et al. 2012; Vaccino et al. 2009).

8. Conclusion

Wheat and other cereals should always be part of a healthy and nutritious balanced diet for most of the population. Its consumption is highly recommended to ensure an appropriate intake of dietary fiber, minerals, vitamins, and other beneficial bio- compounds present in the wheat grain. The approximately 1 percent of the population suffering from congenital immunological celiac disease incapacity should not consume wheat products or any product containing gluten. However, these groups should be aware that the gluten-free food they are going to consume has a composition that will not necessarily positively affect their health, starting with calorie intake from carbohydrates and sugar. For those with gluten sensitivity, it is important to be aware if they are truly gluten sensitive and, if so, to what degree, to determine whether they should eat gluten-containing foods.

The media hype around the supposed “dangers of wheat” is detrimental to the important and ongoing research agenda to sustainably increase wheat production for nutritional needs of the global population.

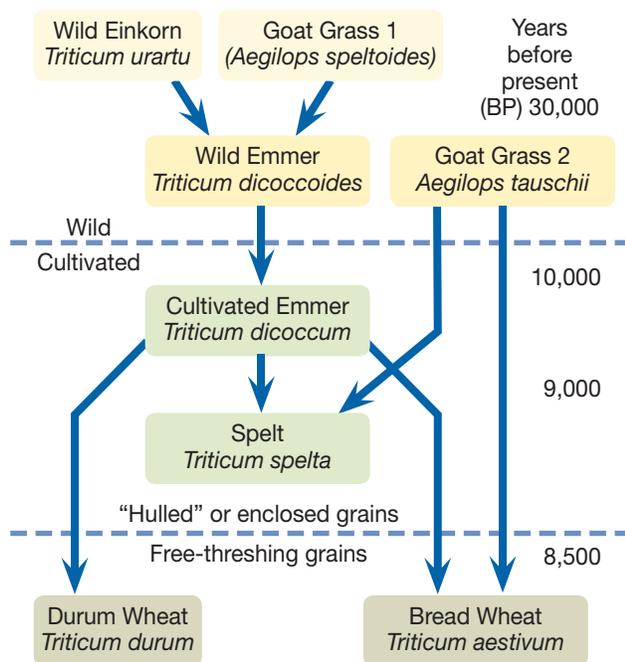


Figure 4. The evolution of wheat from the prehistoric Stone Age grasses to modern macaroni wheat and bread wheat (reproduced from <http://www.newhallmill.org.uk/wht-evol.htm>)

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Wheat in Nutrition and Health: An Overview Part I. Role of Carbohydrates in Health^{1,2}

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Cereal Grains and Carbohydrates as Global Food Staples

History of Grains in the Human Diet.

Cereal grains and other carbohydrate-rich staple foods form the basis of most diets, both ancient and modern, around the world. Despite claims to the contrary, records from pottery shards show that grains were likely eaten prior to the advent of agriculture during the Paleolithic Period. Carbon dating shows evidence of domestication of rice as far back as 16,000 years ago in the Yunan Province of China and of wheat 10,000 years ago in the Fertile Crescent (1,2). DNA from wheat strands has also been found in a hunter-gatherer site that predates the advent of agriculture in the United Kingdom (3).

Cereal grains and carbohydrates (CHOs) have been central components of human diets since the beginning of agriculture due to several factors. First, they are reliable, storable, sustainable, and readily available sources of energy and nutrients. All of these are key in averting malnutrition and promoting health. Second, as a ready source of energy grains and other staples spare proteins. As a result, proteins, which are a more expensive dietary component, are not used for energy. Third, grains are embedded in a variety

of cultural, religious, and linguistic traditions around the globe. In fact, eating patterns and national dishes in most regions combine grain(s) and other protein sources. Such dishes have become traditions within various cultures because they nourish and support the population. Modern nutrition science has documented that when combined and eaten in the right amounts cereals and other plant foods such as legumes or seeds, each of which contains an incomplete protein, work together to form complete proteins.

CHOs and grain-based staple foods played a key role in the development of agriculture, which in turn was vital for the development of human civilization, because a reliable supply of calories and nutrients enabled the specialization necessary for the advancement of humanity. Thus, cereal grains and other CHO sources form a nutritional base that supports life and are associated with other dietary components that enable optimal health and well-being for the world's human population.

Processing and Refining Grains. Nearly all CHO-rich staples must be processed in some way prior to human consumption. Egyptian hieroglyphs and biblical texts document the separation of the wheat grain from the chaff and the making of breads and other grain-based foods. Archeological sites around the world provide ancient evidence of grinding stones used for crushing grains. Some sites even contain evidence of sifting methods and separation of various parts of the grain.

The debate over use of refined flour or whole grains in bread was documented as early as the fourth century B.C.E. Plato advocated good health and longevity through eating locally grown, whole grain breads (4), whereas Socrates deemed Plato's whole grain bread "pig-food"! The debate contin-

ued into Roman times, when the Roman historian and scientist Pliny wrote in A.D. 70 about the consumer preference for whiter breads, noting that "The wheat of Cyprus is swarthy and produces a dark bread, for which reason it is usually mixed with the white wheat of Alexandria." Since Roman times highly refined grains were chosen by those who could afford them. Heartier breads, even today, are often referred to as peasant breads. However, Galen, a prominent Greek physician in Roman times, noted that white bread is the stickiest and slowest to pass and that brown bread is good for the bowels (5). Roman records show that whole grain meals were given to warriors and gladiators for strength. In fact, gladiators were called *hordearii*—literally, "barley men" (6).

The debate continues nearly 2,000 years later with those who champion whole grains and avoid refined grains. Although a large body of evidence, which is summarized in a paper from a recent Grains for Health Foundation Whole Grains Summit, shows that whole grains are important for health (7), there are data showing that refined and enriched grains make important contributions to the diet as well (8). At the same time, however, data also show that overconsumption of certain foods from the grain food group, particularly grain-based snacks and desserts, provides nearly as many calories in the diets of U.S. adolescents as do sugar-sweetened beverages (9,10). Both the benefits of cereal grain consumption and the risks of overconsumption will be discussed in this review.

Debate Concerning the Effects of CHOs and Grains on Health. While debates concerning grains and processing are not new, recent debates charge that wheat and all grains, even whole grains and CHO-rich staples, contribute to chronic diseases and

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Series of Reviews on Carbohydrates, Wheat, and Cereal Grains and Their Impact on Health

To address many claims now occurring that disparage and discourage the ingestion of carbohydrates (CHOs), wheat, and cereal grains, even whole grains, as well as to celebrate the versatility, nutritional and health benefits, and contribution of these foods to the world food supply, we felt compelled to defend their role in the diet and write this series of reviews. Where data exist, cereal grains and wheat as a source of CHOs and other important nutrients will be the focus.

The first grouping of review articles in the series will give some history showing that CHOs and grain-based foods have nourished the world population for millennia. The difference between and nutritional importance of glycemic CHOs and non-glycemic CHOs (e.g., dietary fiber) in nourishing the population will be emphasized. In the first review, the dietary recommendations for CHO and cereal grain consumption published in different countries and by health promotion bodies around the world will not only show striking concordance, but also will showcase their importance in the diet. The recommendations will show that CHO-rich staples, especially grains and whole grains, provide a low cost, versatile dietary base and deserve their important role in providing 45–65% of the calories in the health-promoting diets of most individuals. Further, these worldwide affirmations of the important role of CHOs, grains, and wheat in the diet will derail the arguments of authors and books that suggest otherwise. The second review will outline and discuss terminology associated with grains and whole grains and their processing, including definitions of whole grain, dietary fiber, and resistant starch and the characterization of a whole grain food. This discussion is important because the terms used often create consumer confusion and vary from country to country. The energy, protein, and critical vitamins and minerals contributed by grains as builders of a balanced diet for most healthy individuals around the world will be discussed. The nutritional contribution and bioavailability of nutrients and phytonutrients from grain-based foods will also be discussed.

The second grouping of reviews will include a paper that provides an overview of the physical health impacts of CHO-rich staple foods, including those that are wheat- and grain-based. It will address the impacts of these foods on basic health, including aspects such as blood glucose, inflammation and immunity, and composition and metabolic activity of the microbiome. As part of this discussion, the review will describe how these foods are digested and how their digestion impacts health outcomes in healthy people.

Further, the review will provide data regarding the small segment of the population who have medical conditions that preclude their eating wheat and other gluten-containing grains. This is especially important because many are attributing digestive problems and exacerbation of conditions such as irritable bowel to gluten and wheat. Caveats concern-

ing grain and wheat consumption discussed in the literature will also be reviewed.

The other articles in the second grouping of reviews will discuss the effects of CHO, grain, and wheat consumption on body weight maintenance and loss, blood pressure, metabolic syndrome, diabetes, stroke, cardiovascular disease, cancer, immunity, and longevity. Because inflammation, glycemic response, and insulin resistance all are associated with these chronic diseases, information from the first article in this grouping will be referred to for basic mechanisms.

The third group of review articles will assess the role of CHOs, grains, and wheat in neurological and brain functioning. The first of these will provide an overview of CHOs and other nutrients in brain functioning. It will include an introduction to specific terms and measures used in neuroanatomy and neurophysiology, such as cognition, working memory, attention, and executive functioning. The contribution of nutrients and phytonutrients from CHO-rich staples, with a focus on grains and wheat, in promoting normal brain functioning and fighting ill effects caused by inflammation will also be discussed. This article will also include an overview of dietary patterns, such as the dietary approaches to stop hypertension (DASH) and Mediterranean diets, that are associated with optimal brain health and neurological functioning.

The next set of articles will describe the relationship between CHOs, grains, and wheat and various dementias, such as mild cognitive impairment and Alzheimer's, and degenerative disorders, such as Parkinson's. The articles will include a look at the relationship between diabetes, insulin resistance, and abnormal glucose tolerance and various dementias. The last article in this group will review the scientific literature on the role of nutrition, CHOs, grains, and wheat in autism, attention deficit hyperactivity disorder (ADHD), major depression disorder, epilepsy, foggy brain, headache, multiple sclerosis, and schizophrenia.

The last two articles in the series will deal with the nutritional contributions of wheat and wheat-based foods in the diet and address the role of cereal grains and their global importance in providing a sustainable supply of calories and nutrients for the general population. The final article will have a global focus on wheat and its cultivation and processing and will assess similarities and differences in practices and uses. It will look at how wheat has evolved and continues to evolve and will describe how increases in yield and other factors have impacted different cultures and health. The cultural and nutritional contributions of wheat products in various regions will be compared and contrasted. The role of grains and wheat as part of a sustainable strategy for feeding the global population in 2050 and beyond will also be considered.

that consumption should be curtailed or completely eliminated from the diet.

Epidemiological studies showing that people who overconsume CHOs and grain-based foods have higher risks of developing obesity (11) and type 2 diabetes mellitus are used to support these arguments (12,13). Some suggest that consumption of CHO-rich foods impairs the ability to manage weight and type 2 diabetes. Although such arguments are based on associations found in epidemiological data, they frequently have been promulgated as causal rather than associational (14). Further, although some intervention studies have shown that the reduction or

elimination of CHO-rich foods in the diet, including wheat and grains, may result in short-term success in weight reduction and improvement in blood lipids (15), others show that for most individuals sustained weight loss and dietary adherence are not experienced or are lacking (16).

Finally, some authors and media spokespeople allege that the obesity epidemic and a myriad of other health problems are caused by wheat and/or gluten in the diet (17). Some even recommend the avoidance of all grains (18). The result is that there are many voices advocating the elimination of wheat and grains from the diet. Proponents of low-CHO and paleo-type

diets have questioned dietary advice that suggests 45–65% of daily calories from CHOs is an acceptable macronutrient distribution range. Some claim that in Paleolithic times humans did not eat grains (19) and, therefore, posit that humans have not evolved to include them in their diet (20). Additionally, some social media sources and diet books are claiming that modern wheat and grains, through breeding and other processes, have morphed and no longer deserve to be called the “staff of life.” They further allege that genetic modification has created grains that are not only addictive, but also destructive to many aspects of neurological functioning and mental health (17,18). Some sources even state that grains and CHOs are “chronic poisons.”

Table I. Cereals and pseudocereals^a

Common Name	Scientific Name
True cereals	
Wheat (including spelt, emmer, farro, einkorn, kamut, durum)	<i>Triticum</i> spp.
Rice, African rice	<i>Oryza</i> spp.
Barley	<i>Hordeum</i> spp.
Corn (maize, popcorn)	<i>Zea mays</i>
Rye	<i>Secale cereale</i>
Oats	<i>Avena</i> spp.
Millet	<i>Brachiaria</i> spp., <i>Pennisetum</i> spp., <i>Panicum</i> spp., <i>Setaria</i> spp., <i>Paspalum</i> spp., <i>Eleusine</i> spp., <i>Echinochloa</i> spp.
Sorghum	<i>Sorghum</i> spp.
Teff (tef)	<i>Eragrostis</i> spp.
Triticale	<i>Triticale</i>
Canary seed	<i>Phalaris canariensis</i>
Job's tears	<i>Coix lacryma-jobi</i>
Fonio, black fonio, Aslan millet	<i>Digitaria</i> spp.
Wild rice	<i>Zizania aquatic</i>
Pseudocereals	
Amaranth	<i>Amaranthus caudatus</i>
Buckwheat, tartar buckwheat	<i>Fagopyrum</i> spp.
Quinoa	<i>Chenopodium quinoa</i> , generally considered a single species within the <i>Chenopodiaceae</i>

^a Source: AACC International Whole Grain Task Force (21).

Nutritional Contributions of CHO-rich Staples, with a Focus on Grains and Wheat

Major CHO-rich staples include seeds from cereal grass heads or rice, wheat, maize (corn), oats, rye, barley, sorghum, millet, and teff; roots and tubers such as potato, taro, and cassava; and seeds from pseudocereals such as buckwheat, amaranth, and quinoa. In 2006 the AACC International (AACCI) Whole Grains Task Force compiled the list of cereal grains and pseudocereals found in Table I (21). The proximate composition of a sampling of CHO-rich staples is provided in Table II (22,23).

CHOs as Fuel. CHOs are recognized by national and international authorities such as the World Health Organization/Food and Agriculture Organization (WHO/FAO) (22) as the macronutrient

Table II. Major components of many cereal and root crops (per 100 g edible portion)^{a,b}

Crop	Energy (kJ)	Moisture (%)	Protein (g)	Fat (g)	CHO (g)	TDF (g)	Starch (g)	Sugars (g)
Cereal								
Wheat	1,318	14.0	12.7	2.2	63.9	12.6	61.8	2.1
Maize	1,515	12.0	8.7	0.8	77.7	11.0	71	1.6
Rice	1,531	11.8	6.4	0.8	80.1	3.5	80.1	1.0
Barley	1,282	11.7	10.6	2.1	64.0	17.3	62.2	1.8
Sorghum	1,610	14.0	8.3	3.9	57.4	13.8	(50)	1.3
Millet	1,481	13.3	5.8	1.7	75.4	8.5	60	4
Rye	1,428	15.0	8.2	2.0	75.9	14.6	75.9	NA
Oats	1,698	8.9	12.4	8.7	72.8	10.3	72.8	1.2
Root								
Potato	318	79.0	2.1	0.2	17.2	1.8	16.6	0.6
Cassava	607	64.5	0.6	0.2	36.8	NA	35.3	1.5
Sweet potato	372	73.7	1.2	0.3	21.3	3.0	15.6	5.7
Yam	488	67.2	3.0	0.3	28.2	3.3	27.5	0.7
Taro	451	68.3	1.4	0.2	26.2	2.9	25.1	1.1
Potato	318	79.0	2.1	0.2	17.2	1.8	16.6	0.6
Cassava	607	64.5	0.6	0.2	36.8	NA	35.3	1.5

^a Source: FAO (22).

^b CHO = carbohydrate; TDF = total dietary fiber.

that humans need to consume in the largest quantity. A main function of CHOs is as a source of readily available fuel—glucose. Glucose can be carried in the bloodstream to tissues and delivered to cells, where it can be readily utilized (provided that glucose tolerance is normal), or delivered to the liver for storage as glycogen. The liver has a limited capacity for storing glucose as glycogen, however, so excess glucose is used to make fat. Proper utilization of fat in the body requires CHOs to be present.

Glucose is required by all body tissues, including brain tissue. The brain is a CHO “gas guzzler.” While it comprises only 2% of the body mass, it uses 20% of the fuel (24). Further, more recently evolved brain structures, such as the frontal cortex, are particularly sensitive to falling glucose levels, whereas more primitive regions, such as the brain stem, are less affected (25). This explains why a drop in blood sugar is associated with confused thinking but has little impact on physiological functions such as breathing that are controlled by the brain stem.

The brain and nervous system run optimally on a constant supply of glucose, which either comes from CHOs supplied in recently eaten foods or from glycogen stores in muscles or the liver. Without glucose, the body catabolizes protein to supply it. Fat does provide energy to the muscles, but less efficiently than glucose. This may have advantages for those experiencing caloric surfeit, but not for those experiencing caloric deficit. Ketone bodies result when fat is metabolized without CHOs and can be used by the brain but are not considered an optimal fuel for most individuals (26).

Excess CHOs. Excess circulating blood glucose is an aspect of CHO metabolism that causes great concern for several reasons. First, excess glucose is known to contribute to the synthesis of triglycerides; second, it can trigger a cascade of inflammatory responses; and, third, it can lead to the development of insulin resistance and type 2 diabetes mellitus. The latter conditions can hinder glucose entry into the cell, lead to glycosylation of protein, and impair functioning of all tissues, including brain tissues (27).

While excess CHO may impair glucose tolerance and insulin function (in certain individuals under specific conditions), it is not unique in this ability. Excess intake of fat or calories, as well inadequate intake of nutrients, have all been shown to cause inflammation and can lead to insulin re-

sistance and numerous other adverse effects (28–30).

Grains and Glycemic CHOs

A glycemic CHO is one that can be broken down and absorbed as glucose in the small intestine and deliver glucose to the bloodstream and body. In grains, the major source of glycemic CHOs is starch, a polymer of glucose with α 1 \rightarrow 4 and 1 \rightarrow 6 linkages that is split by human amylases.

Nearly all starch in cereal grains is found in the endosperm, whereas the outer layers (bran, germ, and aleurone) contain almost none. In the endosperm, starch exists in granules, which vary by grain variety in size, shape, and properties such as crystallinity. Less than 1% of the CHOs in most grains are in the form of simple sugars, so these CHOs have little impact on the glycemic response caused by grains.

Digestion and Absorption of Glucose.

During digestion, starch is first broken down by amylases to shorter polymers and then to maltose. Starch is broken down to a minor degree by salivary amylase, but primarily by pancreatic amylases in the small intestine. Maltase in the brush border completes the breakdown by splitting the maltose into its two glucose monomers. How rapidly and completely this occurs depends on a number of factors, including the size and composition of the meal; type, size, and structure of the starch granule; particular starch moiety—amylose or amylopectin, with its chain length in the starch molecule and its degree and pattern of branching; ability of the chain to form helices or crystals (31); and degree of starch gelatinization.

Amylose and Amylopectin. In most grains starch is a mixture of two glucose polymers—linear amylose and branched-chain amylopectin—in a 1:3 ratio. Amylose is smaller (100–10,000 glucose units) and less branched than amylopectin. Amylopectin is larger (10,000–100,000 glucose units) and more highly branched. This branched structure provides free ends that allow amylase attachment and more rapid glucose release. The size and extensive branching of amylopectin contribute to lower gelatinization temperatures and a more porous structure. Both factors favor faster amylase action.

Digestible and Resistant Starches. The amylopectin/amylose ratios in grain varieties and cultivars differ widely. “Waxy” varieties contain mainly amylopectin, whereas some varieties, such as HiMaize or basmati rice, are higher in amylose. For

grains that are higher in amylose, delivery of glucose to the bloodstream is slowed, and starch digestion may be incomplete (32). When digestion is incomplete, the undigested starch fragments move from the small intestine into the large bowel where they become “resistant starch” (RS), which is a form of dietary fiber (33).

Starch crystallinity also affects digestion rate. Highly crystalline networks inhibit penetration by amylases and slow digestion. Repeated cooking and cooling remove some water held between the starch chains and promote crystalline bonding between the chains in a process called retrogradation. Retrograded starch chains also resist digestion and become a type of RS. In parts of Africa, such cooking procedures increase RS in staple grain porridges (34).

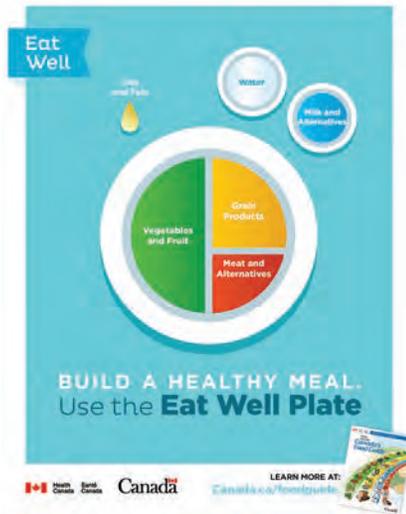
Four types of RS have been delineated by Brown (35). RS1 is starch that is embedded in a food or grain matrix, hindering its availability to amylases. Such starches are common in foods containing unbroken kernels or seeds. RS2 is starch in a native crystalline structure that is poorly degraded by amylase. RS3 results from retrogradation of starches. RS4 is derived from starches that have been chemically cross-linked. Some researchers suggest that amylose helices with an internal fat core should be classified as RS5 (36).

Bread and cereal products are the greatest contributors of RS in most diets, not because they are the best sources, but because they are frequently selected and eaten (37,38). Breads and cereals provide about one-third of the average daily intake of RS (\approx 4 g). Some countries with higher average intakes include China (14.9 g/day), Italy (8.7 g/day), and Spain (5.7 g/day) (39,40).

Glycemic Response and Index. Grains and other CHO-rich food sources of glycemic CHOs directly impact blood glucose. The glycemic impact of a meal or total diet is of great importance because excess circulating blood glucose or dramatic swings in blood glucose levels and attendant hormones, such as insulin, affect health. However, the precise effect varies due to a wide range of factors.

To measure glycemic impact, the glycemic index (GI) was proposed in 1981 by Jenkins et al. (41) as a means of quantifying the effect of a CHO-rich food on postprandial glycemia. Specifically, it measures the increase in blood glucose concentrations (the incremental area under the curve of blood glucose concentrations) after the ingestion of a portion of a

test food containing 50 g of available CHO compared to the area of the glucose curve measured after the ingestion of 50 g of a CHO reference food, usually glucose (sometimes white bread). If the CHO from the test food raises blood glucose the same amount as the reference food, then the ratio is represented as 100; if it raises it less, then the value is smaller than 100. Foods are typically classified as high GI if the GI value is between 70 and 100, medium if the GI value is between 56 and 69, or low if the GI value is ≤ 55 .



Canadian guidelines.

Many recent books and blogs charge that grain-based foods should be avoided because of their high GI. It is true that some grain-based foods have a high GI. However, for several reasons the GI is often misunderstood and misused. First, many assume that the index compares equal amounts of food or even equal amounts of CHO. In actuality, it compares equal amounts of available CHO. For instance, for both whole wheat bread and white bread the GI value is 70, but it takes 3.5 to 4 slices of whole grain bread and 3 slices of white bread to obtain 50 g of available CHO. Thus, eating a slice of whole grain bread will have a lower glycemic impact than a eating slice of white bread.

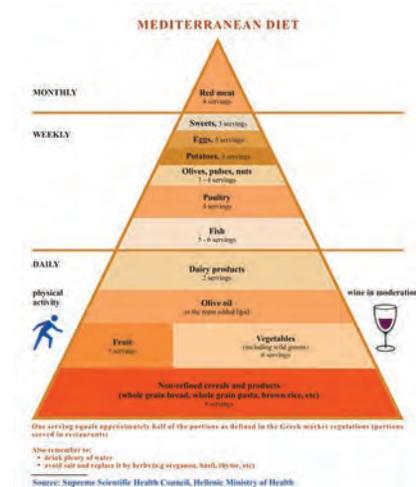
The GI is affected by many components in a food product (42). For example, fat interferes with the action of amylase, thereby lowering the GI. Dietary fibers, especially viscous ones, also impede the action of enzymes and slow the entry of glucose into the bloodstream. The extent and type of cooking or processing, particle size, ripeness, and numerous other factors affect the GI as well (43).

GI values in tables are derived using a single food under strictly controlled con-

ditions. The GI is measured for a single food using 10 subjects with normal glucose tolerance and following a strict protocol that includes an overnight fast and a prescribed dinner. Because foods are rarely eaten either alone or after following a strict protocol, the GI values listed in tables may be wholly inadequate to reflect the blood glucose impact of foods eaten in combination. For example, bread eaten with olive oil or butter has a lower GI value than bread eaten by itself, while bread dipped in vinegar or sushi rice (cooked and cooled with vinegar added) has a lower GI value because of the effects of pH on the enzyme amylase (42). The actual effect of a food on blood glucose depends on how much of the food is eaten, how frequently, and what other foods are eaten in the snack or meal (44).

Popular press publications point out that cereal foods such as whole wheat bread have a higher GI than certain candy bars, such as a Snickers bar (GI = 41) (17). Although the comparison between an indulgent snack and a staple grain is nutritionally ridiculous, it does demonstrate that the nuts, fat, and chocolate in the candy bar combine with the medium GI component sucrose (GI = 68) to slow the entry of glucose into the bloodstream and result in a food with a lower GI than bread. Further, such comparisons say nothing about the volume of food needed to obtain 50 g of available CHO or the nutrition delivered by the food.

Health promotion organizations vary concerning their acceptance of the GI. The American Diabetes Association notes that it may be used as an adjunct to CHO counting (45). The Australian Diabetes Association notes that the “GI is only a small part of the healthy eating plan for people with diabetes” (46). The American



Greek guidelines.

Heart Association (AHA) does not have a formal position on the GI, nor does it express strong support for the GI as an important tool in the evaluation of health risks, CHO quality, or diet planning. The AHA concludes that there are unresolved issues with the use of the GI as a research tool at this time (47).



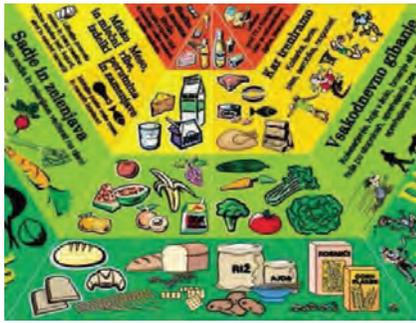
Belgian guidelines.

Non-glycemic CHOs in Grains: Dietary Fiber

Nearly all of the CHOs found in the bran and germ, as well as the CHOs comprising the cell walls in the endosperm, are non-glycemic. They are not digested in the small intestine, which is a key tenet in dietary fiber definitions. Thus, they meet the AACCI (48) and Codex Alimentarius Committee definitions of dietary fiber, i.e., polymers with a degree of polymerization ≥ 3 that are neither digested nor absorbed in the small intestine and are at least partially fermented in the large intestine and have beneficial physiological effects (49,50). (In some countries, these are referred to as nonstarch polysaccharides.)

Dietary Fiber Functions. Dietary fiber is a class of diverse molecules that have many functions. In 2010 an agreed upon list of core dietary fiber functions, which experts attending the international 9th Vahouny Dietary Fiber Symposium suggested had enough scientific evidence to support them, was created and dubbed the “Vahouny 9” (51):

- 1) Reduced blood total and/or LDL cholesterol levels
- 2) Attenuation of postprandial glycemia/insulinemia
- 3) Reduced blood pressure
- 4) Increased fecal bulk/laxation
- 5) Decreased transit time
- 6) Increased colonic fermentation/short-chain fatty acid (SCFA) production
- 7) Positive modulation of colonic microflora
- 8) Weight loss/reduction in adiposity
- 9) Increased satiety



Slovenian guidelines.

Because there are vast differences in the polymers due to different base sugars and attached molecules, as well as different branching structures and matrices, it makes sense that not all dietary fibers perform all physiological functions. However, to be deemed a dietary fiber when added to a food product, the polymer needs to demonstrate at least one of the physiological effects listed above.

Since the 2010 Vahouny meeting, stronger evidence has been gathered for some additional functions. These include bolstering immune functions and exerting anti-inflammatory effects (52).

Dietary Fiber Types. Cellulose is the predominant dietary fiber in many plant-based foods, including grains, because it forms the cell walls of all plants. It is composed of glucose monomers, but human enzymes are unable to split the β -linkage between the monomers. This primary component of many cereal brans is very insoluble and slightly fermentable. Therefore, it is very effective in aiding gut motility, increasing laxation and stool weight, and improving overall gut health.

The polymers that make up a “mortar-like mixture” between the cell walls formerly were called pentosans. More recently, they have been characterized and include β -glucan, fructans, arabinoxylans, pectins, and a variety of oligosaccharides (53). Many of these molecules are soluble, highly fermentable, and able to produce SCFAs. Some are viscous polymers, such as β -glucan found in oats and barley, which may slow absorption by entrapping various dietary components. Through such mechanisms they help maintain healthy serum cholesterol and blood glucose levels (54). The actual functionality is determined by the specifics of the molecule, e.g., branching pattern, molecular weight, concentration, and viscosity.

Fructans, polymers of fructose such as inulin, are soluble, nonviscous, and readily fermentable. They improve mineral absorption and can alter the bacterial

composition of the gut and act as prebiotics. Although they are present in a range of plant foods, wheat and rye are important sources in cereal-based foods (55). Inulin from wheat has been shown to stimulate the growth of bifidobacteria and inhibit growth of pathogenic bacteria such as *Escherichia coli*, *Salmonella*, and *Listeria* (56).

Arabinoxylans are polymers of arabinose and xylose. In grains such as wheat, they exist in both soluble and insoluble forms. They have been shown to act as prebiotics, improving gut health and having some systemic health effects (57). Arabinoxylan from rice bran has been shown to have positive effects on the immune system and gut (58).

Dietary Fiber and SCFAs. Many of the effects of dietary fiber stem from its role in modulating the type and amount of bacteria in the gut. Changing the composition of the gut microbiota can have a positive prebiotic effect on health in that these changes can promote the growth of beneficial bacteria (59).

The fermentation of various CHO polymers in the large bowel produces SCFAs such as acetate, propionate, and butyrate, which are the principal end-products that promote health benefits, both through local and systemic effects. In the colon, they not only lower the pH, which may be helpful in reducing the risk of colon cancer, they also provide energy, promote the growth and differentiation of healthy colonic cells, help repair damage to colonocyte DNA, and induce cell death (apoptosis) in nonrepairable aberrant cells (60–62). These properties provide a credible link between dietary fiber intake and protection against colorectal cancer (63,64).

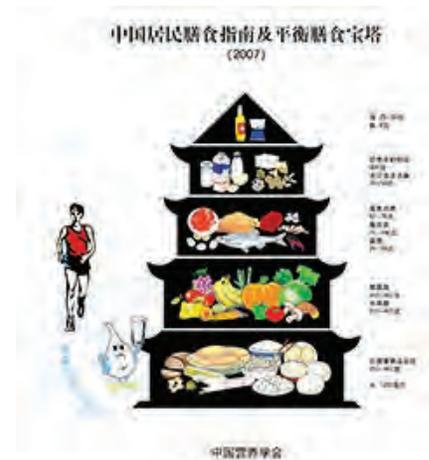


U.S. guidelines.

SCFAs also can affect lipid, glucose, and cholesterol metabolism in various tissues (64). They may help counter diet-induced obesity through their ability to increase fatty acid oxidation in muscle and other

tissues and decrease fat storage in adipose tissue.

Dietary Fiber and Grain Processing. The actual physiological benefits of the various dietary fibers, including RS in grain-based foods, depend on the type and extent of milling; resultant particle size; fiber type, solubility, viscosity, and molecular weight; linkage patterns; and compounds attached to the fiber complex. Thus, processing can both increase and decrease the effects of a dietary fiber by altering its molecular weight (65), viscosity, or the amount of available RS (66–68).



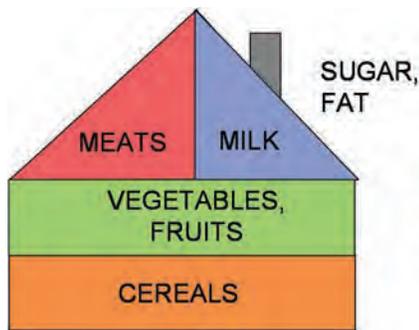
Chinese guidelines.

Recommendations Regarding CHOs in the Diet

With the important nutritional contributions made by CHO-rich foods, it is no wonder that health and government organizations around the world, together with expert consultative committees, recommend that the bulk of calories consumed come from CHOs, particularly from CHO-rich staples, including grains. The WHO/FAO expert consultation on diet (69), U.S. Dietary Guidelines Advisory Committee (70), U.S. Department of Agriculture (USDA) series of systematic reviews on healthy dietary patterns (71), dietary reference intakes established by the U.S. National Institute of Medicine and Health Canada (72), European Food Safety Authority (73,74), Nordic Nutrition Recommendations (75), U.K. Scientific Advisory Committee on Nutrition (76), Singapore Health Promotion Board (77), and Australian Dietary Guidelines (78, 79), as a partial list, all support these recommendations. Most guidelines suggest that at least 45% of calories consumed come from CHOs, with suggested CHO intakes ranging from 45 to 65% of calories; the WHO report recommends as

much as 75% of energy come from CHO (80). Lower GI and higher protein intakes have been recommended by some for individuals with insulin resistance or who are trying to maintain weight (81), but controversy still swirls around this topic, and research continues to try to tease out the answers.

Setting Upper Limit for CHO Intake. The setting of an upper limit for CHO intake is based on two major concerns. The first is the concern that excess CHO intake will upset the dietary balance and impede intake of adequate protein, fat, and other essential nutrients. The second is the concern that excess calorie and CHO intakes can lead to excess circulating glucose and insulin in the bloodstream. Excess glucose in any tissue, including the brain, is known to trigger a cascade of inflammatory responses and insulin resistance that can impair the functioning of all tissues (27). However, the adverse effects of excess CHO intake are not unique to this nutrient; excess intakes of calories and other dietary components (28,29), as well as the lack of them, have also been shown to cause inflammation, insulin resistance, and other adverse effects (30). Although not a basis for setting an upper limit for CHO intake, some have alleged that excess consumption of readily available CHO-rich and grain-based desserts leads to overconsumption of calories.

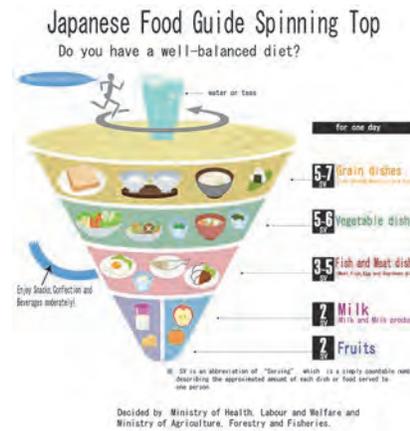


Hungarian guidelines.

Dietary Fiber Intake. Around the world dietary fiber is included as part of general dietary recommendations. Its inclusion is based on evidence produced by epidemiologic and intervention studies indicating that adequate intakes, both in quantity and types, of dietary fiber are associated with improved gut health (82) and reduced risk of death and chronic disease from a number of disorders (83–85).

Despite recommendations, the daily intake of dietary fiber in most developed and developing countries is well below

recommended levels. For example, in North America less than 4% of the population meets the adequate intake recommendation for dietary fiber (86). Therefore, several U.S. Dietary Guidelines Advisory Committees have listed it as a “nutrient of concern.” Consumption of bran and grain-based foods is an important dietary strategy for meeting the dietary fiber requirement.



Japanese guidelines.

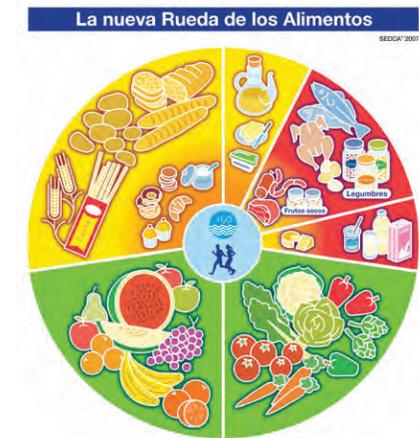
Grains in CHO Recommendations. Translating the recommended balance of calories into food-based dietary guidance is common practice around the globe, according to the European Food Information Council (87). Its compilation of guidelines found that most use verbal descriptions and/or graphic illustrations to assist people in selecting optimal proportions of recommended food groups. While the graphics used vary in form from pyramids and plates to temples and pagodas, the prominence of grain-based and CHO-rich foods in the various recommendations is strikingly similar. Guidance provided by countries around the world, such as the United Kingdom (88), South Africa (89), Singapore (90), France (91), and Australia and New Zealand (92), all urge that grains and starchy foods form the basis of most meals and that they be eaten daily to provide a primary source of energy. Most guidelines suggest that starchy foods



Irish guidelines.

should make up about one-quarter or one-third of the total foods eaten. Grain-based foods (e.g., breads and flat breads, cereals, pastas and noodles, and rice dishes) are included among the starchy foods listed. In some cases, specific amounts are recommended. For example, the U.S. Dietary Guidelines Advisory Committee (71) and USDA MyPlate (93) recommend that the average person ingesting 2,000 cal/day consume 6 servings of breads and cereals, with half of the servings as whole grain foods. Health Canada’s guidelines recommend adults consume 6–8 servings of grains/day (94).

Whole grains have been incorporated into dietary guidelines in many regions. Some specifically mention the need to consume high-fiber, whole grain foods. A recent review by Jonnalagadda (95) contains a compilation of guidelines on whole grain consumption from around the world.



Spanish guidelines.

Despite the general concordance worldwide regarding recommendations for CHO, dietary fiber, and whole grain intake, only a small part of the population consumes the suggested amounts. For example, the French Nutritional Guidelines recommend the consumption of starchy foods from a variety of sources at each meal. Yet, in a survey of more than 80,000 people in the French NutriNet-Santé cohort, only 43% had intakes of starchy food that were in line with the guidelines (96). The authors noted similar data from many Western European countries. Data from U.S. surveys show that 36% of all age and gender categories fail to meet the grain recommendation and 99% fail to meet the whole grain recommendation (9,97).

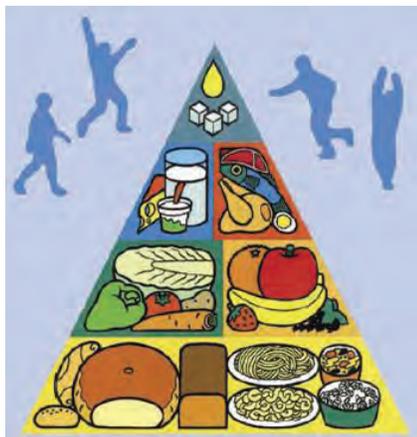
Worldwide agreement concerning the importance of CHO and CHO-rich foods

in the diet does not mean that CHO are free from vigorous debates in both the scientific and popular press about the source and quality of CHO-rich foods. Some advocates argue that the type of CHO-rich foods chosen should be low glycemic, while others argue that only minimally refined or processed grains should be selected and no refined grains should be consumed.



French guidelines.

A few suggest that amounts of CHOs consumed should be decreased or even stripped to a bare minimum of 50 g (200 kcal) for optimal weight control, diabetes prevention, and brain health (17,18). Advocates of the paleo diet claim that grains and legumes should be severely limited because humans did not evolve to eat them. They further argue that adherence to such a diet will bring about weight loss and improve several chronic conditions (19,20). Such claims are appealing in some populations, such as the United States, where as much as two-thirds of the population is overweight or obese (98).



Czech guidelines.

The role of wheat and other gluten-containing grains as a cause of celiac disease and other disorders also has caused some to argue that everyone needs to avoid grains and foods that contain gluten. (Celiac and other gluten-related disorders will be addressed in a subsequent review.)

Conclusions

CHO-rich staple foods, including those from a wide array of whole and refined grains, are inexpensive sources of energy, protein, and other nutrients. Grain-based staple ingredients have been incorporated into an enormous variety of foods, becoming cultural icons and national dishes that are readily accepted by various populations around the world and adapted to specific agricultural necessities and cultural preferences. In many cultures such foods have a long history as dietary cornerstones that continues today.

Dietary guidance by health promotion bodies around the world recommends that 45–65% of total calories be from CHOs and reinforces the message that grains play an important role in the diet. The important health benefits provided by grains argues for their incorporation in the everyday diets of healthy people. Whole grains in particular are associated with decreased risk of certain chronic diseases, and consumption of an optimal mix of whole and refined grains is associated with a number of health benefits.

Cereal grains provide a wide variety of nutrients, dietary fibers, and phytochemicals. This combination uniquely positions them as a source of nutrition to both sustain and nourish a global population.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Wheat in Nutrition and Health: An Overview Part II. Grain Terminology and Nutritional Contributions^{1,2}

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Grain and Whole Grain Terminology and Definitions

Grains are carbohydrate-rich foods that must undergo some degree of processing prior to their ingestion. Even ancient records, such as the Bible and Egyptian hieroglyphs, note the removal of the outer inedible layer (husk, hull, or chaff) of grains. In addition to the removal of the outer grain layer, cleaning to remove dirt, stones, and other foreign matter is basic to any grain processing.

A number of methods can be used to process grains. In some cases, the kernel is eaten after soaking and cooking in its whole (intact) form, but even with soaking long cooking times are this often required. Soaking also may reduce unwanted toxic, bitter, or antinutritional components and improve nutrient availability, which is especially important for certain grains, such as maize (1).

More frequently the kernel is broken to some degree. Cracking, flattening, grinding, or milling enables easy entry of water into the kernel, as do parching, toasting, and other heat treatments. In addition, heat treatments may enhance storage stability and help retain nutrients such as vitamin E by inactivating enzymes that would otherwise cause rancidity. Process-

ing also may involve flaking, extrusion, or other techniques. If various parts of the kernel are retained in their original ratio, they are considered processed but not refined. Refined grains have some part of the kernel removed—usually the outer layers, bran, and germ. This often occurs with milling.

Grain Milling and Flour Fractions.

Milling crushes the grain. After crushing, it is separated by particle size into mill streams for further crushing. If all mill streams are combined at the mill, the end product is a whole grain flour, grit, or meal. However, any of the mill streams can be sold separately. For consumer markets, these would be germ, bran, and endosperm (white flour). The higher the proportion of the grain used to produce flour, the higher its “extraction rate.” Whole meal and flours containing 90% or more of the entire grain are considered “high-extraction” flours, whereas those containing 75% or less of the whole grain are considered “low-extraction” flours (generally called “white” or “refined” flour) and consist of most of the endosperm and a very small part of the inner layers of the bran. Very low-extraction flours are used for cakes, in which the low protein content and small particle size create a product with a finer texture. However, the more the flour is refined, the lower its retention of fiber, vitamins, minerals, and bioactive compounds.

Enriched and Fortified Refined Flours.

In many countries, refined flours are enriched to replace nutrients lost during milling. Figure 1 shows the differences in nutrients found in whole grain, refined, and enriched wheat flours. B vitamins such as thiamine, riboflavin, niacin, and pyridoxine and iron are frequent additions. The specifics as to which micronutrients are added and their amounts vary by grain

type and the nutritional needs of the region. For example, in the United States, each pound (454 g) of flour labeled as enriched contains 2.9 mg of thiamin, 1.8 mg of riboflavin, 24 mg of niacin, 0.7 mg of folic acid, and 20 mg of iron (2). In addition, it may contain added calcium.

Flour may also be fortified to address specific regional needs. In fortification, nutrients are added in amounts higher than are found in the original grain, such as folic acid, or nutrients not naturally present in the grain, such as B₁₂ or vitamin D, may be added.

Enrichment and fortification initiatives, both mandatory and voluntary, have reduced thiamine, niacin, folate, and iron deficiency in many parts of the world (3–5). The World Health Organization (WHO) recommendations for enrichment and fortification of flour are provided in Table I (6).

The fortification of flour with folic acid has been particularly beneficial in preventing neural tube and other birth defects. In some countries, enrichment or fortification of refined flours with folate is mandatory. A comparison of nutrients contributed by a sampling of enriched, fortified, unenriched, and whole grain flours is shown in Table II. The one component that is not customarily added back through enrichment or fortification is dietary fiber.

Whole Grains. In 1999 an ad hoc committee of experts from AACC International formally defined whole grains (7):

Whole grains shall consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components—the starchy endosperm, germ, and bran—are present in the same relative proportions as they exist in the intact caryopsis.

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Other scientific and health-promoting organizations and some regulatory bodies around the world have adopted the essence of this definition. Some groups have tweaked the definition and made slight amendments in the wording to make it easier for consumers to understand (8) or to more accurately reflect milling practices, as in the definition adopted by the European HEALTHGRAIN consortium in 2009 (9). However, all of these whole grain definitions state that whole grain must contain the bran, germ, and endosperm in the same proportions as is found in the original grain.

Consumer Confusion

Cereal, Grain, and Whole Grain Terminology. The terminology used for grain around the world is not standardized and, therefore, creates some confusion among consumers (10). For example, in much of the world the term “cereal” refers to the crop in the field or the raw commodity; however, the term “grain” is also used. As another example, in North America, cereal is commonly used to refer to a hot or cold breakfast entrée, often served in a bowl with milk. In some countries, hot cereals are referred to as gruel or porridge, whereas in others porridge refers only to cooked oats. In addition, some grains sold as “meals” are nearly always whole grains, such as oatmeal, whereas

others, such as cornmeal, are almost never whole grains.

The seed head is referred to variously as the “kernel,” “grain,” “groat,” or “berry.” Whole grain flour in some regions is referred to as wholemeal flour or by the type of grain, such as whole wheat flour. In most countries, the latter is a whole grain flour, but there are a few exceptions. Regulations in Canada allow a small amount of the bran and germ (<5%) to be removed and still allow the flour to be labeled as whole wheat (11).

Processing terms are equally confusing. Many terms are used to describe the removal of the outer layers of grain. For example, wheat is milled, rice is polished, barley is pearled, corn is degermed, and sorghum is decorticated—just to name a few.

Some grains, such as oats, teff, and quinoa, have traditionally been marketed in their whole form and are rarely refined. Thus, some consumers are unaware that foods such as “porridge” or “oatmeal” are whole grain and that barley, except for pot barley, is not. The light color of white wheat, oatmeal, and barley also frequently causes consumers to not believe they are whole grain, while other dark-colored foods may be misidentified by consumers as being whole grain. For example, many North American rye breads are thought by consumers to be whole grain because

caramel color is added. In addition, label descriptions such as “multigrain,” “100% wheat,” or even “organic” may be assumed by consumers to indicate a product contains whole grains, when they may or may not.

Characterization of Whole Grain Food Products. While processing terms confuse most consumers, identifying a whole grain food—one that contains nutritionally significant amounts of whole grain—confuses almost everyone.

Among countries, research papers, and food labels, various criteria exist for the amount of whole grain that must be present for a food to be called “whole grain” (12). For example, a number of epidemiological studies characterize a food as whole grain if 25% of the ingredients, by weight, meet the whole grain definition (13–16). One study characterizes a food as whole grain if the first ingredient on the ingredient statement is whole grain (17), and in yet another study, only fiber-rich whole grains are counted as whole grains (18). The first ingredient is generally reliable as a touchstone for characterizing a food product as whole grain but may fail to identify a product as whole grain if it contains several whole grain ingredients when each is present in amounts smaller than the first ingredient, even when the total whole grains in the food sums to more than 50% of the ingredients.

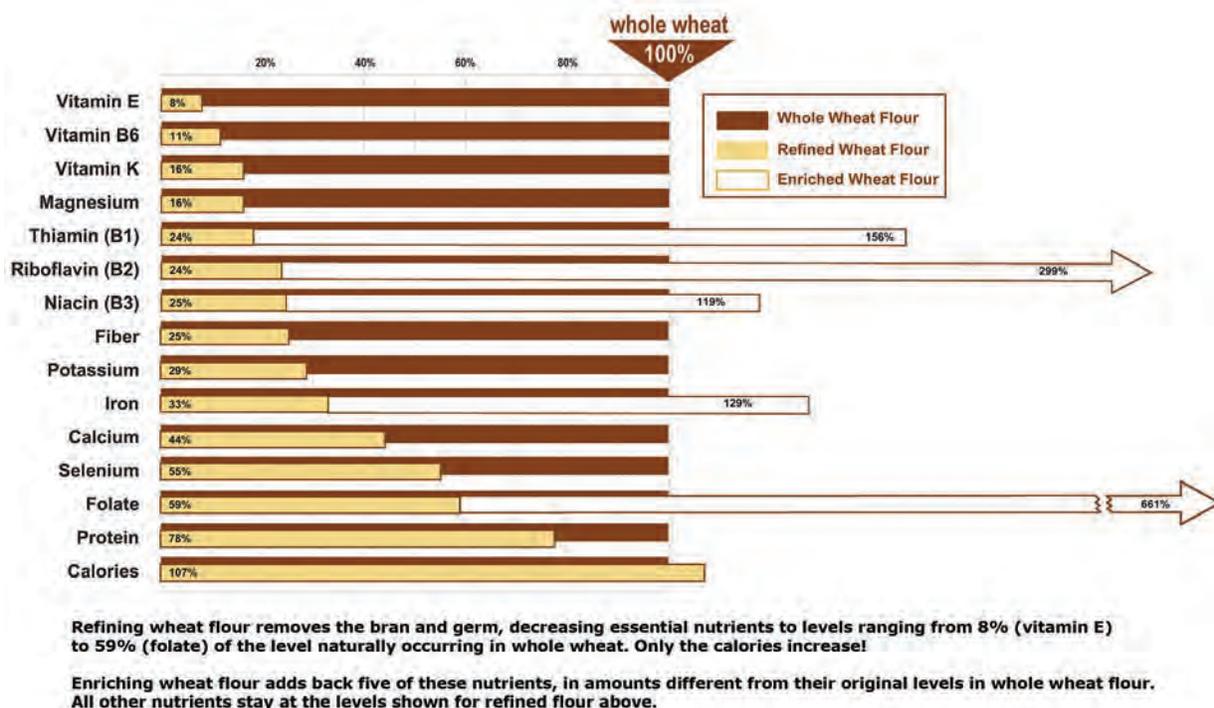


Fig. 1. Comparison of nutrients in whole, refined, and enriched/fortified refined wheat flours. Reprinted with permission from Oldways/The Whole Grains Council.

Some epidemiological studies also have miscategorized whole grain foods by counting all “dark bread,” bran or germ, barley, and couscous as whole grain. In reality, these foods rarely are whole grain at the time of the study (10,19). Reevaluation of studies linking whole grain intake and certain health outcomes has shown that significant inverse associations occur only with the inclusion of bran foods and not with whole grain foods alone (20).

The lack of a standard for characterizing whole grain foods in research carries over into nutrition education and regulations for product labeling. This creates a Wild West atmosphere in the marketplace and is problematic for consumers trying to assess products to meet whole grain recommendations.

Foods containing whole grains may be identified using a unique or trademarked logo or statements such as “contains whole grains” and “made with 100% whole grains.” Some regulatory codes, such as those in the Canadian *Guide to Food Labelling and Advertising* (21), recommend that when the presence of an ingredient, component, or substance is emphasized, the label should include a statement regarding the amount present in the food. However, many countries do not require a statement of an amount, and many consumers would need education or a label declaration of a daily goal to know if the quantity in a particular food contributes a dietarily significant amount of whole grains.

Whole grain health claims are permitted in some countries. Requirements for permitting a health claim in terms of

amount of whole grains and other ingredients vary by country. For example, the U.S. Food and Drug Administration (FDA) requires 51% of the wet weight of the product to be whole grain in order for a health claim to be used. Basing a claim on a percentage of product wet weight gives a clear advantage to lower moisture products, such as crackers and dry cereals, and penalizes foods with higher moisture, such as ready-to-heat oatmeal and sliced breads. Some regions have addressed this unfair advantage by using product dry weight for the basis of their regulations.

Some countries allow a whole grain designation or claim only if the overall nutritional contribution of the product is con-

sidered. For example, in parts of Scandinavia whole grain may be highlighted on the front of a package only if the product does not contain significant quantities of ingredients that may negatively impact health, such as fat and sugar (22,23). Sweden introduced and trademarked a Keyhole logo for packaged foods to designate foods that are better for you than other foods in the category (24). Foods labeled with the Keyhole logo contain less fat, sugar, and salt and more dietary fiber and have a healthier fat composition than other similar foods.

The Whole Grain Council’s Whole Grain Stamp is a fee-based identification logo that certifies the amount of whole

Table II. Nutrient comparison in enriched, whole grain and organic flours (30 g serving [¹/₄ cup]; mg, g, or % DV)

Nutrient	Refined Flour		Whole Grain Flour	
	Enriched All Purpose	Unbleached Organic	Traditional	Organic
Sodium (mg)	0	0	0	0
Potassium (mg)	35	0	51	0
Dietary Fiber (g)	<1	<1	2	6
Sugars (g)	<1	<1	2	1
Protein (g)	3	3	7	9
Vitamin A (%)	0	0	0	0
Vitamin C (%)	0	0	0	0
Calcium (%)	0	0	2	2
Iron (%)	6	0	4	15
Vitamin D (%)	0	0	0	0
Thiamin (%)	10	—	4	4
Riboflavin (%)	6	—	2	2
Niacin (%)	8	—	4	4
Vitamin B ₆ (mg)	0.01	—	0.12	—
Folic Acid (%)	10	—	2	2
Phosphorus (mg)	42	—	106	—
Magnesium (mg)	9	—	41	30
Zinc (mg)	0.28	—	0.74	—
Copper (mg)	—	—	4	10%

Table I. Average levels of nutrients to consider adding to fortified wheat flour based on extraction, fortificant compound, and estimated per capita flour availability^a

Nutrient	Flour Extraction Rate	Compound	Level of Nutrient to Be Added (ppm) Based on Estimated Average per Capita Wheat Flour Availability (g/day) ^{b,c}			
			<75 ^d	75–149	150–300	>300
Iron	Low	NaFeEDTA	40	40	20	15
		Ferrous sulfate	60	60	30	20
		Ferrous fumarate	60	60	30	20
		Electrolytic iron	NR	NR	60	40
Folic acid	High	NaFeEDTA	40	40	20	15
		Folic acid	5.0	2.6	1.3	1.0
Vitamin B ₁₂	Low or high	Cyanocobalamin	0.04	0.02	0.01	0.008
Vitamin A	Low or high	Vitamin A palmitate	5.9	3	1.5	1
Zinc ^e	Low	Zinc oxide	95	55	40	30
	High	Zinc oxide	100	100	80	70

^a Data source: WHO (6).

^b These estimated levels consider only wheat flour as the main fortification vehicle in a public health program. If other mass-fortification programs with other food vehicles are implemented effectively, suggested fortification levels in wheat flour could be adjusted downward.

^c NR = not recommended because the very high levels of electrolytic iron needed could negatively affect sensory properties of fortified flour.

^d Estimated per capita consumption of <75 g/day does not allow for addition of sufficient level of fortificant to cover micronutrient needs for women of childbearing age. Fortification of additional types of food would be the only way to reach adequacy.

^e These levels of fortification with zinc assume 5 mg of zinc intake and no additional phytate intake from other dietary sources.

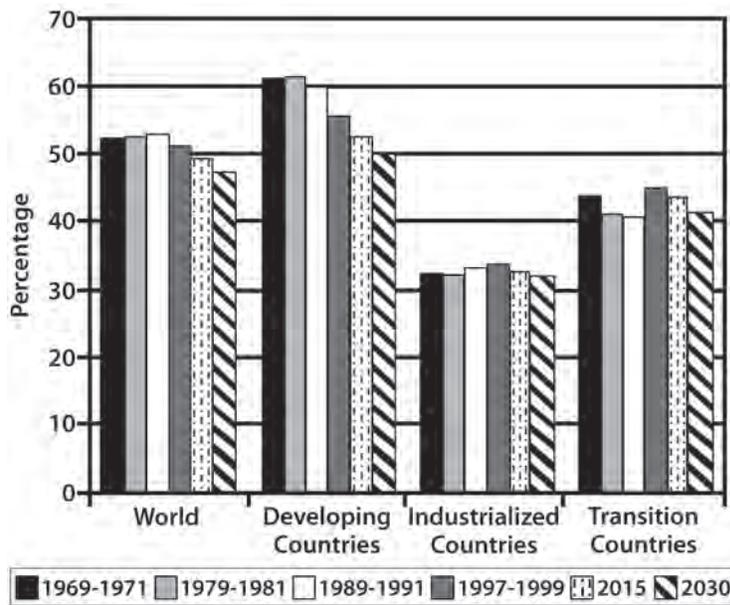


Fig. 2. Changes over time in the share of dietary energy derived from cereals. (Adapted from data in FAO, "World Agriculture: Towards 2015/2030. An FAO Perspective," J. Bruinsma, ed., Earthscan Publications Ltd., London, 2003.)

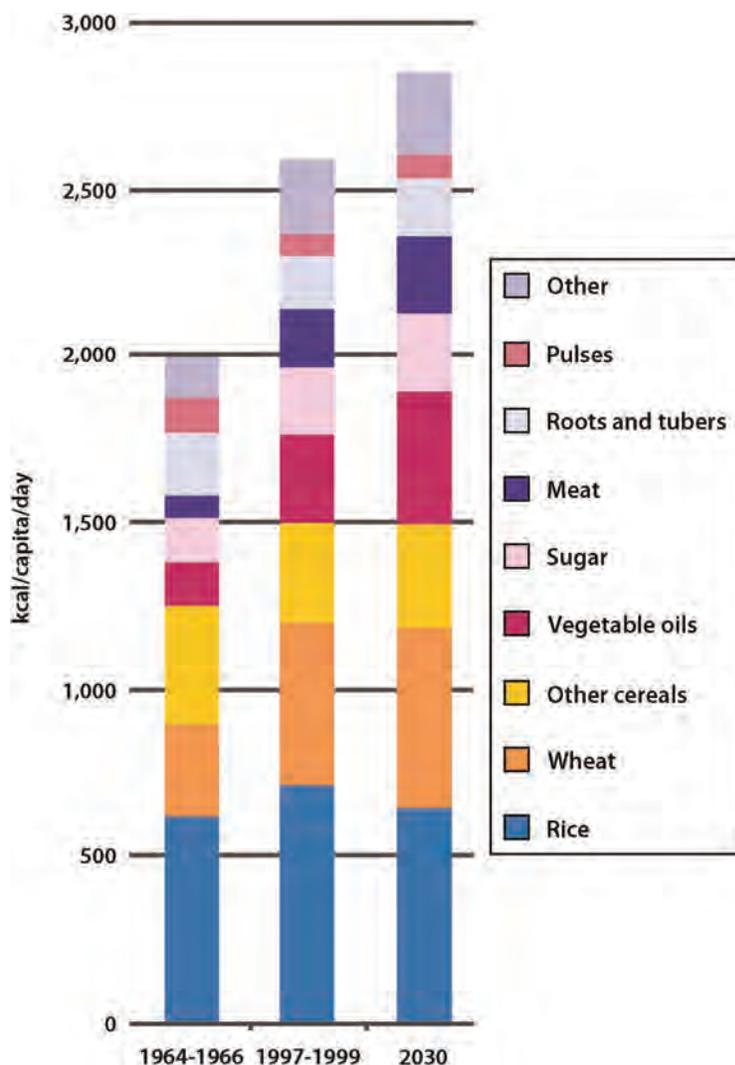


Fig. 3. Calories consumed per day from various food groups. (Adapted from data in FAO, "World Agriculture: Towards 2015/2030. Summary Report," FAO, Rome, 2002.)

grains in a product serving (in grams) with a gold-colored stamp. Products with a large serving size may have an advantage in such a system. Products that contain only bran and whole grain but that contain more bran than whole grain could not receive the stamp even if they contain a significant amount of whole grain. Further, some consumers do not understand that products without the seal may be characterized as whole grain but that the manufacturer did not opt into the program. Thus, guidelines characterizing a whole grain food, also referred to as a "whole cereal food," are important (25).

In 2013 the AACCI Whole Grain Working Group released its whole grain characterization (26). The characterization asserts that a whole grain food product must contain ≥ 8 g of whole grain/30 g of product. This addresses some, but not all, of the issues associated with characterizing a whole grain food.

Nutritional Contribution of Grains

Calories, Protein, and Fat. Worldwide grains contribute around half of calories in the diet—52% in developing countries and 32% in developed countries (27). Changes over time in the share of dietary energy derived from cereals are shown in Figure 2. A breakdown of calories consumed per day from various food groups is provided in Figure 3.

Grains are important protein sources, not because they are notable for either their protein quantity or quality, but rather because they are affordable, readily available, easily stored at room temperature, and found in many commonly eaten foods. Further, the amino acids they contribute complement other plant-based proteins, such as those from legumes, creating combinations that provide all the essential amino acids in quantities needed for maintenance and growth.

Cereal grains as a group are low in lysine (1.5–4.5% versus WHO recommendation of 5.5%), tryptophan (0.8–2.0% versus WHO recommendation of 1.0%), and threonine (2.7–3.9% versus WHO recommendation of 4.0%) but rich in sulfur amino acids. Of the traditional grains, oats have the highest protein content and rice the lowest. Quinoa, a pseudocereal, contains more protein and lysine than most grains but contains limited quantities of tyrosine, phenylalanine, and threonine. The pseudocereals amaranth and buckwheat also are complementary protein sources and can be used to improve protein quality in a variety of ways (28).

Research to develop cultivars with more high-quality proteins is needed given the importance of grains as sources of protein in various parts of the world (29). Protein contents of selected grains are compared in Table III.

Grain proteins are important to the diet, but like all proteins they can pose risks to susceptible individuals. First, grain proteins do have the capacity to be allergenic, and most processing methods do not render these proteins nonallergenic. Currently, only fermentation and hydrolysis may have the potential to reduce allergenicity to a noticeable extent (30,31). Second, some grains contain the composite protein gluten. Gluten in the diet is one of several triggers necessary in genetically susceptible individuals for development of the autoimmune disease celiac, which affects about 1% of the population (32). Third, grains contain antinutritional factors that adversely affect the digestibility of protein, bioavailability of amino acids, and protein quality of foods (33–35). The effects of these are most apparent in regions where traditional diets are marginal and much coarse grain is eaten. Issues associated with the lower digestibility of coarse grains and poor overall diet quality contribute to problems of protein nutrition. For example, protein digestibility in countries such as India, Guatemala, and Brazil is considerably lower than protein digestibility in typical North American diets (54–78% versus 88–94%) (28).

Grains are low in fat, and the fat they contain is found primarily in the germ, which often contains some unsaturated fatty acids, fat-soluble vitamins, and phytonutrients. Corn and oats contain higher levels of fat than some other grains. Oats contain some unusual fatty acids, and the oils from rice bran and wheat germ are sought because of their nutritional properties, such as their high levels of tocotrienols and various vitamin E isomers (36, 37). Fat contents of selected grains are compared in Table III.

Vitamins. Grains are important sources of micronutrients as well, contributing many B vitamins (thiamin, riboflavin, niacin, and folate), vitamin E, and minerals (iron, magnesium, and selenium). The bioavailability of any of these can be increased or decreased by other components in the diet and by processing. Ironically, a factor that may increase the bioavailability of one nutrient may impair that of another. For example, soaking grain to reduce phytate and polyphenols and improve absorption of metals such as iron may also reduce

thiamin. Heating may destroy thiaminases (enzymes), protect thiamin, and disrupt carotenoid–protein complexes, thereby increasing the bioavailability of vitamin A (38), but they also may lower levels of heat-labile components.

The role of grains in contributing to micronutrient status has been examined in studies conducted in developed and developing countries with differing food patterns and ethnic backgrounds (9,39–43). These studies show that the consumption of grains and grain-based foods, including enriched and fortified grains, is an important means of meeting recommended micronutrient intakes. In the Multiethnic Cohort Study conducted with nearly 190,000 adults in Hawaii and Los Angeles, Sharma et al. (44) showed that grain-based foods contributed 30–46% of thiamin, 23–29% of riboflavin, 27–36% of niacin, 23–27% of vitamin B₆, and 23–28% of folic acid in the diet. A comparison of the nutrient contributions of some grain foods containing enriched/fortified grain versus unenriched and/or whole grain is provided in Table IV.

Grains are important contributors of B vitamins. Their bioavailability depends on the processing method used and can be more or less than animal-based foods. In some cases, as with corn, greater bioavailability occurs in finely ground, dry-milled products or in nixtamalized products in which bound niacin is released (45,46). In terms of thiamin, intestinal availability from grain foods is on par with animal-based foods, with an average absorption of ≈85% (47).

Riboflavin. Survey data indicate that in the United States grains contribute 20–30% of riboflavin intake. In countries where

milk and meat intakes are limited, the percentage of riboflavin contributed by grains is higher (48,49). Because riboflavin works with other B vitamins to impart immunity and synthesize and optimize red blood cell function, lack of this vitamin is especially concerning in regions with marginal diets (50).

Niacin. Grains are also a source of niacin, which is important for the metabolism of all macronutrients; utilization of energy from foods; and synthesis, growth and repair, and cell signaling. Its presence in grains may differ from the quantity it delivers because its bioavailability may be impaired. For example, the availability of niacin from non-nixtamalized corn is poor. Nixtamalization, the process of liming corn practiced by Amerindians in Central America, releases the tightly bound niacin from niacytin and thereby increases the availability of certain amino acids and reduces the incidence of pellagra (niacin deficiency) in areas where corn in the form of masa is eaten. At 59%, niacin availability from wheat-based foods is more than 20 points lower than niacin availability from beef-based meals (51). Whole meal bread has a particularly negative nutritional effect on the apparent intestinal availability of dietary niacin relative to other foods.

Pantothenic Acid. Grains and whole grains supply pantothenic acid, but its bioavailability varies. Oat-based cereals and whole grains are among the better sources, supplying from 2 to 9 mg/1,000 kcal (52), whereas corn-based and presweetened cereals were among the poorest sources of this vitamin. Whole grain components, especially those in coarse whole meal bread, appear to decrease the bioavail-

Table III. Crude protein and fat contents of cereal and pseudocereal grains^a

Grain	Crude Protein (% dry weight)	Fat (g/100 g edible portion)
Cereal		
Brown rice	7.3	2.9
Sorghum	8.3	3.1 ^b
Rye	8.7	1.6
Oats	9.3	7.5
Maize	9.8	4.3
Wheat	10.6	2.0
Barley	11.0	2.3
Pearl millet	11.5	1.5–5.2 ^b
Pseudocereal		
Amaranth	15.2	8.0
Cassava	2–5	<1
Quinoa	13.3	7.5
Buckwheat	10.9	2.7

^a Source: Alais, C., and Linden, G. *Food Bio-chemistry. Ellis Horwood Series in Food Science and Technology*. Springer Science+Business Media, Dordrecht, Netherlands, 1991.

^b Source: FAO. Sorghum and millets in human nutrition. FAO Food and Nutrition Series, No. 27. FAO, Rome, 1995. (www.fao.org/docrep/t0818e/T0818E0b.htm)

ability of pantothenic acid to as much as 30% lower than meat-based foods.

Vitamin B₆. Grains can be a source of vitamin B₆, which is a fundamental component in a wide range of metabolic, physiological, and developmental processes. In addition, it is a powerful antioxidant, works with other B vitamins to promote health, and may play a role in the prevention of a number of chronic diseases and help prevent cognitive decline. However, vitamin B₆ is slightly less available from grains (≈70% available) than from other sources of protein (≈79% available) (53), and its bioavailability varies by grain type and is affected by other factors in diets. For example, B₆ from barley is more available than B₆ from wheat bran, which has greater availability than B₆ from rye. Vitamin B₆ availability from boiled brown rice is very low (16%) (53).

Vitamin A. Grains can contain some carotenoid pigments, but most grain-based foods are poor sources of vitamin A unless it is added through fortification, biofortification, or gene transfer. Grains are a prime candidate for increasing intake of this nutrient because these staple foods are more likely to be available to those most at risk for vitamin A deficiency. The development of Golden rice, as well as other measures, to address high rates of childhood blindness and infection related to inadequate amounts of this vitamin in some countries may be an important strategy (54).

Vitamin E. Whole grain cereal and bran foods are one of the main dietary sources for vitamin E and its isomers. The vitamin E content of refined flours is one-third to one-half that of whole wheat flour because vitamin E is concentrated in the bran and germ, which contain 6–15 times more vitamin E than the endosperm. Grains and pseudocereals contain more tocotrienols than most other food products (55). These key antioxidants quench free radicals and inhibit lipid oxidation, thereby protecting cell membranes and other cellular components (56). Studies suggest that vitamin E may have immunostimulatory, neuroprotective, anti-inflammatory, and cholesterol-lowering properties and may be linked to the prevention of certain chronic diseases, including cardiovascular disease (57,58).

The main vitamin E isomers found in wheat, barley, rye, and oats are α - and β -tocopherols; α -tocopherol is the form with the highest vitamin E activity (55). β -Tocotrienol is the main isomer found in wheat and oats. α -Tocotrienol, the isomer with the highest biological activity among the tocopherols, is predominant in barley and rye. Small quantities of γ -tocotrienol have been found only in barley. α -Tocotrienol appears to suppress β -hydroxyl- β -methylglutaryl coenzyme A reductase, the key enzyme in cholesterol synthesis and, therefore, is hypocholesterolemic. In addition, all tocotrienol isomers have been suggested to have antithrombotic and antitu-

mor effects. The contribution of these antioxidant isomers may be one way in which whole grains are associated with reduced risk of cardiovascular disease (55).

The bioavailability of vitamin E varies widely and is affected by numerous factors, such as the particular isomer, food matrix and its processing, and presence of other dietary components, as well as the nutritional status of the individual (59,60). In some cases a particular isomer is affected by a certain type of processing.

Minerals. Because of their high consumption in a variety of food products, grains are important contributors of minerals to the diet. Minerals play both structural and catalytic roles in many enzymatic and other reactions. Specific mineral deficiencies not only lead to specific disorders, such as anemia caused by deficient iron intake, but also are associated with a higher risk of many chronic diseases. More than one-third of the global population, especially in developing countries, suffers from anemia, zinc deficiency, and poor mineral status, which negatively effect growth, learning, immune function, and capacity to work (61). Thus, adequate dietary intake of minerals is important, and grains play an essential role.

The bioavailability of minerals can be even more problematic than it is for vitamins and is affected by many factors. The mere presence of a mineral does not mean that it will be absorbed. For example, although comparisons of mineral concen-

Table IV. Comparison of vitamin and mineral nutrient composition of some grain food products

Nutrient	Corn Flake Cereal (30 g serving [1 cup]; mg, g, or % DV)			Spaghetti Noodles (56 g serving [1 cup]; mg, g, or % DV)			
	Refined Grain		Whole Grain ^a	Refined Grain		Whole Grain	
	Enriched/Fortified	Organic	Organic	Enriched/Fortified	Organic	Traditional	Organic, Enhanced ^b
Sodium (mg)	200	80	110	0	0	0	0
Potassium (mg)	45	—	70	0	0	0	0
Dietary fiber (g)	11.8	<1	2	2	2	5	6
Sugars (g)	3	2	3	2	2	2	1
Protein (g)	2	2	2	7	7	7	9
Vitamin A (%)	10	0	0	0	0	0	0
Vitamin C (%)	10	0	0	0	0	0	0
Calcium (%)	0	0	0	0	0	2	2
Iron (%)	45	2	4	10	4	10	15
Vitamin D (%)	10	0	—	0	0	—	—
Vitamin E (%)	—	0.96	—	—	—	—	—
Thiamin (%)	25	0.364	—	35	—	10	10
Riboflavin (%)	25	0.109	—	15	—	—	—
Niacin (%)	25	5.2	—	20	—	—	—
Vitamin B ₆ (%)	25	—	—	—	—	—	—
Folic acid (%)	25	36	—	30	—	—	—
Vitamin B ₁₂ (%)	25	—	—	—	—	—	—
Phosphorus (mg)	29	81	—	29	—	10	10
Magnesium (mg)	11	225	—	11	—	12	12
Zinc (mg)	0.28	1.5	—	0.28	—	—	—
Copper (%)	—	—	—	—	—	10	10

^a Enriched/fortified whole grain was not found.

^b Fiber and nutrients added.

trations in whole grain foods show them to be much higher than those in refined grains, the actual amount absorbed may differ little due to various factors impacting bioavailability (62). In some cases the mineral in the whole grain kernel is inaccessible or is bound to the fiber or phytic acid, which inhibits the absorption of iron, calcium, zinc, and magnesium (63).

The concentration of minerals in grains is determined genetically by species and variety and by growing conditions. Mineral bioavailability can be improved through biofortification and processing. Biofortification, the amplification of a mineral or minerals in staple crops, is performed through field applications or biotechnology and has been used successfully to improve mineral status in both developed and developing countries (64). Processing techniques such as soaking, germination, enzymatic treatment with phytase, sourdough and long fermentations, and addition of minerals through enrichment and fortification are some of the strategies used to improve mineral nutriture. Such techniques can not only decrease the influence of inhibitors but also offset losses from processing.

Iron and Zinc. Iron and zinc are the two most abundant trace minerals in the human body. These minerals share common dietary sources, such as cereals, and their absorption is inhibited and enhanced by similar dietary constituents. Dietary fiber, tannins and other phenolic antioxidants, and phytate inhibit absorption of both minerals. As a consequence, iron and zinc deficiencies often occur simultaneously.

According to the WHO, iron deficiency is the most common and widespread nutritional disorder in the world, causing anemia in 30% of the global population (65). Low iron intakes and status not only affect a large number of children and women in developing countries, it also affects those in developed countries, 50–100% of the elderly in Europe not meeting the estimated average reference (EAR) (66). According to a study by Lindenmayer et al. (67), zinc deficiency affects 20% of the global population and leads to substantial morbidity and mortality, especially in children under 5 years of age in low- and middle-income countries (67).

Iron plays a part in a wide variety of metabolic processes, including its critical role in electron transport and DNA synthesis for all cells, in synthesis of some hormones and connective tissue, and as a component in the heme portion of blood

and muscle necessary to facilitate oxygen transport (68). Inadequate iron is linked to anemia, impaired physical and mental development, decreased capacity to work, reproductive problems, cognitive impairments, and behavioral changes, including changes in attention span, intelligence, and sensory perception (69).

Zinc deficiency not only impairs growth, but also contributes to significant diarrhea and pneumonia- and malaria-related morbidity and mortality among young children (70). In Sub-Saharan Africa and southern Asia, low zinc intake has been estimated to account for 800,000 child deaths a year. Surveys in various parts of Europe show that roughly 1–16% of males and 3.7–31% of females were below the estimated average requirement (66).

In some developing countries such as India, nearly 75% of pregnant women were deficient in zinc; nearly 55% were deficient in both zinc and iron; 25% were deficient in zinc, magnesium, and iron; and ≈10% were deficient in zinc, magnesium, iron, and folic acid (71). Cereals, including those that are enriched and fortified, offer important sources of low-cost iron and zinc and other nutrients. Even in developed countries, cereal and bread products provide 40–47% of iron and 25–33% of zinc intake (72).

The bioavailability of these minerals from grains, especially whole grains, may be impaired. In fact, iron availability from enriched and fortified grains, especially those fortified with an available iron chelate (e.g., iron EDTA) as recommended, usually surpasses that from whole grains (73,74). However, many countries continue to use nonrecommended, low-bioavailability, atomized, reduced, or hydrogen-reduced iron powders. Zinc bioavailability has also been shown to be better from fortified, degermed grain than from whole grain (75). Ingestion of vitamin C-rich foods or beverages with cereals also improves the bioavailability of both these minerals (76,77). In summary, the fortification and biofortification of grains, especially wheat, with iron and zinc are successful, proven public health strategies for both developed and developing countries.

Magnesium. The role of magnesium in more than 600 enzymatic reactions emphasizes its critical role in vital processes, including those key to signaling transduction, energy metabolism, protein synthesis, DNA replication and repair, and cell proliferation (78). Magnesium inadequacy may play an important role in the etiology

of cardiovascular diseases, including thrombosis, atherosclerosis, ischemic heart disease, myocardial infarction, hypertension, arrhythmias, congestive heart failure, and diabetes, as well as a variety of other conditions. Supplementation of magnesium intake has shown success in treating pre-eclampsia, migraine, depression, and asthma.

Magnesium intake is often below that recommended in both developed and developing countries because dietary sources rich in magnesium, such as whole grains, may not be consumed in adequate quantities. Although whole grain products are one of the main sources of magnesium in human nutrition, its availability from whole grains is inhibited by phytate and dietary fiber (79).

Selenium. Selenium is an essential micronutrient because selenocysteine is a component of a key detoxifying enzyme, glutathione peroxidase. Health benefits attributed to selenium include decreased cancer risk, protection against cardiovascular diseases, and development of and boost in immune function.

The selenium content of grain is dependent primarily on the amount of selenium in the soil the crop is grown in, but also on the effects of processing (80). Thus, cereal grains grown in regions with adequate selenium in the soil are important dietary contributors. There are regions of the world with very low levels of selenium in the soil, including parts of China and Russia. Up to 47% of the European population is below the EAR for selenium (66). If soil levels are low, then there is the risk of endemic selenium inadequacy, which can be dealt with either by importing grains from regions with adequate selenium in the soil or biofortification strategies that incorporate selenium fertilizer. Lack of selenium leads to Keshan disease, a type of heart disease (81). However, excess selenium is toxic (82).

Effects of Excess Nutrient Intake. Excess intake of nutrients can create problems, and excess intake of minerals can be a particular problem. Studies on the fortification of foods have shown that foods fortified with ≤25% of the required intake would not be problematic, whereas excess consumption of foods that are fortified to 100%, termed “multivitamin and multi-mineral supplement cereals” could be potentially harmful.

Excess iron can form free radicals that act as a pro-oxidant and can damage a wide range of tissues. Excess iron stores have been associated with insulin resis-

tance and neurodegenerative disorders. Excess zinc and magnesium intake from foods is unlikely as these are not customarily part of enrichment and fortification formulas.

Phytochemicals. The positive contributions of dietary phytochemicals from grains are well documented and have been reviewed (83). Whole grains are a good source of anti-inflammatory and antioxidant compounds. In fact, the *in vitro* antioxidant activity of whole grain foods is similar to that of vegetables and fruits (84). This activity is due not only to antioxidant vitamins and minerals, as already discussed, but also to phytochemicals such as phytates, phenolics such as ferulic acid in corn and wheat (85), lignans (86), alkylresorcinols in wheat and rye (87,88,89), oryzanol in rice, and avenanthramides in oats (90,91). Some of these have antiatherogenic activity through mitigation of nitric oxide production (92). Certain other flavonoids, phenolics, and phenolic lipids boost immune function, as well as being antimutagenic and anti-inflammatory (83,84). Alkylresorcinols, which are particularly high in wheat and rye, may be markers of whole grain intake (93). Betaine, which is particularly high in quinoa and wheat, is involved in methyl transfers, improved vascular functioning, and enhanced performance.

The amount and type of phytochemical in grain depends on the cultivar, species, and agronomic conditions and can vary markedly even for the same cereal grain. Environmental stresses may increase levels of certain phytochemicals.

The synergy among whole grains, dietary fiber, vitamins, minerals, and phytochemicals has important effects on health. The availability of certain phytochemicals and where they exert their action in the body and gut depends on how a food is processed. Components not absorbed in the upper gut may act locally in the lower gut. A mix of processing methods may be used to optimize availability for the body.

Nutrition and Health Benefits of Whole and Refined Grains

Refined Grains. Intake of refined grain foods was not associated with risk of cardiovascular disease, diabetes, weight gain, or overall mortality in a systematic review of 135 relevant papers published after 2000 (95). The authors stated that the “consumption of up to 50% of all grain foods as refined-grain foods (without high levels of added fat, sugar, or sodium) (e.g. staple foods) is not associated with

any increased disease risk” (95). Studies using National Health and Nutrition Examination Survey (NHANES) data show that an optimal mix of whole grains and refined staple grain foods in the diet, with only limited intake of indulgent grain foods, not only cost-effectively delivered key nutrients, it was associated with lower weight and equal or better nutrient intakes than grain food patterns that did not include refined grains (96–98).

Additional studies also show health benefits for a mix of both whole and refined grains in the diet—hence the recommendation to make “half your grains whole.” A recent analysis of NHANES data shows that a mix of whole and refined grain staples was associated with smaller waist circumference (96) and lower visceral adipose, which is the fat around the midsection that is related to increased risk of coronary disease and diabetes (16). Further, refined grains often enable greater absorption of certain components, such as minerals, than occurs with whole grains (75,76). However, excess consumption of grain-based desserts and snacks, especially those that cause high postprandial glucose excursions, has been associated with excess weight and adverse health outcomes (99–101).

An optimal mix of whole and refined grain intake can be beneficial as a way to protect against toxicity that can occur in regions where sludge and overuse of certain agricultural chemicals and other questionable practices are employed or where grains are not regularly monitored for contaminants. Because heavy metals and many other contaminants primarily reside in the outer layers of whole grains, recommendations for consumption of whole grains exclusively may not be the best dietary advice in these regions (102). Also, as mentioned earlier, intake of phytates, tannins, and other phytochemicals can cause problems if excess amounts are ingested and no measures are taken to reduce their effects, especially in plant-based diets (103).

Whole Grains. Whole grains have long been regarded as healthy dietary components; however, the documentation of health benefits beyond their nutrient contribution is much more recent. As mentioned earlier, whole grains deliver important dietary components such as magnesium and dietary fiber, both of which are often low in Western diets. Beyond their nutrients, the ingestion of whole grains is associated with lower risk of coronary disease, diabetes, hypertension,

overweight, and even overall mortality (104). As a result, dietary guidance by a variety of government and health promotion organizations recommends the inclusion of whole grain foods in the diet. Most call for an increase in whole grain intake by replacing some refined grain products (105,106). For example, the last three U.S. Dietary Guidelines Advisory Committees (DGAC) have recommended that consumers “make at least half their grains whole” (107–109), with the 2010 DGAC recommending that the replacement of refined grains should be with high-fiber whole grains (109).

The upcoming reviews will detail studies linking whole grains with lower risks of a variety of chronic diseases. In many cases staple grains are also associated with lower disease risks. In general, consistent links with better health outcomes have occurred across widely different population groups, often with culturally very different diet patterns and genetic make-ups. For many chronic diseases, risk reduction was $\geq 25\%$ for those ingesting somewhere between 2 and 3 servings of whole grains each day. Because the average intake of whole grains in many countries is < 1 serving of whole grains/day, it is critical that grains and whole grains are emphasized in dietary guidance (110).

Conclusions

Carbohydrate-rich staple foods, including those from a wide array of whole and refined grains, are inexpensive sources of energy, protein, and other nutrients, e.g., dietary fiber, minerals, vitamins, and other beneficial phytochemicals. Grain-based staple ingredients are incorporated into an enormous variety of foods. In nearly all of these dishes, grain-based staple ingredients provide complementary amino acid patterns that combine to make complete proteins.

The important health benefits provided by grains argues for their incorporation in the everyday diets of healthy people. Whole grains, in particular, are associated with decreased risk of certain chronic diseases, and consumption of an optimal mix of whole and refined grains is associated with a number of health benefits, including decreased visceral adipose tissue.

Cereal grains provide a wide variety of nutrients, dietary fibers, and phytochemicals. This combination uniquely positions them as a source of nutrition to both sustain and nourish a population.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Wheat in Nutrition and Health: Their Relation to Digestion, Digestive Disorders, Blood Glucose, and Inflammation^{1,2}

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This review of carbohydrates (CHOs), grains, and whole grains looks at their digestion and absorption, their impact on the microbiome, and how they influence gut function and health and gut-related diseases such as irritable bowel syndrome (IBS). Their impact on glycemic response, insulin resistance and inflammation, and the immune system is discussed, and wheat, gluten and grain allergies, and gluten-related disorders, including celiac disease, are addressed. Much of the information on inflammation, glycemic response, and immunity provides a basis for assessing the relationship between CHOs, including starch, dietary fiber, and resistant starch, provided by grains and whole grains and longevity, health, body weight, and chronic diseases, including obesity, blood pressure, metabolic syndrome, diabetes, stroke, cardiovascular disease, and certain cancers.

CHOs, Grains, and Whole Grains and the Digestive Tract and Microbiome

The impact of grains and CHOs on health begins as they travel through the digestive tract, where they deliver useable

energy and important nutrients. In the small intestine, the CHOs, grain phytochemicals, and grain matrix all impact the rate of blood glucose entry and attendant insulin release. Speed of CHO breakdown varies markedly. Some CHOs escape digestion and become resistant starch. Resistant starch and other CHO components that are not digested in the small intestine act as dietary fiber. Dietary fiber governs a number of aspects of laxation and gut health, as well as feeding bacteria and modulating their balance in the gut microbiome, which can produce profound local and systemic health effects.

CHOs in the Upper Gut. Available CHOs (starches and sugars) in grains are nearly all metabolized in the small intestine. Starches are split by α -amylases into branched (if amylopectin) or nonbranched (if amylose) glucose polymers and maltose. In the brush border of the intestinal villi, maltose, in turn, is split by glucosidases into glucose. Breakdown rates of both are affected by the properties of the starch molecule (1).

Glucose is moved from the gut and throughout the body by a series of transporters (GLUT1, 2, and 3) that moves glucose from the gut lumen across the cell and then across the cell membrane into the hepatic portal system for delivery to the liver. There, it can be metabolized further, stored as glycogen, or sent into systemic circulation to provide energy for body tissues (2). Most tissues require insulin-activated GLUT4 to move glucose from the bloodstream. Glucose fuels heart and skeletal muscles and is the preferred energy source for red blood cells and the nervous system, particularly the brain. Interestingly, physical activity also stimulates GLUT4, thereby enhancing insulin

sensitivity and facilitating glucose entry into cells (3).

How rapidly glucose is delivered to the bloodstream depends on many factors (4). For grain-based foods, the following factors have a major impact:

- 1) **Food form and matrix.** As an example, a whole grain kernel may not deliver its available starch, which becomes resistant starch type 1 (5,6). In porous food structures such as bread, starch is easily accessible to amylases and, thus, delivers its glucose quite quickly (i.e., rapidly available glucose); such products have a high glycemic index. In contrast, dense food structures such as pasta impede enzyme penetration and deliver glucose slowly (i.e., slowly available glucose) (7).
- 2) **Starch source.** Starch granule properties vary by plant source. The source determines starch granule size, architecture, and number of pores on the membrane-like lipid-protein surface (8). This layer encases the native (ungelatinized) starch architecture, which contains crystalline and amorphous regions—the latter of which is much more accessible to amylases. Intact starch granules inhibit digestion because water entry through the membrane is impeded and amylase activity is slowed (9). Therefore, starches from different grains have different rates of digestibility due to the accessibility of their components and the arrangement of the starch in the granule (10–12); however, all raw starches are much less digestible than gelatinized starches (Table I).

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- 3) **Degree of gelatinization.** Gelatinized starches are many times more digestible than nongelatinized starches. During gelatinization both the granules and the compact, crystalline granular structure are disrupted (24,25). This allows enzymes to enter and attack the polymer. The amount of available water in the food can control how much gelatinization occurs and, thereby, the extent of gelatinization.
- 4) **Amylose and amylopectin.** The balance of amylose and amylopectin and the number of branch points in the polymer affect starch digestibility (26,27).
- 5) **Helicity and crystallinity of starch polymers.** Pseudocrystalline regions are far more resistant to digestion than amorphous regions (28).
- 6) **Processing (cooking) parameters.** Processing can increase or decrease resistant starch and impact the degree of gelatinization or integrity of the starch granule (29). The same process can have different impacts depending on process parameters and the CHO composition of the original food. For example, extrusion of foods with high amylose contents can increase the amount of resistant starch but may decrease resistant starch in foods with low amylose contents (12).
- 7) **Size and composition of meal.** Large meals slow movement through the upper gut, especially if they are

high in fat. Fat and dietary fiber, especially viscous types, may impede the action of enzymes. Acid may also slow starch digestion by lowering pH past the optimum level for amylase activity (30).

Thus, many factors can modulate the total amount of starch digested, how much becomes resistant starch, and the rate of glucose entry into the bloodstream. All of these factors also impact the rate of insulin release.

Effects of CHOs, Grains, and Dietary Fiber on Glucose and Insulin. Glucose in the bloodstream that does not return to fasting levels within a normal time frame results in impaired glucose tolerance and can lead to insulin resistance, prediabetes, diabetes, metabolic syndrome, and obesity. Thus, clearing glucose from the bloodstream through the action of insulin is important for homeostasis and good health. Continuously elevated levels of circulating glucose and insulin can increase inflammation, promote growth of adipose tissue and elevation of blood triglycerides, and increase the risk for many chronic conditions (31). Excess circulating glucose also can form adducts with proteins such as hemoglobin or other critical cell components. These adducts, called advanced glycation end products, produce negative health effects (32). Thus, especially in conditions of excess calorie intake, CHOs from any source, including grains, can have negative health impacts. It is important, therefore, to discuss the mechanisms of glucose

uptake and insulin activity with respect to the intake of grains and their CHOs.

Data from early feeding studies with pure starches, including those from grains, showed that they elevate blood glucose and insulin levels. Each starch type showed a slightly different glucose and insulin curve. However, most curves were lower than that observed with a glucose control (33). When starch was part of the grain kernel or food matrix, the glucose and insulin curves often showed lower areas under the curve. The degree of change observed depended on grain type, particle size, product type, texture, degree of gelatinization, ratio of amylose to amylopectin, amount of slowly available starch and/or resistant starch, and amount of dietary fiber, especially viscous fiber (34–38).

Prospective cohort studies and randomized controlled trials revealed that diets rich in refined CHOs are associated with elevated levels of circulating blood glucose, impaired glucose tolerance, and decreased insulin sensitivity or increased insulin resistance. However, these findings must be considered carefully because in most of these studies the category of refined CHOs includes both grain-based staple foods (e.g., breads, cereals, rices, pastas) and grain-based indulgent foods (e.g., desserts, snacks). Such categorizations can confound conclusions regarding the role of refined grains compared with whole grains for two reasons. First, when most of the studies were conducted few, if any, indulgent whole grain or bran foods

Table I. Characteristics of some grain starch granules ($1 \mu\text{m} = 1.10^{-6} \text{m}$)^a

Grain	Starch Granule Size (μm)		Granule Shape	Notes	Average DP ^b	Ratio of Amylose to Amylopectin (% Amylose)	M_w (g/mol)		
	Range	Average					Range	Amylose	Amylopectin
Maize	2–36	15	Round and irregular polyhedron	Bimodal	200–2,000	25 (70–75 in high-amylose varieties)	52–196 × 10 ⁶	2.20–8.31 × 10 ⁵ DP 100–1,000	82–2,650 × 10 ⁶ 1–4 chains, 12–60
Wheat	1–45	25	Small, round, and larger lenticular	Bimodal	Amylose: 570 (2 chains)	27–32	310 × 10 ⁶		DP 4,700–5,800
Rice	3–8	25	Irregular polygons and compound granules			20 (9–15 in short grain; 17–20 in long grain)	2,680 × 10 ⁶	2–3 × 10 ⁶ DP 1,000	40–50 × 10 ⁶ average; can be as high as 130
Waxy maize	3–26	15	Irregular and smooth, rod-like			<10		215–239 × 10 ⁶	
Barley	5–25		Elliptical disk-like, round	Bimodal; small granules, more amylose		25		2.3 × 10 ⁶	280 × 10 ⁶ DP 7,800–8,700
Rye	2–36		Round and elliptical	Bimodal; 15% small granules	Amylopectin: 6–24	20–25			

^a Data sources: Food-Info.net (13); Bathgate and Palmer (14), Schierbaum et al. (15), Shevkani et al. (16), Hegenbart (17), Park et al. (18), Jane et al. (19), BeMiller and Whistler (20), Zhong et al. (21), Verwimp et al. (22), and Bertolini (23).

^b Degree of polymerization.

were available on the market. Thus, a possible conclusion might be that diets high in indulgent foods rather than refined grains are associated with impaired glucose tolerance and increased insulin resistance. Analyses that separate indulgent grain-based foods from refined grain-based food staples have shown improved nutrient intake and health outcomes associated with intake of grain-based food staples (39,40). Second, any adverse outcomes observed might be due to the sugar and fat in the indulgent foods, as well as other dietary and lifestyle choices associated with subjects who consume many indulgent grain-based desserts and snacks.

Studies assessing dietary patterns also suffer from confounding. For example, diets high in meat and refined CHO are associated with increased risk of impaired glucose tolerance and increased insulin resistance; however, a clear connection between a specific health outcome and refined-CHO intake is difficult due to the potential adverse effects of a high intake of less desirable dietary components or the low intake of healthy dietary components such as fiber, whole grains, or fruits and vegetables that often occurs with such a pattern. Further adding to the confounding associated with these dietary patterns are differences in activity and socioeconomic levels (41). In fact, dietary patterns such as the Mediterranean or DASH (Dietary Approaches to Stop Hypertension) diets that include grain-based food staples (e.g., breads, cereals, rice, pastas) as part of a healthy, balanced dietary pattern are associated with a lower risk of impaired glucose tolerance or increased insulin resistance (42–44).

The specific glycemic impact of CHOs from cereal grains has been extensively studied using the glycemic index (GI) and glycemic load (GL) as measures. Some studies suggest that diets with a high GI and/or high GL or that deliver rapidly available glucose are particularly problematic with respect to blood glucose and insulin. However, associations are often confounded by other dietary and lifestyle impacts (45). Due to the inconsistency and confounding observed in the medical literature, the 2010 U.S. Dietary Guidelines Advisory Committee (DGAC) (46), using an evidence-based library assessment, and the 2012 Nordic Nutrition Recommendations (47) concluded there is a “moderate body of inconsistent evidence” supporting a relationship between GI and disorders associated with impaired glucose tolerance and increased insulin resistance. Further,

the DGAC noted that strong, convincing evidence shows little association between GL and disorders associated with impaired glucose tolerance and increased insulin resistance, such as type 2 diabetes mellitus (T2DM) (48).

Prospective cohort studies indicate that diets containing a recommended balance of whole and enriched refined grains, dietary fiber, and cereal fiber help reduce the risk of chronic conditions that involve elevated glucose and insulin, such as metabolic syndrome, cardiovascular disease, and T2DM (49). To date, the collective evidence suggests that diets rich in low-GI CHOs, cereal fiber, and resistant starch and balanced with healthy fats and protein should be emphasized, while diets that control consumption of excess fat, calories, refined sugars, and high-GI CHO foods may help control swings in blood sugar and insulin and disorders associated with them (46,50).

Effects of CHOs, Grains, and Dietary Fiber on Inflammation. Inflammation in the body can be a protective response that readies the body to fight infection and initiate tissue healing and repair. However, a continuously stimulated immune response promotes the steady release of inflammatory molecules, such as cytokines. The result is a reduced innate antioxidant defense and chronic low-grade inflammation. Excess body weight; the inability to clear glucose from the bloodstream, as in prediabetes, metabolic syndrome, and diabetes; and elevated blood lipids are examples of conditions in which oxidative stress and chronic inflammation exist.

Certain dietary patterns are associated with oxidative stress and low-grade inflammation (51). Western diets, which are typified by high fat intake, excess calories, and often inadequate vitamin and anti-inflammatory phytochemical intakes, potentiate chronic low-grade inflammation (52,53). Such diets not only promote lipid oxidation and deposition of plaque in the arteries (54), they also foster the growth of gut bacterial species that produce the inflammatory endotoxin lipopolysaccharide (LPS) (55). For example, Kelly et al. (56) found that a meal including an egg and sausage sandwich and fried potatoes (40% CHO, 42% fat) eaten by healthy lean adults increased LPS compared to a meal that included oatmeal or an English muffin, fruits, and nuts (58% CHO, 27% fat). Higher CHO and phytochemicals appeared to be helpful in reducing LPS and its attendant inflammation.

The inflammatory impacts of Western-type diets appear to be amplified in over-

weight and obese subjects (57) and appear to be mitigated by Mediterranean-style diets. Both contain CHOs, including refined CHOs, but typical Western diets are low in good fats, many nutrients, dietary fiber, and phytochemicals, which are high in Mediterranean-style diets (58).

Epidemiological studies show that diets high in refined CHOs, sugars, and refined grains are associated with increased insulin resistance and inflammation (59,60). In some cases, refined grains are part of what is called “Western pattern” diets—high in meats and sweets and low in vegetables and fruits (60–62). Thus, it is difficult to conclude that increased inflammation and insulin resistance are caused by refined grains when they may be due to a dietary pattern that deviates significantly from recommendations and delivers an imbalance of macronutrients and too few micronutrients (63,64).

Evidence concerning the role of CHOs in GI and GL with regard to inflammation is mixed. A systematic literature review found that 5 of 9 observational but only 3 of 13 intervention studies showed lower GI/GL was associated with or resulted in lower concentrations of markers of inflammation. However, a trend was observed. Four studies that did not reach statistical significance suggested low GI/GL might reduce markers of inflammation for certain subgroups (65). In some cases there was confounding between dietary fiber intake and dietary GI/GL.

An interaction between age and gender appears to modify the effects of dietary GI and GL on inflammation. For example, older women with diets in the highest tertile for GI had a nearly threefold increase in risk of death due to inflammatory disease compared with those whose diets were in the lowest GI tertile (66). While high intakes of refined sugars and starches predicted greater risk of death due to inflammatory disease in the elderly, decreased intake of breads, cereals, and vegetables also predicted greater risk. Thus, although breads, breakfast cereals, and fruits may have relatively high GIs, they are important sources of dietary fiber and anti-inflammatory compounds, which may explain their apparent protection. For young adults, higher intake of CHOs and higher-GI foods with lower whole grain consumption predicted greater interleukin-6 (IL-6) concentrations (67). Thus, CHOs from fibers and components in whole grains appear to prevent inflammation.

Effects of Whole Grains on Inflammation. Polyphenolic and other phytochemicals in cereal fibers and whole grains may explain why they are associated with reduced inflammation in some, but not all, intervention studies of obese adults and children (68–70) and in a variety of epidemiological studies (65,71). These components, as well as the dietary fiber in whole grains, may have a significant impact on the microbiome by affecting not only the species of organisms present, but also their metabolism and the fate of metabolites. All could impact markers of inflammation (72,73). Thus, although some suggest that wheat and grains are a major source of inflammation and immune system overactivation (74), others also show data indicating anti-inflammatory impacts (75).

CHOs and Fermentation in the Lower Gut. CHOs that are neither metabolized nor absorbed in the small intestine (e.g., dietary fiber and resistant starch) move into the large intestine, where gut microorganisms metabolize (ferment) them. The resulting fermentation not only affects the colonic environment, but also bolsters the immune system, impacts metabolism, and modulates health throughout the body.

The amounts and types of undigested CHO polymers reaching the colon determine not only the number of microorganisms, but also the range and types of species in the microbiome (76). Because bacterial diversity is considered one of the hallmarks of a healthy microbiome, a variety of dietary fibers from different grains and other food sources is important for supporting diversity.

More than 50 bacterial phyla have been described in the human microbiome. However, there are phyla that have not been identified, so characterization of the species present remains imprecise. Further, no “ideal” profile has been identified. Rather, it appears that a number of profiles are associated with health. It is known that *Bacteroidetes* and *Firmicutes* dominate the human microbiome, while *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, *Cyanobacteria*, and others are present in smaller proportions. Two particularly abundant groups, estimated to comprise 7–24% of the total gut bacteria in healthy subjects, are related to *Faecalibacterium prausnitzii* and to *Eubacterium rectali* and *Roseburia* spp. (77). In a variety of chronic conditions, decreases in these classes of bacteria are observed; however, it has also been shown that in-

gestion of prebiotics such as inulin (as found in wheat) can increase the populations of some of these bacteria (78). In addition, *Bifidobacterium* spp. associated with health show a marked decline with age.

CHOs, Grains, and Fermentation to Short-Chain Fatty Acids. Digestive physiology, gut motility, and a healthy gut milieu depend on the microbial fermentation of dietary fiber and resistant starch from grains and other CHO sources to short-chain fatty acids (SCFAs) (79). As reviewed in the overview articles (80,81), the SCFAs acetate, propionate, and butyrate have many functions, and some effects are dependent on the specific type of SCFA. They all lower colonic pH, change oxidation potential, provide energy, promote growth and differentiation of healthy colonic cells, enable repair of damaged colonocyte DNA, induce cell death (apoptosis) in nonrepairable aberrant cells, reduce cell movement (chemotaxis) and adhesion, and mediate signaling pathways (82–84). SCFAs also can mitigate the potentially adverse effects resulting from the breakdown of proteins, including the neutralization of ammonia and other breakdown products, and interfere with the potentially problematic metabolism of bile acids to secondary bile acids (85).

SCFAs impact immunity through three modes of action. First, they impact T-cell differentiation, proliferation, and activation. This occurs not only in the intestine and gut-associated lymphoid tissues, but also in immune tissues throughout the body as they are transported in the bloodstream to various sites. SCFAs also can inhibit infiltration of immune cells from the bloodstream into tissues such as adipose. Second, SCFAs appear to prevent adhesion of molecules to antigens, which could be important in a variety of situations, including inflammation associated with obesity. Third, SCFAs affect the production of mucin and gastrointestinal peptides important for gut barrier function.

The formation of propionate and butyrate are of particular interest in terms of their beneficial health effects, including inhibition of the production of proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNF- α] and nuclear factor kappa B [NF- κ B]) (86). Evidence suggests that inflammatory molecules and bacterial overgrowth or imbalance, termed dysbiosis, are involved in the pathogenesis of a variety of conditions, such as gut disorders, obesity, atherosclerosis, T2DM, and various cancers. Thus, it appears that production of SCFAs from dietary fiber in

grains, whole grains, and other CHO-rich foods plays a key role in the maintenance of a healthy immune system and the prevention of inflammatory diseases ranging from obesity to cancer (87).

Fermentation in the large bowel not only produces SCFAs, but also releases phytochemicals, such as ferulic acid, that are tightly bound in the dietary fiber–whole grain matrix (88). Such antioxidant and anti-inflammatory compounds benefit not only colonic cells, but also the colonic milieu. The antioxidant capacity delivered by whole grains and cereal brans is comparable to or exceeds that of many fruits and vegetables, and their antioxidant and anti-inflammatory compounds are more likely to be released in the colon than are those from fruits and vegetables (89–93).

Phytochemicals that are unique to grains, such as certain alkylresorcinols, are used as biomarkers in the bloodstream to verify the ingestion of the outer layers of grains from brans and whole grains (94,95). The precise quantities and types of phytochemicals contained in grain-based foods vary with species, genotype, and agronomic conditions. The impact of these can also be increased or decreased by various types of processing (96).

Fermentation of Dietary Fiber in the Lower Gut. Grains deliver a variety of types of dietary fiber. Fiber sources such as oat bran, pectin, resistant starch, inulin, and guar are highly fermented in the gut, whereas cellulose and wheat bran may be poorly fermented but can hold greater quantities of water, which increases stool bulk and fluidity. As a result, dietary fibers that are less fermented in the gut tend to have more impact on stool weight than those that are highly fermented.

Dietary Fiber and Laxation. Grain brans, especially wheat bran, and their dietary fibers are most well known for their positive effects on laxation through faster gastrointestinal transit time; increased fecal output; softer, more readily passed stools; and increased bowel movement frequency (97–100). Insoluble dietary fiber from grains such as wheat and corn improve transit time, both by increasing water-holding capacity in the gut and fecal bulking (101,102). Wheat bran is the most effective fiber when it comes to fecal bulking. Based on a meta-analysis of 140 studies, the ability of different fibers to increase stool weight (average per gram of fiber fed) is as follows: 5.4 g for wheat, 4.7 g for fruits and vegetables, 4.0 g for psyllium, 3.5 g for cellulose, 3.4 g for oats,

3.3 g for corn, 2.2 g for legumes, and 1.2 g for pectin (99).

However, soluble fermentable fibers such as inulin and arabinoxylan from wheat and rye and β -glucan from oats and barley, as well as added fibers such as soluble corn fiber, also increase stool weight (97,103). Increased biomass resulting from the metabolism of dietary fiber accounts for some of the increased stool weight (97). Combinations of wheat bran and resistant starch have been found to be more effective in increasing fecal bulk than either alone, indicating a synergy among some types of fiber (104).

Grain particle size also impacts fecal bulking and laxation, but results vary by grain and other parameters, leading to mixed results reported in the scientific literature. In one study, 20 g of coarse bran caused a 40% increase in water holding and was much more effective at increasing stool weight than finely milled bran (105). Similar results were seen in a study of healthy young men (106) and a study of patients with diverticular disease (DVD) (107). However, particle size was not shown to cause a measureable difference in stool weight, transit time, or other measures in randomized controlled trials for either healthy adults or those with IBS (108). The lack of consistency may be due to marked differences in subject responsiveness, especially among those who are inactive or prone to severe constipation (109). For such individuals, the added fiber can create great discomfort (110).

Although the effects of particle size on laxation remain to be clarified, what is clear is that bran cereals are an effective way for many to speed intestinal transit time and increase bowel movement frequency while maintaining a good level of tolerance. Further benefits have been observed when bran is fortified with additional fiber such as psyllium (111). Similarly, porridge plus oat bran combinations have been effective in reducing laxative use in nursing home populations (112,113). Modeling data from several European countries predict that diets with adequate intakes of whole grains, especially cereal brans, translate to greater regularity, less straining at the stool, and, for many, reduced incidence of constipation. One added benefit is lower health-care costs (114).

CHOs, Grains, Dietary Fiber, and Digestive Disorders

Hemorrhoids. Early pioneers (115) in the dietary fiber field suggested that high-fiber diets might protect against hemor-

rhoids and DVD. Yet, the results of studies attempting to determine the impact of dietary fiber from whole grains, including cereal brans, on hemorrhoids are inconclusive. Still, high-fiber diets and dietary fiber supplements, in part because they are inexpensive and somewhat effective, continue to be recommended for both treatment and prevention of hemorrhoids. Data from clinical studies show that dietary fiber supplements can reduce the risk of persistent symptoms and bleeding by \approx 50% (116,117).

DVD. The role of diet and grains in the etiology and treatment of DVD remains a topic of discussion (118). It has been suggested that typical Western diets and lifestyle patterns contribute to increased risk through alterations in gut microbiota and host inflammatory response. Both of these aspects appear to affect the development and severity of acute and chronic diverticulitis (119). Thus, the potential anti-inflammatory and prebiotic effects imparted by whole grains and dietary fiber may be important in treatment of DVD.

Findings from the Harvard Male Health Professional Study ($n > 45,000$) and the U.K. Million Women Study indicate that those with the highest dietary fiber intakes reduced their risk of DVD by 18–37% compared with those with the lowest intakes (120,121). For men, the best protection was observed with diets high in cellulose from fruits and vegetables and low in total fat and red meat (122). For women, the risk was reduced with diets high in total dietary fiber, especially fibers from cereals and fruits. In these studies, cereal intake contributed as much as 40% of the dietary fiber in the diet. Thus, it is not surprising that the guidelines published by the German Society for Gastroenterology, Digestive and Metabolic Diseases recommend a diet that includes 25–40 g of dietary fiber/day for both prevention and nonpharmacological treatment of uncomplicated DVD (123).

IBS. IBS (formerly referred to as colitis, spastic colon, or functional bowel disorder) is an intestinal condition characterized by gas, abdominal pain, and bloating; changes in bowel movements (diarrhea, constipation, or both); and other symptoms, including low-grade inflammation. There appears to be no cure, but symptoms can be managed with dietary changes, drugs, and cognitive-behavioral therapy (124). The condition, although not uncommon, remains poorly understood, and the cause is even more elusive.

Most IBS patients believe diet affects their symptoms and avoid foods they feel worsen their symptoms. One hypothesis suggests that IBS is a systemic disorder induced by certain foods (e.g., food allergy or hypersensitivity), although the same percentage of IBS patients as the general population (1–3%) show positive reactions to classic food allergy tests (125). Wheat-containing foods are some of the most commonly avoided, but the long list includes dairy; certain meats; fats; gas-producing vegetables and fruits; legumes and nuts; spicy, fried, or smoked foods; and others.

Low-FODMAP (fermentable oligo-, di-, and monosaccharides and polyols) diets are recommended by some practitioners. Meta-analyses indicate that such diets reduce gastrointestinal symptoms and total colonic bacterial load (126,127). One meta-analysis indicates the low FODMAP diet is superior to a gluten-free diet for managing symptoms in people with self-reported non-celiac gluten sensitivity (NCGS) (128). Data from another study also show a reduction in symptoms but raise questions concerning the long-term health impact of the observed reduction in bacterial load and microbes with prebiotic properties (127).

Concerns have been raised not only about recommendations to exclude brans, but also about the nutritional adequacy of low-FODMAP diets because they may eliminate a number of fruits and vegetables, as well as grains such as wheat and rye (Fig. 1) (129). Various soluble dietary fibers, such as inulin, and anti-inflammatory compounds found in many eschewed foods have been shown to be beneficial for managing IBS symptoms (127). For example, a meta-analysis of randomized controlled trials shows that diets with adequate soluble fiber intakes reduce IBS symptoms by \approx 17% (130). Further, it brings into question the avoidance of wheat bran, which in the meta-analysis was found to have neither beneficial nor harmful effects (130). It is possible, therefore, that the elimination of wheat and brans and the potential reduction in dietary fiber and associated phytochemicals in those adopting low-FODMAP diets may carry some risks.

The lack of clarity concerning the inclusion of grains in diets for IBS patients in the scientific literature may be, in part, due to the nature of syndromes such as IBS, which are affected by stress, have periods of remission, and show marked individual variability. Determining causa-

tion in such disorders is nearly always confounded.

Inflammatory Bowel Diseases. Inflammatory bowel diseases (IBDs) include Crohn's disease and ulcerative colitis (UC). Both are characterized by an inflamed lining of the digestive tract: Crohn's affects the ileum, and UC affects the colon. Some IBD symptoms are similar to those of IBS and include abdominal pain, diarrhea, fatigue, weight loss, and malnutrition.

The precise cause of IBDs is unknown, although they appear to result from an interaction of genetic, gut microbial, immune, environmental, and nutritional factors, such as low vitamin D levels. They may even be due to a hypersensitive response against commensal microbiota (131), resulting in an increase in facultative anaerobic bacteria (e.g., *Enterobacteriaceae*, *Bacilli*) and an attendant decrease in obligate anaerobic bacteria (e.g., *Bacteroidia*, *Clostridia*) (132). Such dysbiosis has also been shown to impair intestinal barrier function and disrupt mucosal T-cell homeostasis; however, it is unclear whether dysbiosis is a cause or a consequence of IBDs. Findings suggest that dysbiosis and dysregulation of the immune system in older patients play a more significant role than in younger patients (133). Overproduction of inflammatory cytokines resulting from dysregulation causes uncontrolled intestinal inflammation.

Crohn's Disease. Diets associated with increased risk of Crohn's disease are low in fruits, vegetables, and dietary fiber and

high in sugar, meat, and fat (134,135). Studies suggest that meat and some fats may increase relapse. In the Nurses' Health Study those in the highest quintile of dietary fiber intake (24.5 g/day) had a 40% lower risk compared with those with intakes in the lowest quintile (11.6 g/day) (136). In this cohort, dietary fiber from fruits, but not from grains, reduced risk, perhaps due to the low intakes of bran and whole grains. A more recent meta-analysis shows that for every 10 g/day increase in dietary fiber intake, there is a decrease in Crohn's disease risk of 13% (137).

Exclusionary diets to treat Crohn's continue to proliferate and are being tried by patients, although "evidence is limited... anecdotal reports of success abound" (138). Concerning inclusion of grains and brans to help manage Crohn's disease, there is much controversy. Although an evidence-based review by the Dietetics Department at the Royal Liverpool Hospital concludes there is some "indirect evidence" that insoluble fiber intake should be kept low, the review also states there is "little evidence from interventional studies to support specific dietary recommendations" (139). In contrast, German gastroenterological nurses are on record advocating wheat bran therapy (140).

UC. In a systematized review of randomized controlled trials linking UC and dietary fiber intake, Wedlake et al. (141) conclude, "There is limited weak evidence for the efficacy of fiber in improving disease outcomes in UC." However, they also state that only if there is an obstruction does

evidence support the restriction of dietary fiber in treating UC (141). Further, they suggest that the anti-inflammatory role of dietary fiber needs to be investigated further in adequately powered clinical trials.

Grains, Celiac Disease, Allergies, and Toxicity

Grain proteins are a cause of allergies, and the gluten protein is a trigger for a variety of autoimmune diseases, including IBDs and celiac disease. Although more than 80 autoimmune disorders have been identified, this section will focus on celiac disease, NCGS, and grain-related allergies.

Celiac Disease. Celiac disease is an autoimmune condition that occurs in genetically susceptible individuals who carry the human leucocyte antigens (HLA) DQ2 and DQ8 and a few other minor variants. For the disease to occur, a person needs to carry the gene; consume gluten found in wheat, rye, or barley; and have a trigger. The latter is frequently some form of physiological or extreme psychological stress, often an infection. Another common factor is an opening in the gut mucosal barrier usually caused by bacterial overgrowth (dysbiosis). The net result of this dysbiosis is that the functioning of zonulin, the protein whose role it is to keep gut mucosal cells tightly joined together, is impaired. This "leaky gut" enables the entry of materials normally prevented from crossing the gut membrane, including gluten peptides that range in length from 7 to 33 amino acids. These peptides trigger a T-cell-mediated auto-

Excess Fructose	Lactose	Fructans	Galactans	Polyols
<p>Fruit Apple, mango, nashi, pear, tinned fruit in natural juice, watermelon</p> <p>Large Total Fructose Dose Concentrated fruit sources, large servings of fruit, dried fruit, fruit juice, honey, corn syrup, fruit sugar</p>	<p>Milk Milk from cows, goats, and sheep; custard; ice cream; yogurt</p> <p>Cheese soft unripened cheeses, e.g., cottage, cream, mascarpone, ricotta</p>	<p>Vegetable Artichoke, asparagus, beetroot, broccoli, brussels sprouts, cabbage, fennel, garlic, leek, okra, all onions, shallots</p> <p>Cereal Grain Wheat and rye, in large amounts, e.g., bread, crackers, cookies, couscous, pasta</p> <p>Fruit Custard apple, persimmon, watermelon</p> <p>Miscellaneous Chicory, dandelion, inulin, pistachio</p>	<p>Legume Baked beans, chickpeas, kidney beans, lentils, soybeans</p>	<p>Fruit Apple, apricot, avocado, blackberry, cherry, longan, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon</p> <p>Vegetable Cauliflower, green capsicum (bell) pepper, mushrooms, sweet corn</p> <p>Sweetener Sorbitol (E420), mannitol (E421), isomalt (E953), maltitol (E965), xylitol (E967)</p>

Fig. 1. Foods recommended for elimination as part of a low-FODMAP (fermentable oligo-, di-, and monosaccharides and polyols) diet.

immune inflammatory cascade that attacks the mucosa and leads to malabsorption (142).

Incidence. Celiac disease affects $\approx 1\%$ of the population worldwide (143). Data from several countries suggest that the incidence is increasing and is only partly due to better awareness and diagnosis (144). The extent to which other dietary, environmental, medical, and lifestyle factors are involved in the increasing incidence of celiac disease is an area of continued research.

Symptoms. Although a number of celiac disease patients in a recent study by Leffler et al. (145) exhibited gut symptoms such as stomach/abdominal pain, gas, bloating, constipation, and diarrhea, as many as 50% of individuals with celiac disease exhibited no or mild, nonspecific gut symptoms. Common symptoms included iron deficiency anemia, fatigue, osteoporosis, bone or joint pain, infertility, neuropathy and “brain fog,” low antioxidant status, anorexia, and weight loss—although about half of the celiac disease patients in the study were overweight (145). Many celiac disease symptoms are the direct result of nutrient malabsorption.

Grains and Grain Proteins. Gluten is found in foods containing wheat and ancient wheats (einkorn, kamut, dunkel, emmer, spelt), triticale, barley, or rye. The prolamin gliadin, one of the proteins in the gluten complex, is the offending protein. It is rich in proline, an amino acid that causes the protein chain to twist. This limits the accessibility of portions of the protein to proteases in the human digestive tract. The result is oligopeptides of various chain lengths that can cause adverse reactions in the gut. For example, one oligopeptide contains 33 amino acids and is called the “33-mer.” This and other offending peptides trigger the release of an array of proinflammatory cytokines that damage and eventually can destroy the intestinal villa. When the villa are damaged, absorption of nutrients is partially or completely impaired.

Celiac disease patients must completely eliminate all offending grains by adopting a gluten-free diet. Despite reports to the contrary in print and on the Internet, there is no wheat species, parent, or variety that is safe to consume for those with celiac disease. Although it is true that their immunotoxicity may vary, all wheats can trigger celiac disease reactions (146). In addition, processing such as baking can create a gluten–starch complex that further reduces its digestibility (147). Ongo-

ing research is looking for varieties and processes that lower its toxicity (145).

NCGS. NCGS (formerly referred to as gluten intolerance or gluten sensitivity) is a newly identified condition. Although its symptoms are similar to those of celiac disease, such as bloating, abdominal pain, “brain fog,” and tiredness (148), there is no validated diagnostic test for it, and it is not thought to be an autoimmune disease or related to celiac disease. Because most of the symptoms are subjective, there is an ongoing argument among gastroenterologists and other health professionals as to both its existence and incidence.

Some argue that it is not a unique disorder, but instead a subset of IBS (149, 150). Others suggest NCGS is related to other food sensitivities (151) and that its symptoms may not be caused by the gluten protein complex, but instead are caused by FODMAPs, amylase-trypsin inhibitors, or other factors in foods. In fact, one study found that well over half of those with self-reported NCGS failed to react when fed pure gluten (152). Further, if gluten is the trigger, it is not known how much is needed to cause symptoms. It also is unclear whether gluten can be added back when symptoms abate. Some suggest that NCGS is due to gastrointestinal hypersensitivity to amylase-trypsin inhibitors in wheat, but confirmatory evidence is lacking (153,154).

The incidence of NCGS in the 2010 U.S. National Health and Nutrition Examination Survey was reported at 0.6%, while centers specializing in celiac disease found it in 6% of patients between 2004 and 2010 (155,156). These numbers are certainly lower than the large numbers of consumers in the United States and Europe who are avoiding gluten-containing foods or choosing gluten-free products (157,158).

Grains and Allergies. Most grain allergies, as is true of other allergies, are the result of an antigen–antibody reaction with a protein, specifically an immunoglobulin E (IgE)-mediated reaction, that cause the mast cells to release inflammatory mediators and histamine (159). Glycoproteins are the most common offenders (160).

Symptoms of food and grain allergies may occur in the gastrointestinal tract or may be systemic, and thus, they present in a number of ways. This includes swelling, itching, or irritation of the mouth or throat; gastrointestinal upset, nausea, vomiting, or diarrhea; headache; hives, itchy rash, or swelling of the skin; nasal congestion and itchy, watery eyes; and difficulty breathing. For some people with extreme sensitivity,

anaphylaxis may result. In some cases, only trace amounts of the offending protein need to be present to cause a reaction.

There are also non-IgE-mediated gastrointestinal food-induced allergic disorders. They are quite rare, their incidence unknown, and they can be severe. Food protein-induced enterocolitis syndrome occurs with consumption of rice and oats by infants (161).

Wheat. Wheat is one of the top eight food allergens. According to studies on allergies documented by medical food challenge, $\approx 6\%$ of European and $\approx 4\%$ of U.S. adults suffer from food allergies (162,163). Incidence of wheat allergy documented by food challenge is 0.5% of U.S. adults and 0.1% of European adults (self-reported allergy may be as much as 10 times higher) (157,164,165). Approximately 0.5% of young children have a wheat allergy, but 50% outgrow the allergy by age 7 and 80% by their teenage years (166). Among the major allergens, wheat ranks fourth for children and fifth for adults in Europe and the United States.

There are 27 proteins in wheat that have been identified as having allergic potential (153,167). Glutenins, including wheat glutelin, which has nine possible low molecular weight allergenic subunits, cause more allergies than other wheat proteins. However, gliadins cause the most severe wheat allergies. ω -5 Gliadin can be a cause of allergies in children and wheat-dependent exercise-induced anaphylaxis (WDEIA) (168).

Albumins, globulins, and several enzyme inhibitors have also been shown to be allergenic for some individuals through either ingestion or inhalation, as in the case of baker’s allergy. The culprits have been identified as ω -5 gliadin, lipid transfer protein (LTP), and other soluble enzymes, such as those in the amylase-trypsin inhibitor (ATI) family (169). These compounds are problematic because they are neither inactivated by normal heat processing, such as cooking and baking, nor easily attacked by digestive enzymes. Data suggest that these naturally occurring plant protection compounds may enhance the production of inflammatory markers in the gut. Some of the newer disease-resistant wheat varieties contain much higher levels of ATIs (170).

However, it must be pointed out that many other plant foods contain amylase and protease inhibitors, and these may actually be beneficial for some in that they can reduce absorption of some starch (171,172). In lab experiments greater in-

hibition of digestion occurred in older animals (173).

Fermentation of wheat products and hydrolysis of proteins appear to be processes that can reduce their allergenicity to some degree (174).

Other Grains. Cross-reactivities occur with proteins that are the same or closely related, such as those found either in the parents of or species closely related to wheat, rye, triticale, and barley. For example, secalin from rye and hordein from barley can cause WDEIA in susceptible individuals (175).

Grains that do not contain gluten have a lower incidence of allergenicity. Rice and rice bran are considered to be non-allergenic for most individuals (176). Although oats have been shown to precipitate contact dermatitis in some individuals, they most often exhibit anti-inflammatory and anti-itch activities due to their avenanthramides and polyphenolics (177,178). However, for those with celiac disease or severe gluten allergy, only oats that have not been comingled with other gluten-containing grains at any stage along the supply chain would be completely free of the other grains and their proteins.

Beyond proteins unique to grains, all grain proteins have the capacity to be allergenic to some (179). For example, all plants contain LTPs, which are involved in pollen transfer. Because the LTP in maize is similar to one in the peach family (*Prunoideae* subfamily), individuals with a peach/plum allergy also may react to maize (180). Grains also contain enzymes such as trypsin inhibitors. The maize trypsin inhibitor can be allergenic; however, it is important to point out that the allergenicity of genetically modified maize is equal to that of traditionally grown corn varieties (181). Further, there is as much or more variation in the levels of these enzymes in traditional varieties than is observed in transgenic varieties (182). Nonetheless, allergenicity and the expression of new proteins is one concern regarding transgenic crops. For this reason, testing for allergens is required prior to the introduction of a transgenic crop (183).

The relationship between the microbiome and inflammation, gluten disorders, and allergies deserves further discussion. As mentioned, inflammation and dysbiosis are both contributors to and a result of celiac disease. Similarly, allergic reactions release inflammatory markers that trigger inflammation.

The microbiome appears to play a key role in protecting against inflammation

and allergic sensitization. Evidence suggests that alterations in the composition of the microbiota, caused by factors such as antibiotic use and diet, contribute to increased sensitization to dietary antigens and an increase in allergies (184). Further, the activity of commensal anaerobes associated with the mucosa promotes the formation of an immuno-protective barrier that limits the access of food allergens to systemic circulation (185). More needs to be learned to understand the complex interaction between the host, diet, and microbiome in relation to grain allergies, celiac disease, and many other disorders.

Grain Compounds with Potential Toxicity. Lectins are CHO-binding proteins that protect plants from insect pests and fungal growth. Ingestion of plants such as castor beans that have toxic levels of lectins is clearly contraindicated. However, no adverse health effects of dietary lectins from common grain-based foods that are cooked, baked, or extruded, such as those made from wheat, were found in humans in a recent review on this subject (186).

Conclusions

CHOs, enriched refined grains, and whole grains impact health in many positive ways. In addition, their rates of digestion and absorption impact their physiological effects. As with all nutrients, their presence in recommended amounts in the diet is important for health. Imbalances, however, can be problematic. For example, many grain-based desserts are high in calories, fat, and refined CHOs, while lacking in dietary fiber, bran, and whole grains. This combination can decrease the diversity of the microbiome, change fermentation patterns, elevate glycemic response, increase the risk of insulin resistance, and increase levels of inflammation. In contrast, adequate intakes of whole grains and dietary fiber, including resistant starches, are critical for slowing the absorption of glucose and insulin release, modulating the movement of materials through the gut, providing substrates to feed beneficial gut bacteria, releasing phytochemicals, and favoring beneficial reactions in the large bowel, while improving laxation and bowel health, as well as preventing and managing gut disorders. Fermentation in the large bowel produces SCFAs that lower colonic pH and promote growth and division of healthy colonic cells, which is a key step in maintaining gut and overall health.

The gut and microbiome play a key role in modulating immunity and addressing many gut disorders, such as IBS and IBDs, as well as other immune system impacts, such as allergies. All proteins, including those found in grains, are capable of causing allergies. Among grains, wheat ranks as one of the big eight food allergens. Wheat allergy has an incidence documented by food challenge of <1% of the population. Baker's asthma and exercise-induced allergy are other wheat-related allergies.

Celiac disease is an autoimmune disease affecting \approx 1% of the population worldwide. Gluten-containing grains, including all wheat relatives (even parents such as spelt or emmer), barley, rye, and triticale, can trigger celiac disease and should not be eaten by individuals with celiac disease. Gut dysbiosis also plays a key role in celiac disease.

Another disorder, NCGS, is controversial. It is characterized by a group of symptoms, and to date, there is no medically vetted test to confirm its diagnosis. As a result, there is continued discussion about its existence, cause, and incidence, which may vary from <0.6 to 6% or higher. Some studies indicate that NCGS may not be related to gluten intake but rather to dietary factors such as FODMAPs. Both celiac disease and NCGS exhibit symptoms that overlap with other gut disorders such as IBS and IBDs. Further complicating the understanding of these disorders is the fact that inflammation, bacterial overgrowth, the state of the tight junctions in the gut mucosa, and the microbiome all appear to have an impact on these conditions.

Because only \approx 1% of the population has celiac disease, <1% has grain allergies, and an estimated 0.6–6% have NCGS, it is clear that the elimination of gluten by much of the population is unwarranted. Elimination of any specific grain, such as wheat, or a dietary component, such as gluten, should be done only when medically necessary. Elimination diets are not inherently healthier and may put individuals at risk for certain deficiencies, so care must be used when gluten-free or other such diets are warranted.

Although CHOs and grains should form the basis of a health-promoting diet, there is cause for concern regarding inclusion of too much refined CHOs in a diet because increased inflammation and impaired glucose tolerance can occur. However, data from a variety of epidemiological studies show reduced risk of inflammation, im-

proved microbial diversity in the microbiome, better glucose tolerance and reduced insulin resistance, and improved immunity occur when diets contain the correct overall balance of nutrients and CHO- and grain-based foods that deliver adequate dietary fiber and whole grains.

The sad fact is that dietary intake of dietary fiber and whole grains is far below recommended levels in nearly every country around the globe. Regulatory bodies such as the World Health Organization strongly urge higher intakes. In 2010 the U.S. DGAC suggested that high-fiber whole grains be selected as part of its “make half your grains whole” recommendation (46).

CHOs, enriched refined grains, and whole grains are essential components in a health-promoting diet and remain key to dietary guidance around the world for optimal health, sustainability, and interesting and enjoyable foods. Severe reduction or elimination of wheat, grains, and other staple CHO-rich foods is not a recommended as a health-promoting dietary strategy for the well over 90% of the general population who are neither allergic nor intolerant to grains. Healthy individuals need to strive to obtain the right proportion of healthy CHO- and grain-based staple foods in their diets so they can achieve an optimal balance of calories, macro- and micronutrients, dietary fiber, and phytochemicals that are important for health.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Whole Grains and Disease Prevention Part I. Body Weight and Obesity^{1,2}

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The prominence of carbohydrates (CHOs) and grains in dietary guidance as the base of the diet and as core components for promoting health and preventing disease has recently been called into question. Grain-based foods, and the CHOs they contain, have been accused of promoting obesity, which can be a factor in increased risk of developing certain chronic diseases, such as hypertension, metabolic syndrome (MetS), and diabetes. Increased consumption of CHOs and grains is alleged to initiate changes in the microbiome and metabolic pathways that create conditions that negatively impact health. Specifically, some have charged that wheat- and grain-based foods, especially those with added sugars and highly refined CHOs, add calories to the diet and contribute to increases in obesity, hypertension, MetS, diabetes, and other chronic diseases (1,2). Some even claim that these foods “constitute a greater threat to health than the added effects of smoking and alcohol abuse” (3).

In contrast, a review of the literature discussing the findings from numerous epidemiological and intervention studies

shows that grains and grain-based foods, when consumed as part of a healthy and balanced dietary pattern, may actually reduce the risk of weight gain, obesity, hypertension, MetS, and related chronic diseases. In short, studies show that these foods are not part of the problem, but rather can be part of the solution when included in the right amounts as part of a balanced dietary pattern.

The current review is the fourth in a series of papers looking at the role of CHOs, grains, and whole grains in health and will build on the earlier reviews, which addressed their roles in inflammation and glycemic response (4–6), to assess their roles in body weight. Although it is known that different grains may have different effects on health, this review focuses on grains as a group, contrasts the roles of refined and whole grains, and discusses in more detail where specific grains or grain-based foods stand out.

Relationship of CHOs, Grains, Whole Grains, and Dietary Fiber to Body Weight and Obesity

CHO Intake and Measures of Body Weight

Grains, both whole and refined, as well as the CHOs they contain, are among dietary constituents that have been alleged by some to be one of the causes of the worldwide increase in obesity. This charge exists not only in countries with developed economies, but also in countries with emerging and developing economies. At the same time, adequate dietary fiber intake and consumption of an optimal balance of CHO-rich foods are considered by many to be important in maintaining body weight and preventing obe-

sity. Thus, the debate concerning optimal dietary macronutrient distribution, both for attaining optimal body weight, preventing overweight, and promoting and maintaining weight loss, continues unabated.

One prevailing position is that CHO, as it occurs in grains and other staple foods, provides 4 kcal/g, enabling lower calorie intake than fat, which provides 9 kcal/g and, thus, can help to address weight issues. An accompanying view is that excess fat intake, especially saturated fat, can have adverse health effects. Hence, most government regulatory agencies and health promotion organizations suggest that CHOs should contribute a majority of energy (40–65%) in the diet; fats should contribute 20–35% of energy; and proteins should provide the remainder (7).

The opposite position is that CHOs and grains should be eliminated or drastically reduced in the diet because they contribute to obesity and hinder weight loss. Proponents of this theory cite time series data showing that decreasing the percentage of energy ingested from fats while increasing the percentage of energy ingested from CHOs is associated with increased obesity in a population (8). However, drawing such a correlation results in an erroneous deduction. First, associations between increases in body weight and increases in the percentage of energy ingested from CHOs fail to consider total calorie intake. In reality, during the 40 year period cited, calorie intake increased by more than 600 kcal/day (9). Although there have been increases in calorie intake from grain-based foods, there have also been increases in calorie intakes from nearly all food categories. Figure 1 shows the distribution of calorie intake by food

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group using U.S. Department of Agriculture (USDA) disappearance data (9). Thus, the correct deduction is that total calorie intake and calorie intakes from nearly all food groups have increased and are responsible for increases in obesity, rather than the erroneous deduction that the rise in obesity is due mainly to consumption of CHOs and/or grain-based foods.

Furthermore, proponents of the theory that CHOs are the primary cause of increasing obesity rates also state that analysis of National Health and Nutrition Examination Survey (NHANES) data for the past 50 years shows that “general adherence to recommendations to reduce fat consumption has coincided with a substantial increase in obesity” (10). Some even suggest that following government and public health nutrition guidelines are the root cause of the dramatic rise in obesity. As an alternative, these proponents advocate following either a paleo, a low-CHO, or even a very low-CHO (ketogenic) diet, with suggestions that only 10% of energy should come from CHO (11,12). As a consequence, such diets totally eliminate or severely curtail the consumption of grains.

Claims that increases in body weight are attributable to consumption of CHOs and grain-based foods and promises that elimination of grains will address obesity do not accurately describe what is occurring. In fact, these dietary suggestions may not be helpful because of other problems that contribute to increased body mass index (BMI), including increases in 1) stress, which is a documented contributor to overconsumption, especially of foods not only high in CHOs, but also high in saturated fats (13); 2) screen time; and 3) sedentary pursuits. As a result, while total calorie intake has increased,

energy expenditure has decreased dramatically (14).

Population data from many parts of the world do not support the contention that CHO consumption increases body weight. For example, the U.K. Whitehall II Study of more than 6,000 adults shows a link between higher intakes of CHO and lower waist/hip ratios and BMIs (15). A review by Gaesser (16) reveals an inverse relationship in most large prospective cohort studies between CHO intake and BMI or other measures of overweight and body fat, such as waist circumference. Studies done after the Gaesser review (16) continue to show that diets that are higher in fat are associated with measures of increased body fatness and, conversely, that diets that are higher in CHO are associated with measures of decreased body fatness (17–20). CHO intake documented in cohorts around the world show either that there is no relationship with measures of body fatness or that there is an inverse relationship. Data from epidemiological studies have been validated in intervention trials. For example, findings from the Women’s Health Initiative Dietary Modification Trial (21) showed that as intake of fruits, vegetables, and whole grains increased, causing CHO intake to increase, body weight decreased. However, as CHO intake increased, dietary fiber also increased, creating a significant confounding.

Expert advisory panels around the world disagree with claims made in the popular press. For example, the U.K. Scientific Advisory Committee on Nutrition (SACN) concluded their analysis with the following statement, “The hypothesis that diets higher in total CHO cause weight gain is not supported by the evidence...” (22). Similarly, in an evidence-based review

(EBR) (23) the German Nutrition Society concluded, “The available studies regarding adults mainly suggest that CHO intake or dietary CHO proportion, respectively, is not associated with the risk of obesity. The evidence regarding the lack of a long-term effect of a change in CHO intake on the development of obesity is judged as probable.”

Such pronouncements have not quelled the continuing debate, however. Those who hold that CHO causes overweight also sometimes suggest that it is not the amount of CHO, but rather the quality. However, CHO quality has no generally agreed upon definition. The following criteria for CHO quality have been suggested: 1) foods that are whole grain; 2) foods that have a low glycemic response, e.g., low glycemic index (GI) and/or glycemic load (GL) (24); 3) foods that have a proper fiber ratio (25); and 4) foods that are from grains that have neither been bred, modified, nor refined (2,26,27).

Parameters of CHO quality, such as GI, do not necessarily reduce confusion. More studies show either a lack of association or an inverse relationship, rather than a positive relationship, between measures of body weight and the GI or GL of the diet (16,28–30). Confounding occurs because diets that have a low GI often contain foods that have more dietary fiber and contain more recommended dietary components and food groups. So, despite a recent consensus paper (24) stating that GI and GL were useful in preventing and treating obesity, both a recent review of randomized control trials (RCTs) and a meta-analysis show either no or a mixed response when dietary fiber and whole grain intake were considered (31,32).

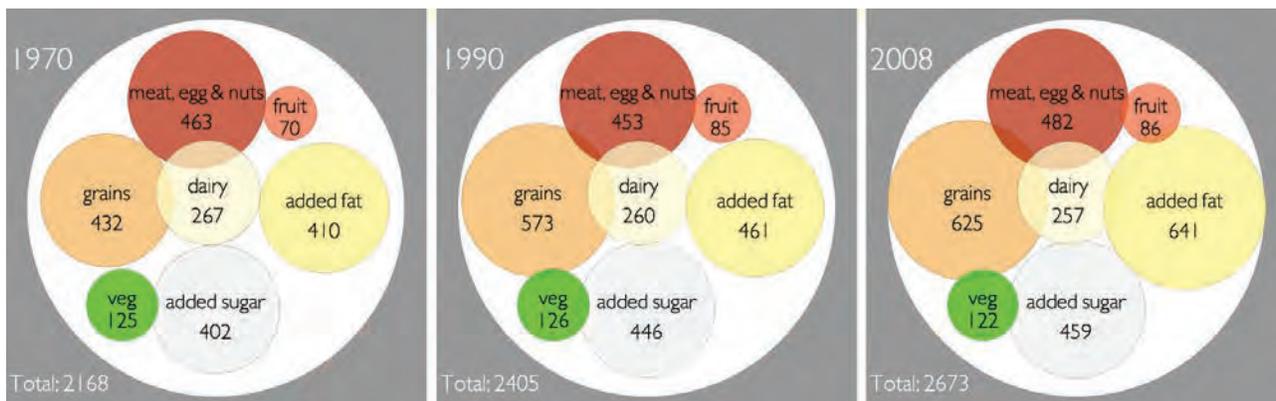


Fig. 1. Comparison of average daily calories per capita available from the U.S. food supply (adjusted for spoilage and other waste) in 1970, 1990, and 2008. Data source: USDA ERS Food Availability (Per Capita) Data System (www.ers.usda.gov/Data/FoodConsumption). (Republished from Norén [7] under CC BY-NC-SA 3.0 US license)

CHOs and Weight Loss and Maintenance

Just as the role played by CHOs in overweight remains unclear, their role in weight loss has been contested in health and nutrition arguments for years. In 1863 William Banting, a noted English undertaker, published the dietary recommendations of physician William Harvey in *A Letter on Corpulence* (33). The pamphlet suggests that diets eliminating CHOs would help with weight loss. Since then, both scientific studies and popular literature have continued to support and refute this approach to dieting (34). Proponents of higher CHO diets recommend them over high-fat diets because fat, compared to CHO, is more efficiently absorbed and relatively resistant to oxidation. Both of these observations support the idea that high-fat diets can impede weight loss and may lead to weight gain. Further, high-fat foods often are highly palatable and only weakly satiating. As such, they may contribute to passive overconsumption and excess energy intake (35).

Lower fat diets may, in fact, be helpful for those trying to maintain their weight. A 2015 systematic review of 32 RCTs of populations not actively trying to change their weight ($N \approx 54,000$ participants) shows that diets with a higher CHO content and lower proportion of energy from fat had a more consistent effect on body weight measures (36). Those ingesting higher percentages of CHO had somewhat lower body weights (≤ 2 kg on average) than those ingesting a typical percentage of fat. The differences became greater for those following diets with more stringent fat reductions (36).

Despite the more than 170 years since Banting's essay on which type of diet is best for weight loss, a definitive answer remains elusive. Findings from RCTs provide evidence that supports both high- and low-CHO diets. However, differences in the number of kilograms lost are small, and any advantage of one diet over another diminishes the longer a group is on a low-CHO diet. For example, data from a number of RCTs show greater short-term weight loss for low-CHO diets than those higher in CHOs (37–40). However, many of these studies fail to show any weight loss advantage at longer time points (41–43). In many studies showing statistically greater weight loss, the actual differences were deemed too small to be physiologically important. On the positive side, there is substantive evidence that for many individuals low-CHO diets can effectively pro-

mote weight loss and lead to favorable changes in blood lipids (44). These positives are balanced, however, by the fact that low-CHO diets often lead to decreased intakes of phytochemicals and dietary fiber and may result in decreased glycogen stores. Nevertheless, for those with insulin resistance or those classified as having MetS or prediabetes, there is experimental support for consumption of a moderately restricted CHO diet ($<44\%$ of calories from CHO) that emphasizes high-quality CHO sources. This type of dietary pattern also could lead to favorable changes in cardiovascular disease risk factors and minimize possible concerns associated with very restrictive low-CHO diets (45,46).

For certain body weight measures and health outcomes, a low-fat diet may be better than a low-CHO diet. For example, in an RCT of isocaloric diets, body fat loss was significantly greater with a very low-fat diet than with a very low-CHO diet (47). The authors of this study suggest that this finding gives a low-fat (higher CHO) diet an edge when it comes to overall health, arguing that the loss of fat is more important to health than overall loss of weight. Such findings also debunk claims that fat loss does not occur in the presence of CHO as has been alleged by some (48). However, as is discussed in the fifth review in this series, which focuses on blood pressure, MetS, and diabetes (44), some health outcomes are better when diets are lower in CHO. Nonetheless, an EBR conducted by the Spanish Federation of Nutrition, Food and Dietetic Associations (FESNAD) with the Spanish Association for the Study of Obesity (SEEDO) concluded that there are fewer adverse long-term health effects for those following a low-fat diet than for those following a low-CHO diet, especially if the latter is high in animal fat (43).

More research is needed because many things impact weight. Gender, sleep duration, and the metabolic state of the dieter all interact with the level of CHO intake and may account for variations in study outcomes (49). For example, in a short-term study, in individuals with diabetes a decrease in CHO intake from 50 to 40% of calories was associated with a reduction in visceral adipose tissue in men, but not in women (50). However, in insulin-sensitive obese women high-CHO (60% of energy), low-fat (20% of energy) diets caused significantly greater weight loss than low-CHO (40% of energy), high-fat (40% of energy) diets (3.5 versus 6.8% of

initial body weight, respectively). In insulin-resistant women, significantly more weight was lost by those following a low-CHO diet than by those following a high-CHO diet (3.4 versus 8.5% of initial body weight, respectively). Furthermore, dietary adherence varied with insulin sensitivity. There was poorer adherence to a low-fat diet for those with insulin resistance (51). This is significant because adherence to a diet has been shown to be necessary for success with weight loss and maintenance (52–54). Dietary advice tailored to individual preferences also appears to be key to adherence to a diet.

Dietary Fiber, Cereal Fiber, and Whole Grains and Body Weight

The data concerning the impact of dietary fiber on body weight measures is mixed, with clinical trials and epidemiological studies showing lack of agreement. Several clinical trials show little or no effect on body weight of dietary fiber alone or as part of whole grain (55–57), whereas many epidemiological studies do show a relationship. In a cross-sectional study of the dietary patterns of $\approx 1,800$ men and women entering a weight loss trial, baseline intakes of both total dietary fiber and cereal fiber were associated with lower BMIs at the study outset (58). In the Baltimore Longitudinal Study of Aging, inverse correlations were shown between BMI and cereal fiber intake (59). In the Male Health Professionals' and the Nurses' Health Study cohorts, intake of bran was associated with less weight gain over the 8–12 year follow-up period (60,61). In a subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of 89,423 men and women, those with the highest total and cereal fiber intakes at baseline had the least weight gain and increase in waist circumference over the 6.5 year follow-up period (62). Intake of total dietary fiber and cereal fiber in the Netherlands cohort study ($N = 4,237$ adults, 55–69 years old) was inversely associated with BMI only in men (63). However, a retrospective analysis of this cohort looking at weight gain after the age of 20 years found that baseline dietary fiber intake showed a slight inverse association. A recent review combining data sets for the 12 publications from Diet, Obesity and Genes (DiOGenes) and 6 from EPIC-PANACEA showed that dietary fiber, especially cereal fiber, was inversely associated with changes in measures of body weight (64).

Although many studies show some relationship, albeit weak, between dietary fiber intake and body weight and weight gain, not all show a significant relationship. For example, for the 18,146 women aged ≥ 45 years who participated in the Women's Health Study who had BMIs in the normal range, intakes of dietary fiber at baseline were not associated with a lower risk of gaining weight over time (65).

Data from cohort studies on cereal fiber and whole grains are often derived from the same groups and, therefore, yield similar findings; only inclusion of the intake of cereal bran and germ would make the data different (66). In an EBR using 45 years of scientific research on populations and subgroups from around the world, both cereal fiber and whole grain are associated with small, but significant, reductions in weight gain (66). According to a review of epidemiological studies, for adults higher intakes of whole grain is associated with lower body weight, BMI, waist circumference, abdominal adiposity, and weight gain (67). The evidence is graded as moderate. Similar trends have been found in studies of young children. For example, rural elementary school children who consumed 1.5 servings or more of whole grains/day had a 40% lower risk of being obese compared with children who consumed < 1 serving/day (68).

Prospective observational studies of both men and women also have shown that whole grain consumption is associated with a tendency toward lower weight gain over time (60,61,69,70). Such studies show that higher intakes of whole grains (≈ 3 servings [a minimum of 48 g of whole grain] per day) are associated with lower BMI, smaller waist circumference, and lower body fat levels. However, the findings must be considered with the knowledge that people who eat more whole grain servings tend to have healthier lifestyles and dietary habits than those who eat less than 1 serving of whole grains/day.

Data from RCT diets comparing those whose diets are rich in whole grain foods with those whose diets are low in whole grain foods present a less consistent picture than findings from epidemiological studies. Although a few short-term studies show a possible trend toward lower weight with more whole grains in the diet, many fail to show significant differences in body weight or BMI (71–73). A few intervention trials show changes in other measures, such as percent body fat, body mass, or waist circumference (74–76). These studies are consistent with the find-



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ings of a review of 26 studies, which shows no overall effect of whole grains on body weight but a possible beneficial effect on the level of body fat (77). The authors of the review theorize that the conclusions may be partly due to short duration, as well as sample size and composition. Another possible reason for the inconsistency among study findings is the lack of an agreed upon definition of whole grain and differences caused by the effects of whole grain processing (66).

The evidence linking refined grain product intake and risk of obesity also is confusing because it shows both increased and decreased risk. For example, data from the Danish Diet, Cancer and Health Study ($N \approx 43,000$) show that higher CHO intake due to refined grain products and potatoes was associated with an increase in waist circumference (78). However, two EBRs assessing the existing data regarding the role of refined grains conclude there is weak evidence that high intakes of refined grains may cause small increases in waist circumference in women (79). Similarly, after conducting an EBR the German Nutrition Society concluded “the evidence regarding the relevance of refined grain products for the risk of obesity is judged as insufficient” (23). In contrast, the same EBR found strong evidence that a diet high in whole grains is associated with lower BMI, smaller waist circumfer-

ence, and reduced risk of being overweight; a diet high in whole grains and legumes can help reduce weight gain; and significant weight loss is achievable with energy-controlled diets that are high in cereals and legumes (79).

Grain-Based Foods and the Affect of Satiety on Body Weight

Satiety. Satiety is thought to influence how much is eaten, although a direct link has been difficult to show. In some studies bread has been shown to impact satiety, but not all bread types have this impact. For example, in a 2010 study participants consuming whole grain breads reported feeling fuller and more satiated than those eating refined grain breads (80). Puzzlingly, despite these differences in satiety ratings, there was no difference in overall energy intake. Other studies showed that breads containing a variety of flours, seeds and nuts, legumes, and whole kernels had higher satiety values compared with breads containing refined flour, although not all studies found significant differences (81–84). In addition, sourdough breads made with refined flours were shown to be more satiating than some whole grain breads due to their effects on the satiety hormone, a glucagon-like peptide (85). To date, increases in satiety due to whole grain intake have only been weakly associated with lower calorie intake or body weight (67).

Whole Grain Breads. Some popular authors and bloggers recommend restricting or even eliminating bread from the diet. However, these recommendations are at odds with the findings of a review of 38 epidemiological studies published over the past 30 years. The review found that dietary patterns that include whole grain breads are not associated with weight gain and might be beneficially linked to one or more measures showing reduced body fatness (86). Diets including the recommended amount of whole grain and whole grain breads have been shown to help with weight management. In healthy, postmenopausal Finnish women whole grain rye bread as 20% of energy intake was shown to help in weight control (87).

Refined Grain Breads. Findings are mixed concerning the role of refined grain (white) breads in weight, both among and between epidemiological studies and clinical trials. Although the majority of cross-sectional studies show that dietary patterns, including refined grain breads, are associated with lower measures of body fatness, most cohort

studies demonstrate a possible positive relationship between white bread intake and excess abdominal fat (86). For example, increased consumption of refined grain breads by those in the Danish Diet, Cancer and Health Cohort ($N \approx 43,000$) was associated with an increase in waist circumference, but only in women (78). Although the ingestion of high amounts of bread may be partially to blame, such results may be due to an interaction or occur because of confounding. For example, those who eat refined grain breads may make other lifestyle choices that adversely impact their weight (88–90). One review focused on the effects of changing the type of bread chosen in Mediterranean-style food patterns. It showed that reducing white (refined) bread, but not whole grain bread, consumption was associated with lower gains in weight and abdominal fat over time (91). Among the more than 2,000 participants in the Spanish cohort of the PREDIMED study of the Mediterranean diet, those in the highest quartile of change in white bread intake gained 0.76 kg more than those in the lowest quartile and increased waist circumference 1.3 cm more than those in the lowest quartile (92). However, bread consumption during the 4 year follow-up period was not associated with gaining more than 2 kg of weight or increasing waist circumference by more than 2 cm. Those in the highest quartile of changes in white bread intake had a 33% lower chance of losing >2 kg or reducing waist circumference by >2 cm. This suggests that decreasing white bread consumption, but not whole grain bread consumption, within a Mediterranean-style food pattern is associated with lower gains in weight and abdominal fat.

Furthermore, bread inclusion versus exclusion in an RCT with reduced-calorie diets for middle-aged, overweight or obese women was shown to actually help with weight loss (93). Not only did those assigned to the bread group increase their percentage of calories from CHO, they reduced their percentage of calories from fat, which resulted in a net decrease in calories. Further, fewer (2%) subjects in the bread group than the nonbread group (6%) dropped out, and those in the bread group reported feeling more satiated (94). Inclusion of bread for those on low-calorie regimens appears to help with satiety and compliance, both of which may be helpful in long-term weight reduction success.

Rice and Oats. The few studies looking specifically at the impact of rice intake, the

main source of CHOs in many cultures, suggest it is not related to measures of body weight. For example, a recent cross-sectional study of Iranian men (95) found no difference in BMI based on rice consumption. In fact, mean BMIs were not significantly different for those consuming white rice fewer than 7 times per week and those consuming rice 7–14 times per week. Some studies actually show lower measures of body weight for those consuming higher levels of rice.

Analysis of the NHANES databases shows that adults who consume higher amounts of rice, including white and brown rice (96), or oats (97) are more likely to have a lower body mass and waist circumference. Similarly, a study of elderly Chinese adults shows that individuals consuming more than 400 g of rice/day had lower weight gain (but increased elevated glucose) than those consuming 200 g/day (98).

Breakfast Cereals. Breakfast cereal intake, including both whole and refined grains, tends to be inversely related to measures associated with body weight. An EBR of studies of large prospective cohorts shows that men who frequently consumed



breakfast cereals (regardless of type) consistently weighed less than those who consumed breakfast cereals infrequently. Further, over an 8 year time span, those who ate breakfast cereals were less likely to gain weight than those who consumed little or no breakfast cereal (99). The reviewers concluded “there is no evidence that LCDs [low-CHO diets] restricting cereal intakes offer long-term advantages for sustained weight loss” (99).

Both a meta-analysis (100) and a study of minority children and adolescents (101) show a similar positive effect on weight for those who ate breakfast cereals. Regular consumers of breakfast cereals compared with children and adolescents who consumed breakfast cereals infrequently had a lower prevalence of overweight. This is interesting because the analysis

shows that energy intakes tended to be higher for regular consumers of breakfast cereals, suggesting the possibility that those who eat breakfast cereals may be less likely to underreport intakes on questionnaires or that they have other healthy lifestyle aspects, such as increased exercise, that help with weight control. There was even weak support (“grade C” rating on a scale of A [can be trusted] to D [weak, apply with caution]) in one EBR showing consumption of presweetened breakfast cereals did not increase the risk of overweight and obesity in children (102).

Assessing Studies on Refined and Whole Grains and Body Weight

It is often difficult to tease out the facts concerning the impact consuming refined grain-based staple foods has on body weight because of the way in which grains are categorized in epidemiological studies. In most studies grain-based foods are classified as either refined or whole. Confounding is inherent in such a categorization structure. First, refined grains include both grain-based staple foods, such as breads and pastas, and indulgent grain-based foods, such as cakes and doughnuts. At the time many cohort studies were undertaken to assess health outcomes associated with intake of refined and whole grain foods, indulgent grain products nearly always were formulated with refined grains. Only rarely were such products formulated with whole grains. Further, the intake of whole grains was <1 serving. Thus, combining refined indulgent and refined grain-based staple foods into a single category called “refined grains” confounds the attribution of the cause of observed health outcomes. The observed association could be due to 1) consumption of too many grain servings overall (103); 2) overconsumption of refined grains overall; 3) consumption of too many indulgent grain-based foods; 4) an imbalance in consumption of indulgent and refined grain-based staple foods; or 5) inadequate fiber and micronutrient intakes due to lack of whole grain consumption or poor diet quality.

Further, the research definition of whole grain varies markedly among studies, with some using 51% of the product by weight, some 25%, and others using 8 g/serving (66). Still others count grams of whole grain. In addition, some epidemiological studies have errors in classification, such as counting all couscous and all dark breads as whole grain, and many counting either bran- or germ-based foods as whole grain

foods. These categorization errors may account for some of the variability found among studies (104).

Another problem in data analysis is that there is inadequate intake of both dietary fiber and whole grain across populations; as a result, <4% of the population meets recommendations for whole grain, fiber, and other constituent intakes (103). Those who come closest to meeting whole grain and fiber recommendations tend to come closer to meeting other lifestyle and dietary recommendations than those who do not consume adequate levels of dietary fiber or whole grain. For example, a cross-sectional study of adolescents that used data from NHANES, 1999–2004, found that higher whole grain intake was associated with lower BMI and waist, thigh, and arm circumferences only among boys, but the association in boys lost its statistical significance after adjustment for intake of other food groups (105). For measures of body weight this confusion presents special difficulty. Studies show that individuals ingesting foods with lower energy density have lower body weights and higher intakes of dietary fiber, cereals, fruits, vegetables, and grains, including rice, and that a lower percentage of these individuals consume baked goods and fried potatoes (106,107).

Grains, Whole Grains, and Dietary Fiber and Body Weight—A Summary

Habitual whole grain consumption is related in many epidemiological studies to lower measures of body weight and a decreased tendency to gain weight over time. Whole grains and cereal fiber may help with weight control for the following reasons:

- 1) Diets with adequate dietary fiber tend to include nutrient-rich fruits and vegetables and whole grains; as a result, they are usually more nutrient dense and less energy dense.
- 2) Diets with adequate whole grain and cereal fiber intakes may affect food volume and gastric emptying. Because these types of diets include larger food volumes, they tend to stay in the stomach longer and may enhance feelings of fullness and reduce hunger (108).
- 3) Fermentation of fiber, including resistant starch, from whole grains may alter the secretion of gut hormones that influence satiety or cause other changes in the gut and microbiome that impact satiety (109,110).

- 4) The intake of whole grain foods and cereal fiber is associated with lower markers of inflammation, such as C-reactive peptide and other cytokines. This may cause beneficial changes in metabolism and enable weight maintenance.

Dietary patterns that include CHOs, whole grains, breads, and cereals in the right balance are associated with lower measures of body weight and less weight gain over time. Although diets high in refined grain breads and meats are associated with greater measures of body fatness in some studies, the data are unclear with respect to the role of refined grain breads and cereals, especially when the refined grain category contains not only refined grain-based staple foods but also grain-based desserts and snacks. More research is needed regarding the optimal balance of these CHO-rich staple foods.

Conclusions

Body weight and obesity appear to be addressed and prevented best by diets enabling weight maintenance and loss, when necessary, that focus not on the elimination of CHOs and grains, but rather on the consumption of foods and nutrients within tested, balanced dietary patterns. Such diets generally would contain from 45 to 65% CHO, including high levels of the dietary fiber and phytochemicals present in whole grains. Both are associated with a lower risk of elevated body weight, as well as a lower risk of hypertension, MetS, and diabetes (44).

Patterns such as the DASH (Dietary Approaches to Stop Hypertension), Mediterranean, and New Nordic diets and the USDA MyPlate recommendations, as well as many others, that include balanced amounts of all macronutrients, vitamins, minerals, and phytonutrients do not eschew any food groups, including grains and breads, meet this balance (103). Sadly, only 3–8% of Americans eat according to such patterns. Less than 4% of Americans meet the dietary fiber intake requirement, and less than 1% meet the whole grain intake requirement. Data from many other countries also show a large gap between recommended patterns and actual intakes. For many, servings are too large, and grain-based desserts and other high-calorie, low-nutrient foods provide too many calories at the expense of nutrient-rich fruits and vegetables and whole and refined grain staple foods. General diets

do need improvement, but elimination of CHOs and grain-based foods will not provide the improvements needed for most individuals.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Whole Grains and Disease Prevention Part II. Blood Pressure, Metabolic Syndrome, and Diabetes^{1,2}

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The prominence of carbohydrates (CHOs) and grains in dietary guidance as the base of the diet and as core components for promoting health and preventing disease has recently been called into question. Grain-based foods, and the CHOs they contain, have been accused of promoting obesity, which can be a factor in increased risk of developing certain chronic diseases, such as hypertension, metabolic syndrome (MetS), and diabetes. Increased consumption of CHOs and grains is alleged to initiate changes in the microbiome and metabolic pathways that create conditions that negatively impact health. Specifically, some have charged that wheat- and grain-based foods, especially those with added sugars and highly refined CHOs, add calories to the diet and contribute to increases in obesity, hypertension, MetS, diabetes, and other chronic diseases (1,2). Some even claim that these foods “constitute a greater threat to health than the added effects of smoking and alcohol abuse” (3).

In contrast, a review of the literature discussing the findings from numerous epidemiological and intervention studies

shows that grains and grain-based foods, when consumed as part of a healthy and balanced dietary pattern, may actually reduce the risk of weight gain, obesity, hypertension, MetS, and related chronic diseases. In short, studies show that these foods are not part of the problem, but rather can be part of the solution when included in the right amounts as part of a balanced dietary pattern.

The current review is the fifth in a series of papers looking at the role of CHOs, grains, and whole grains in health and will build on the earlier reviews, which addressed their roles in body weight, inflammation, and glycemic response (4–7), to assess their roles in blood pressure, stroke, glucose tolerance, MetS, and diabetes. Although it is known that different grains may have different effects on health, this review focuses on grains as a group, contrasts the roles of refined and whole grains, and discusses in more detail where specific grains or grain-based foods stand out.

Relationship of CHOs, Grains, Whole Grains, and Dietary Fiber to Blood Pressure

CHOs and Blood Pressure

High blood pressure, also called hypertension, occurs when there is too much pressure exerted against the walls of the blood vessels. Chronic hypertension causes the heart to work too hard, can damage the arteries and kidneys, and can put the individual at risk for cardiovascular disease and MetS. In the United States and the United Kingdom, 33–40% of the population has hypertension, with the percentage nearly doubling for people over the age of 65. In the United States,

10% of children have hypertension. Although there is no identifiable cause for most cases of primary hypertension, there are many contributing factors—genetics, ethnicity, obesity, lack of exercise, smoking, stress, age, and diabetes are all factors. In terms of diet, the types of fat and balance of fatty acids, amount of salt, and amounts of potassium and other minerals consumed and dietary patterns have all been implicated, as have the amounts and types of CHOs consumed, with some suggesting that grains and refined CHO-rich foods are part of the problem. However, the percentage of CHO in the diet does not seem to be associated with adverse changes in blood pressure. If anything, it may be associated with lower blood pressure (8).

Until the advent of effective blood pressure medications in the 1940s, a diet consisting only of rice and fruit was used to successfully treat “malignant hypertension” (9). Although the blood pressure-lowering effect of the rice and fruit diet was similar to that of many drugs, the diet fell out of favor due to difficulties with compliance. Nonetheless, the effects of this diet suggest that high-CHO diets are not a cause of elevated blood pressure and may help with blood pressure management.

Most epidemiological or interventional studies show that following diets or dietary patterns containing the recommended amount of CHO as well as other nutrients either has no impact on blood pressure or is associated with lower blood pressure. For example, in the OmniCarb randomized control trial (RCT) of 63 overweight adults following a Dietary Approaches to Stop Hypertension (DASH) diet, neither high (58%) nor low (40%) CHO diets had any impact on blood pressure (10). The glycemic index (GI) of the

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CHO ingested also was not shown to impact blood pressure.

Epidemiological evidence is similar to that from intervention studies. For example, in the Korean National Health and Nutrition Examination Survey (NHANES), 2007–2010, neither the percentage of calories from CHO nor the actual amount of CHO consumed had an impact on blood pressure (11). Further, Chinese adolescent males consuming diets high in CHO (>55%) were shown to have lower systolic blood pressure than males consuming diets lower in CHO (12). Similar trends were observed in elderly Chinese adults, for whom a moderate CHO intake was associated with lower blood pressure (13). Those eating >400 g of rice/day versus those eating <200 g/day had a 40% lower risk of hypertension (14).

CHOs consumed as part of a balanced dietary pattern have been shown to play an important role in hypertension. For example, analysis of Korean NHANES IV data (15,16) showed that the traditional Korean dietary pattern, which is high in rice (and kimchi), was associated with a 40% lower risk of hypertension than a pattern rich in meat, alcohol, fast foods, and fried noodles. Unbalanced Korean dietary patterns, characterized by high intake of CHOs and sodium and little food variety, were associated with a higher risk of elevated blood pressure only in women (17). These studies suggest that it is not the CHO itself, but rather the overall dietary balance that impacts blood pressure. The Mediterranean diet, which is balanced for all dietary constituents, including grains, was associated with lower blood pressure in an RCT (18). Although studies from India show that diets containing 67% CHO and 440 g of refined grains/day were associated with higher blood pressure (19), it should be pointed out that those in the quartile eating the most refined grains followed diets that were far from the recommended pattern.

Dietary Fiber and Grains and Blood Pressure

Dietary Fiber. Dietary fiber intakes in prospective cohort studies are inversely associated with high blood pressure. This was true for the segment of more than 17,000 NHANES III participants living in the southeastern United States who had the lowest intake of dietary fiber (20). Similarly, for a French cohort of 6,000 men and women, those with the highest total and insoluble dietary fiber intakes had the lowest blood pressure (21).

In a Spanish cohort of nearly 6,000 university graduates, those with the highest intakes of cereal fiber decreased their risk of elevated blood pressure by up to 40% compared with those with the lowest intakes of cereal fiber. A meta-analysis of 25 RCTs shows that dietary fiber added to the diet of hypertensive subjects for 8 weeks lowered diastolic blood pressure (22). In the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) (23) of older men and women at risk for cardiovascular disease (CVD), higher dietary fiber intake was associated with lower systolic blood pressure. Insoluble fibers, like those found in most grains, appeared to have a much greater impact on blood pressure than soluble fibers.

Although dietary fiber intake appears to be important, overall diet quality matters as well. In a cohort of black Americans (24), those with higher blood pressure not only followed a diet low in dietary fiber, the diet was high in other dietary components with negative health impacts. Thus, the authors of the study concluded that poor diet quality and low dietary fiber intake, rather than CHO or grain intakes, contributed to higher blood pressure (24).

Whole Grains. An association between whole grain intakes and lower blood pressure has been shown in some, but not all, studies. For example, a large French cross-sectional study showed whole grain intakes were inversely associated with blood pressure (25). Further, subjects who substituted 48 g of whole grains/day for refined grains for a short time showed a decrease in systolic blood pressure (26). Both nonmalted and malted whole grain cereals consumed in a crossover design lowered the blood pressure of obese subjects (27). Replacing 3 servings of refined grains with 3 servings of a mix of whole grain wheat and oats caused a decrease in systolic blood pressure in just 3 weeks (28). After 12 weeks, systolic blood pressure decreased with consumption of either all whole wheat or a mix of grains. On the other hand, intervention studies in Europe and the United States failed to show that consumption of whole grain cereals resulted in lower blood pressure in consumers with low whole grain intakes (29,30).

Refined Grains and Grain-Based Foods. A number of studies show an association between dietary patterns high in refined grains and elevated blood pressure. For example Qatari women of child-bearing age who followed a “traditional, sedentary pattern” consisting of refined

grains, dairy products, and meat in addition to low physical activity had a two-fold risk of elevated blood pressure (31). In India a dietary pattern of refined grain intake also was associated with higher blood pressure (19). In the latter study, those with the highest intakes of refined grains consumed more calories and less protein (including dairy and fish), >400 g of refined grains/day, and >65% of calories as CHO and had significantly lower intakes of potassium and fiber-containing fruits, vegetables, and legumes.

Breads and Cereals. The role of breads and cereals in the diet with respect to blood pressure is often difficult to discern because of their close association with other components in the diet that affect blood pressure. One intervention trial compared the breakfasts of adults 18–35 years of age. It showed that a breakfast composed of a refined flour bagel resulted in the same blood pressure as a breakfast composed of an egg; however, insulin sensitivity was improved with the bagel breakfast (32). In terms of dietary patterns, Japanese individuals who followed a “bread and dairy products” pattern had a lower risk of elevated systolic blood pressure compared with those following a “seafood” or “high-fat/Western” pattern, which were associated with slightly elevated risk (33). Further, the bread and dairy products pattern lowered blood pressure nearly as much as the “prudent” diet (i.e., containing lower levels of fat, cholesterol, and protein).

In addition, bread has been used as a vehicle to add functional ingredients such as resistant starch, soy, or other components known to impact blood pressure to the diet (34). If bread itself had a significant impact on blood pressure, it would be a poor vehicle for addition of these functional components.

Dietary guidance often recommends the replacement of refined grain breads and cereals with whole grain versions. However, the impact of such substitutions has not been consistent across studies. When 6 servings of refined grain (5 of 6 were breads or breakfast cereals) were replaced by whole grain counterparts in a crossover design, dietary fiber intake went up, but there was no effect on blood pressure (35). Similar findings were observed when whole grain bread, biscuits, and pasta were substituted for refined grain versions (36). In contrast, one study comparing the impact of refined grain cereals with non-malted and malted whole grain cereals found that the whole grain foods decreased blood pressure (27). Whole grain oats and

its β -glucan content has also been shown in a number of studies to lower blood pressure (37).

Rice. A number of studies show an association between inclusion of rice in a balanced dietary pattern and lower blood pressure (13). For example, in a 5 year study of more than 1,200 adults in Jaingsu, China, a 10% increase in the percentage of rice included in staple food patterns was associated with a 9% decrease in the risk of high blood pressure (38).

Intervention studies do not provide a clear picture concerning the impact of brown rice versus white rice intake on blood pressure. In a crossover design intervention study with overweight and obese females of childbearing age, brown rice intake decreased blood pressure compared with white rice (39). However, in a 6 week study of middle-aged Chinese men

and women at risk for diabetes, substituting brown rice for white rice offered no advantage for many endpoint measures, including blood pressure (40).

Grain-Based Foods and Sodium. Many grain-based foods are major contributors of sodium to the diet (discussed in the text box). Salt consumption has been linked to elevated blood pressure, which is a leading cause of premature mortality worldwide. Salt consumption generally is 5–10 times greater than physiological requirements, leading the World Health Organization to suggest modest salt reduction in diets as a public health measure to reduce the risk of chronic disease (41). There appears to be a strong association between high sodium intake (>6 g/day) and both blood pressure and CVD events in hypertensive and some elderly individuals. However, there may be a U-shaped risk curve be-

cause there seems to be no association between sodium and clinical events at intake levels of 3–6 g/day, while there are higher rates of clinical events at intakes under 3 g/day (42).

CHOs and Grains and Blood Pressure—A Summary

CHOs and grain-based foods consumed as part of a balanced diet do not appear to elevate blood pressure and, in some instances, may lower it. The latter appears to be true even though grain-based foods are major contributors of dietary sodium. The results from studies in which whole grain products are substituted for refined grain products are mixed. However, the DASH diet, which emphasizes whole grain breads and cereals as part of its healthy dietary pattern, has documented success in lowering blood pressure. Further, products with viscous fibers, like those found in whole grain oats, have been shown to lower blood pressure, and studies on rice show that it may be associated with lower blood pressure.

Because grain and whole grain products provide dietary fiber, including soluble dietary fiber, and whole grains contain phenolics, these foods are likely to have marked effects on the microbiota, which may lower blood pressure. From a mechanistic view, whole grains and the dietary fibers they contain, can impact blood pressure through compounds generated or formed during their digestion, hydrolysis, or fermentation. For instance, short-chain fatty acids formed during fermentation can impact receptors that control blood pressure (52). In addition, compounds associated with the blood pressure-lowering, angiotensin-converting enzyme (ACE inhibitory) are produced (53–55). However, more needs to be known about the quantity of the compounds formed, their half-life, the concentration needed for impact, and how they are transported to target tissues in humans. Nevertheless, it is highly likely that both dietary fiber and whole grains can change the microbiome and that this could impact blood pressure (56).

Both whole grains and dietary fiber are recommended as part of blood pressure management regimens by health promotion organizations such as the American Heart Association, the American College of Cardiology, and the Canadian Hypertension Education Program (57). These recommendations emphasize the inclusion of both as part of a balanced dietary pattern.



Amount Per Serving		Calories from Fat 49	
Calories 180		% Daily Value*	
Total Fat 6g			9%
Saturated Fat 1g			3%
Trans Fat 0g			
Cholesterol 42mg			14%
Sodium 345mg			14%
Total Carbohydrate 29g			10%
Dietary Fiber 2g			7%
Sugars 5g			
Protein 3g			
Vitamin A	1%	Vitamin C	17%
Calcium	3%	Iron	3%

Sodium, Bread, and Grain-Based Foods

Sodium Intakes—Many populations in both developed and developing countries consume sodium in excess of daily guidelines. For example, the U.S. Centers for Disease Control and Prevention (CDC) (43) determined that, excluding salt added at the table, the mean daily sodium consumption for U.S. adults (2007–2008) was 3,266 mg and for children was 3,279 mg.

Of the sodium in the diet of U.S. adults, 44% came from 10 food categories. Five grain-based food categories were among the top ten contributors: bread and rolls, cold cuts/cured meats, pizza, poultry, soups, sandwiches, cheese, mixed pasta dishes, mixed meat dishes, and savory snacks. For children, 43% of sodium was contributed by the same five grain-based food categories as for adults, with the addition of a sixth category, mixed Mexican dishes, and soups. Very similar data exist for special populations of children, such as diabetics, in other parts of the world (44–48).

Sodium in Breads and Cereal Foods—According to a CDC survey of U.S. packaged foods (49), the sodium content of 72 breads and buns sampled varied from 320 to 857 mg/100 g, with a mean of 512 mg/100 g. Sodium content of cereals ranged from 407 to 670 mg/100 g, with a mean of 421 mg/100 g. Thus, depending on the food products chosen, breads and cereals may account for between 20 and 67% of the recommended daily intake of sodium for healthy adults. A study of hypertensive individuals in Europe showed that bread accounted for about one-fourth of all daily salt intake and was one of six foods shown to be associated with urinary sodium (50).

The discussion concerning salt in grain-based foods may help explain the variability seen in studies linking grains and blood pressure. Although one might deduce that with this food group contributing so much sodium in the diet, there would be a consistent blood pressure-elevating effect, this is not the case. These data highlight the ongoing debate about the role of dietary salt overall and the role of salt in grain-based foods in particular in modulating blood pressure (51).

Relationship of CHOs, Grains, and Whole Grains to MetS

MetS

MetS is described by a constellation of conditions that includes elevated blood pressure, visceral obesity, elevated blood lipids, and impaired glucose tolerance. MetS generally stems from the combination of an atherogenic diet, sedentary lifestyle, and overweight or obesity. The constellation of symptoms represents a significant risk for developing diabetes and CVD and increases mortality rates from 20 to 80% (58). It has been estimated that 30–40% of the adult population over the age of 65 worldwide has MetS (59), although incidence varies by ethnicity, country, age, etc. No single diet is currently recommended for individuals with MetS; however, epidemiological studies have shown the Mediterranean, DASH, and New Nordic (60) diets to be beneficial. Whole grains and dietary fiber are some of the many dietary components common to these dietary patterns, which also include fruits, vegetables, dairy, calcium, vitamin D, mono-unsaturated fatty acids, and omega-3 fatty acids (61).

The discussion on MetS will build on the previous review on obesity (4), especially visceral obesity, and on the earlier discussion of blood pressure and will look at these in concert with impaired glucose tolerance and elevated blood lipids and the evidence from dietary patterns.

CHOs and MetS

As with obesity, the amount of CHO in the diet required to prevent or treat MetS is the subject of much debate. High CHO intake has been shown to increase the risk of MetS in some studies, but not in others. For example, in a cohort from northern China, the quartile ingesting the highest amount of total CHO, compared with the lowest, had triple the risk of hyperlipidemia and more than double the risk of MetS (62). Starchy CHO foods were strongly linked to MetS, while other CHO-rich foods were not. Similarly, high CHO intake also was associated with a nearly threefold increase in risk of MetS in low-income men over the age of 60 in Malaysia (63). A Thai national survey documented an association between high CHO intake (especially high consumption of glutinous rice) and increased risk of MetS (64). The authors postulate that the consumption of high-GI glutinous rice elevated triglycerides and lowered

HDL cholesterol. However, the same study showed that those with a high intake of meat products were more likely to have symptoms associated with MetS, including elevated blood pressure, elevated fasting blood glucose, and abdominal obesity. Intakes of CHO much higher than recommended (only 5% of energy from fat) for subjects in the Korean NHANES survey ($N \approx 34,000$) also increased the risk of MetS (65).

Gender, physical activity, body mass index (BMI), and dietary fiber content all appeared to modify the effect of high CHO intake on MetS risk. For example, in Korean adolescents, high CHO and rice intake and glycemic load (GL) were associated with increased blood lipids in girls, but with reduced HDL cholesterol levels in boys (11). In boys high GL also was significantly associated with increased fasting glucose levels.

In a national Thai survey (66), the adverse effect of high dietary CHO intakes on MetS was lower among those who were physically active and higher among those who were sedentary. Among participants in the Korean NHANES survey, high CHO intake increased risk of MetS, but only



among those who had BMIs $> 25 \text{ kg/m}^2$ (67). Another review observed a detrimental effect of a high CHO diet on MetS, but only when the CHO foods were low in fiber and had a high GI (68).

No effect of CHO intake on MetS was shown in some cohorts. For example, in the Whitehall II study of more than 5,000 British men and women, no dietary component was related to MetS (69). Similar findings were observed in adult Iranian women and older Brazilian women, in that CHO intake was unrelated to risk of MetS (70,71). Neither CHO nor GI was related to MetS in obese subjects in the DiOGenes study (72).

Low-CHO diets have been shown in some studies to elevate MetS risk because of their complement of high-fat, energy-dense foods (73). For example, Japanese

diabetics choosing a low-CHO diet were at higher risk of having more MetS risk factors (74). Although some support the argument that diets that somewhat or severely limit CHO may be useful in treating diabetes and MetS (75), there seems to be no clear answer regarding an optimal macronutrient mix (76).

Dietary Fiber and Whole Grains and MetS

Diets low in dietary fiber are associated with increased risk of MetS (77). The role of dietary fiber often not only involves the fiber itself, but also involves the dietary fiber complex of the bran and its attached phytonutrients.

Dietary fibers, specifically some viscous fibers such as β -glucan, are associated with lower risk of MetS. A recent review showed how variables linked to MetS, including appetite control, glucose control, hypertension, and gut microbiota composition, are impacted by β -glucan (78,79). The data supporting adequate dietary fiber in the diet to prevent and treat MetS are so convincing that dietary fiber recommendations are included in published guidelines (80).

Whole grains and minimally processed cereals appear to be associated with decreased risk of MetS, while highly processed cereal-based foods, especially grain-based desserts with high GI or added fat, are associated with higher risk (81). A number of studies have shown an association between higher whole grain intake and decreased risk of MetS and between low intake of these types of foods and increased risk (82,83). For example, in an Iranian sample population (84), the risk of having hypertension, hypertriglyceridemia, and MetS decreased dose dependently as whole grain intake increased. In like manner, the risk of having hypertension, hypercholesterolemia, hypertriglyceridemia, and MetS increased as refined grain intake increased.

Higher refined grain intake was significantly associated with increased risk of all symptoms associated with MetS in a population of Asian Indians who habitually consumed high-CHO, often marginal, diets (19,85). In fact, those in this population with very high rates of insulin resistance and type 2 diabetes mellitus (86) were in the quartile with the highest intake of refined grains and were nearly eight times more likely to have MetS than those in the lowest quartile. In the Framingham Offspring cohort, which had a lower risk of diabetes than South Asian

individuals (87), the “refined grains and sweets” dietary pattern was associated with increased risk of insulin resistance (85). In this pattern, refined grains and cereals contributed 13.3% of calories, whole grains contributed 5.3% of calories, and sweet baked foods and other sweets contributed 13.8% of calories. In the dietary pattern described as “fruit, reduced fat dairy and whole grains,” refined grains contributed 11.3% of calories, whole grains contributed 8.8% of calories, and sweet baked foods and other sweets contributed 4.8% of calories. It is important to note that the largest difference in food intake was not between refined and whole grains but between consumption of sweet baked foods and other sweets. In fact, diets in the refined grains and sweets pattern contained the highest percentage of energy from sugar and total fat, including cholesterol and saturated fat, and more sugar than all categories other than the soda category. The GI of the two dietary patterns was not significantly different, but the refined grains and sweets pattern had significantly lower adherence to a healthy pattern as evidenced by lower potassium levels, which is a marker of fruit and vegetable intake. Such studies attribute the increase in risk of elevated blood pressure to dietary patterns high in refined grains and sweets. However, the grouping of refined grains as breads and cereals with indulgent grain-based foods and lack of fruits and vegetables may lead to the erroneous deduction that refined grains are the cause of elevated blood pressure, when the cause may be overconsumption of grain-based desserts and underconsumption of fruits and vegetables. As a result, attribution of cause is challenging due to the confounding that results from bundling staple grain-based foods with grain-based desserts and to the lack of other important components in the diet.

The effect of refined grains on MetS risk is inconsistent among epidemiological studies. Refined grain intake in the multiethnic U.S. Atherosclerosis in Communities cohort was not related to MetS risk, and whole grain intake resulted in reduced risk (83). However, in a cohort from northern China, wheat and rice intakes were found to be risk factors in MetS. In this study both cereals were part of the grouping called “starchy CHOs,” and these were associated with increased risk of MetS (62).

Intervention studies that replaced some whole grains with refined grains produced

more consistent findings. For example, in a study of 50 overweight and obese subjects with increased waist circumference, substitution of whole grains for refined grains had a modest effect on markers of inflammation, lipid levels, and other measures associated with MetS (88). Especially in individuals with prediabetes, replacement of refined grains with whole grains helped to normalize blood glucose. Similarly, in an Italian cohort substitution of refined grains with whole grains reduced postprandial insulin and triglyceride responses (89). In overweight, postmenopausal Mexican women, elimination of high-energy refined grain-based foods increased the probability of having normal fasting glucose (90).

Specific Grains and Grain-Based Foods and MetS

Bread and Pasta. Bread and pasta are major sources of CHO and wheat in most Western diets. Therefore, studies showing the benefits or risks of CHO and grain-based foods in these cohorts would show primarily the effect of wheat. Further, for many adults bread and pasta would make up a significant dietary contribution. Therefore, studies showing the benefits of whole grains in many Western cohorts would show the benefits of wheat-based foods (91).

With regard to MetS, however, the role of these foods is unclear. It is known that bread as part of a balanced dietary pattern is associated with lower risk of MetS (92). So, if a food is associated with higher risk, it is hard to determine whether the effect is due to the specific food, such as bread, or to the overall dietary pattern. What has been documented is that in more than 5,000 French adults, bread, as well as dairy, intake was inversely related to the frequency of MetS in men, but not in women (93). Men who ate more than 50 g of bread/day had at least a 40% lower prevalence of MetS (93). However, when patterns were assessed, as occurred in the Malmo Diet and Cancer Cohort study, the “white bread” food pattern (8% of energy from white bread) was associated with a higher risk of several components of MetS, including higher risk of hyperinsulinemia in women and higher risk of dyslipidemia in both men and women. In contrast, there was a lower risk of central obesity and dyslipidemia with the “fiber bread” food pattern (2% of energy from fiber bread) for men (94). In the CASPIAN study (95), consumption of bread made with white (refined) flour in-

creased the risk of MetS in both boys and girls 8–14 years of age.

Thus, in some studies high intakes of bread were associated with decreased risk or increased risk in some genders, but the overall dietary pattern appears to be important. The cause is probably not bread per se, because some interventions use it as a vehicle for addition of functional foods, enhancing absorption of phenolics to reduce inflammation, and addressing problems associated with MetS (96–99).

Pasta and bread, although both are often made from wheat, frequently cause different blood glucose and insulin responses and, therefore, may have different impacts on MetS risk. In a Finnish study (100), pasta together with rye bread lowered risk of MetS more than a combination of oats, wheat, and potatoes. In a British crossover study with more than 800 subjects aged 40–65 years, those with a lower risk of abnormal glucose tolerance followed a healthy balanced diet with frequent intake of raw and salad vegetables, fruits, fish, pasta, and rice and low intake of fried foods, sausage, fried fish, and potatoes (101). A Korean study showed that the addition of instant noodles to either the “Korean traditional pattern” or the “meat and fast-food pattern” changed the patterns from having no increased risk of MetS to increasing the risk of MetS, but only for women (15). Further analysis of the patterns showed that those who added noodles and bread for breakfast also ingested more fat throughout the day (102). Hence, the role of bread and certain pasta or noodle dishes may impact the risk of MetS, but the impact appears to be modulated by gender and total diet.

Barley, Oats, and Rye. Barley (103), oats (104), and rye (34,98) are all associated with reduced risk of symptoms associated with MetS, not only because of their dietary fiber contributions, such as β -glucan, but also because of their phytochemical contributions, such as avenanthramides and secoresorcinols. A Finnish intervention study compared a diet with about one-third of the calories delivered by rye bread and pasta to one delivering the same number of calories from a combination of oats, wheat, and potatoes. The results showed that the rye combinations improved insulin and blood glucose more than the other combination in subjects with risk factors for MetS.

Rice. Analysis of data showing the effects of white rice on MetS produced mixed results. In the Iranian Tehran Lipid and Glucose Study of 1,476 adults aged

19–70 years, the relative risk of MetS was higher (RR = 1.66) for those in the highest quartile of white rice consumption compared with the lowest (105). The risk increased for participants who had central obesity, were sedentary, who consumed a low-fiber diet, and for whom white rice constituted >25.6% of total energy intake. Other studies (106–108) also showed that consumption of rice and glutinous rice were associated with increasing risk factors for MetS. In Korean adolescents, high white rice intake was significantly associated with an increased risk of insulin resistance and MetS in girls, but not in boys (11). However, the effect of rice appeared to be related to the balance of other foods in the diet. Findings from the Korean NHANES survey show that the risk of MetS increased among those eating white rice but only if they were not eating rice with beans or multigrains (109).

In more than 200 adults in Jaingsu, China, who were followed for 5 years, rice intake was associated with only one risk factor for MetS—hyperglycemia (38). Furthermore, in this study although rice increased fasting blood glucose, it also had some beneficial effects. A 10% increase of rice in staple foods was associated with reduced blood pressure and slightly less weight gain. The authors conclude that rice intake was not associated with the risk of MetS and that risk was associated with food patterns.

Dietary Patterns that Include CHOs and Grains and MetS

Balanced dietary patterns that include CHOs, grains, and cereals are associated with lower risk of MetS (64). Western-type dietary patterns, which are characterized by high intakes of meat or meat products, snacks, baked desserts, and sugar-sweetened beverages and which provide high amounts of saturated fatty acids and simple CHOs as added sugars, are associated with higher risk of MetS. In contrast, dietary patterns such as the Mediterranean, DASH, and New Nordic diets, which are characterized by high intakes of whole grain foods, vegetables, fruits, whole cereals, and fish, are associated with reduced risk of MetS (92). The greater the adherence to such diet plans, the more various symptoms of MetS return to normal and the lower the risk for MetS (110). Principal components analysis by Panagiotakos et al. (111) showed that in the Attica region of Greece a dietary pattern that included cereals, fish, legumes, vegetables, and fruits was inde-

pendently associated with reduced levels of clinical and biological markers linked to MetS, whereas the opposite association was found for meat and alcohol intakes. In subjects with MetS, those who followed the New Nordic diet, which included whole grains and a balance of berries, fruits, vegetables, fish, nuts, and low-fat dairy products, for 2 weeks had reduced blood pressure compared with those following the control diet, which included wheat products, dairy fat-based spread, and lower intake of fruits, vegetables, and fish (112).

The results are similar for other non-Western-type dietary patterns. For older Chinese adults two dietary patterns—the “traditional food pattern,” consisting of vegetables, fruits, rice, pork, and fish, and the “soybean, grain, and flour food pattern”—were associated with end points that would reduce risk of MetS. The other two patterns, the “fast and processed food pattern” and the “dairy and animal food pattern,” were associated with increases in factors contributing to MetS (13). The mixing of beans and rice was important in reducing the risk factors for MetS in a study of Korean adults (113).

Similarly, the “balanced Korean diet,” a typical Korean diet of rice and kimchi (a spicy, pickled cabbage dish) supplemented by a variety of foods, not only lowered the risk of elevated blood pressure in men and women by >40%, it lowered the risk of hypertriglyceridemia in men and MetS in women by >30% (17). On the other hand, analysis of the Korean NHANES survey data for the “unbalanced Korean diet,” a diet characterized by high intakes of CHO and sodium and little food variety, showed it was associated with a higher risk of elevated blood pressure and MetS in South Korean women.

Grains and Whole Grains and MetS—A Summary

Refined grains and CHOs may be associated with increased risk of MetS, but not all studies show this association. In fact, some studies show that consumption of wheat breads and foods prepared with other grains reduce the risk of MetS, whereas low-CHO diets increase the risk of MetS. What is clear is that adequate dietary fiber intake and healthy dietary patterns that include the right mix of CHOs, grains, whole grains, and other dietary components decrease risk of MetS and its components. Certain whole grains, such as rye, may be especially beneficial for those with MetS.

In short, it is difficult to attribute MetS to high CHO or grain intake, high saturated fat intake, or inadequate intakes of other nutrients. Dietary patterns that are high in fat and low in dietary fiber and whole grains can be problematic in terms of preventing and managing MetS. Inclusion of dietary CHOs, balanced with respect to type and amount, as part of diets containing other recommended components is fundamental to reducing the risk and management of MetS. The key appears to be dietary patterns, such as the DASH, New Nordic, or Mediterranean diets, which provide all the food groups in an optimal balance and deliver adequate levels of nutrients.

Relationship of CHOs, Grains, and Whole Grains to Diabetes and Its Treatment

The role of dietary CHOs in preventing and treating diabetes was discussed well before the discovery of insulin nearly 100 years ago. Reviews by diabetes associations and professionals from around the world suggest that consumption of CHOs be managed rather than eliminated (114–116). However, there is much discussion about the amount and type of CHOs recommended for preventing type 2 diabetes mellitus (T2DM) and treating both type 1 diabetes mellitus (T1DM) and T2DM.

CHOs and Diabetes

Data from prospective cohort studies suggest that the percentage of CHO in the diet does not appreciably influence diabetes risk (117,118). In the U.S. Nurses' Health Study, with more than 70,000 participants, higher CHO intake was not related to increased risk of diabetes (119). However, higher starch intake was associated with increased risk in the Nurses Health Study, but not in postmenopausal women in Iowa or in the Women's Health Study (120–122). Also, in a subcohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), digestible CHO intake, which would include starch, was not associated with incident diabetes in either men or women (123). In fact, in the EPIC cohort (124) CHO intake was associated with lower risk of T2DM, but the association was attenuated by controlling for lifestyle and dietary confounders, including waist circumference and dietary fiber intake. It appears that CHO by itself is not associated with increased risk.

The combined amounts of CHO, fat, and fiber consumed appear to be important. An early study of the effects of high-fat, low-CHO diets showed that they were associated with increased risk of T2DM (125). More recent studies have reported similar findings. For example, for the 20,000 participants in the Chinese NHANES survey, high-fat, low-CHO diets were associated with higher incidence of T2DM than were traditional high-CHO Chinese diets (126). In the U.S. Male Health Professionals' Follow-Up Study ($N \approx 40,000$), those following low-CHO diets high in animal fat and protein were almost 75% more likely to develop T2DM than those who followed a more moderate diet (127).

Dietary Fiber and Diabetes

Dietary fiber content is one aspect of CHO quality that modifies T2DM risk. Diets rich in dietary fiber, especially cereal fiber, appear to reduce the risk of T2DM. Data from prospective cohort studies demonstrate an inverse association between dietary fiber from cereal products and T2DM risk (128). Compared to fruit fiber, cereal fiber showed a stronger inverse association with diabetes risk (119). Data on black U.S. women ($N = 59,000$) show that cereal fiber was associated with reduced risk of T2DM; this inverse association was much stronger for those with BMIs < 25 (129). Data from the Nurses' Health Study show that cereal fiber and starch/cereal fiber ratio were critical for favorable levels of the T2DM risk factors adiponectin and C-reactive protein (CRP) (118,119,128). In a meta-analysis, 13 of 16 observational studies showed an inverse relationship between dietary fiber intake and these markers of inflammation (130).

Glycemic response, usually measured as GI or GL, is another aspect of CHO quality that may modify T2DM risk. A meta-analysis of prospective studies shows that low-GI and -GL diets, compared with diets with higher GI and GL, were associated with lower risk of T2DM (118,131, 132). However, the effect of GL alone was small, with those subjects following diets in the highest quintile of energy-adjusted GL showing a 10% higher risk of T2DM. Those who consumed a diet that was both high in GI or GL and low in cereal fiber had an $\approx 50\%$ higher risk of T2DM (132).

The effect of GI and GL on diabetes is modified not only by dietary fiber intake,



but also by gender, obesity, and other dietary components. In the Japan Public Health Center-based Prospective Study, in which diets were high in CHO, particularly from white rice, the relationship between GI and GL and diabetes was affected by body weight and gender, as well as diet composition (133). Both GI and GL were positively associated with the risk of T2DM among women, and the relationship was stronger for women with BMIs < 25 , as was observed in black U.S. women (129,131). The fat content of the diet pattern mattered, but its impact varied by gender. In women, diets low in GI and high in fat were associated with lower risk than for those women following a diet with low-GI and lower total fat intakes. In men, high dietary GI together with high fat intake was positively associated with risk of diabetes (133). In the Nurses' Health Study, consumption of moderate amounts of alcohol attenuated the effect of GL on diabetes risk (134). In a cohort of black U.S. women, GI was positively associated with risk of diabetes, with an incident relative risk for the highest versus the lowest quintile of 1.23. The impact of a high-GI diet was greater in women with a BMI < 25 (129).

Some studies show no relationship between either dietary GI or GL and incident T2DM. In the eight country subset of the EPIC cohort (123) and the more than 7,000 white Britons in the Whitehall II study, neither high dietary GI nor GL was associated with increased risk of incident diabetes (135). The lack of consistency among findings from various cohorts may be due to the high variability of the GI measure and the very difficult problem of assigning GI and GL to foods in a food frequency survey. Further, diet

quality can vary markedly with differences in GI and GL, and all of these variables can impact T2DM risk (136,137).

Grains and Whole Grains and Diabetes

Epidemiological studies suggest an inverse association between the intake of whole grains (including bran) and risk of T2DM (138). For example, a recent systematic review and meta-analysis of 16 prospective cohort studies shows that the consumption of 3 servings of whole grain/day was associated with a 32% reduced risk of T2DM (118). Further analyses showed the same protective association for whole grain bread, whole grain cereals, wheat bran, and brown rice (139). Similarly, analyses by de Munter et al. (140) showed the same relative protection for whole grains and bran in the diets of women in the Nurses' Health Studies I and II. In a large systematic review and meta-analysis, Aune et al. (141) found an inverse dose-response relationship between whole grain consumption and incidence of T2DM in postmenopausal women. However, in the Women's Health Initiative Observational Study ($N = 72,215$), the inverse association observed between high whole grain intake and reduced risk of incident T2DM was attenuated after adjustment for dietary fiber (142). This finding emphasizes the importance of dietary fiber intake in preventing T2DM.

Studies assessing associations between refined grain intakes and risk of T2DM report mixed results. In their meta-analysis Aune et al. (141) showed that refined grains had an RR = 0.97, indicating that risk of T2DM was neither increased nor decreased. In the Atherosclerosis Risk in Communities (ARIC) cohort (880 middle-aged adults), analyses of dietary patterns showed that the intake of low-fiber breads and cereals was one factor associated with increased risk of insulin resistance and T2DM (143). It may be that dietary fiber and resistant starch intakes are key factors because replacing refined grains with whole grain appeared to help protect against T2DM (144).

Specific Grain-Based Foods and Diabetes

Breads and Cereals. Whole grain breads, whole grain cereals, wheat bran, and brown rice all were associated with lower risk of diabetes in a systematic review and meta-analysis of cohort studies

of postmenopausal women (136). Breakfast cereal intake also was associated with a 37% reduced risk of T2DM in the Physicians' Health Study cohort of more than 20,000 men (145). The inverse association between cereal intake and T2DM became stronger when only whole grain breakfast cereal was considered. Studies of more than 4,000 9–10 year old children in the United Kingdom showed that those eating a high-fiber breakfast cereal had lower insulin resistance than those eating other breakfast product types. Further, the children had more favorable T2DM risk profiles (146). A recent evidence-based review gave a B grade (graded on a scale of A [can be trusted] to D [weak, apply with caution]) to evidence linking consumption of whole grain or high-fiber breakfast cereals to a lower risk of diabetes (147).

Six dietary factors, two of which were oatmeal and rye bread consumption, were used to measure adherence to the New Nordic Diet as assessed in 57,053 Danish men and women. Those with a high rate of adherence had a 25% lower risk of T2DM than those with poor adherence (148).

Rice. A few studies have shown that consumption of white rice was associated with increased risk of T2DM (149,150). One study only showed that increased risk occurred, but only in women (151). Further, modeling studies predict that the replacement of white rice with brown rice would be associated with a 16% decreased risk of T2DM (149).

In terms of risk of mortality due to diabetes, consumption of dietary fiber and ready-to-eat breakfast cereals was associated with lower mortality from all causes and specific causes, including diabetes (152). Whole grain and cereal fiber intakes were associated with lower risk of death from diabetes in the more than 360,000 subjects in the NIH-AARP cohort (153).

CHOs, Grains, and Whole Grains and Treatment of Diabetes

CHOs. The causes of T2DM and T1DM are very different, but the recommendations regarding dietary treatment are closely aligned. Because CHOs impact postprandial blood sugar, counting CHOs is critical to keep blood glucose levels consistent. Counting is based on the principle that 15 g of CHO equals 1 serving (or choice) of CHO. Counting enables the amount of CHOs ingested to stay the same while allowing consumption of a wide variety of CHO-based foods without

wide swings in blood glucose and, thus, ideally keeping glycated hemoglobin A1c (HbA1c)—a major marker of the degree of blood glucose control over time—at levels that are as low as possible. Advanced CHO counting is useful for determining insulin dose and is used by those with an insulin pump or who regularly inject insulin. In a recent review, this latter method was shown to result in a trend toward slightly lower HbA1c on average (154).

For those with diabetes, some recommend following diets that minimize dietary CHO to manage fasting blood glucose and other measures. However, in a meta-analysis of 19 RCTs of overweight subjects (3,209 participants), low-CHO diets compared to those with recommended CHO levels showed no differences in mean fasting blood sugars at any point measured during the 24 months of the study (155). Similarly, studies, including a meta-analysis of 53 studies of diets for those with diabetes lasting at least 4 weeks, found no significant differences between diets deemed to be low CHO (<45 g/day) and those that included more CHO with respect to metabolic markers and glycemic control (156,157). In the year-long Canadian Trial of Carbohydrates in Diabetes—a controlled trial looking at 62 individuals with T2DM whose dietary control was deemed to be good—the percentage of energy from CHO (39–55%) did not affect most markers of T2DM, including HbA1c (158).

Despite these findings, however, some continue to recommend a lower percentage of energy from CHO as part of a diabetic diet, especially if weight loss is desired. For example, Diabetes UK suggests that low-CHO diets can lead to improvements in HbA1c and reductions in body weight in the short term (<1 year) (159). However, they note that weight loss may be due to reduced calorie intake and not specifically result from CHO restriction. Further, they note a lack of evidence related to long-term effects of low-CHO diets (159). Thus, this organization and others such as the American Diabetes Association recommend CHO counting (160).

GI and GL. Data both for and against the use of GI and GL as part of dietary management of diabetes exist. The largest of the RCTs is the year-long Canadian Trial of Carbohydrates in Diabetes (155). In diabetics with good control through diet, changing the GI or GL of their diets did not impact HbA1c. In other words,

after subjects consumed a high-GI diet with 47% of energy from CHO, a low-GI diet (GI = 55) with 52% of energy from CHO, or a low-CHO diet (GI = 59) with 39% of energy from CHO, no significant difference was observed in their HbA1c. While following the low-GI diet, fasting glucose was significantly higher, but 2 hr postload glucose was significantly lower. The only documented advantage of the low-GI diet over the diet with total CHO controlled or the high-CHO diet was 30% lower CRP (158). In a review of the effects of GI and GL in the diet on management of diabetes, there were no significant differences in HbA1c and fasting glucose, but there were significantly greater drops in CRP and fasting insulin with low-GI/GL diets (161).

Although a number of studies show little difference, others show low-GI/GL diets have advantages. In a systematic review and meta-analysis, low-GI and high-GI food groups were compared (162). The low-GI food group resulted in more beneficial effects on HbA1c and fructosamine than did the high-GI food group. Similarly, in a cross-sectional study with 640 T2DM patients 28–75 years of age a high-GL diet was associated with a 2.5-fold increase in the risk of hyperglycemia and a 3-fold increase in HbA1c (163). In overweight men, insulin sensitivity increased with a diet low in GI and moderate in CHO content (i.e., low GL) (164). Thus, it appears that the findings are too variable to make a recommendation for one diet over another.

Dietary Fiber, Resistant Starch, Whole Grains, and Treatment of Diabetes

Dietary Fiber. Consumption of dietary fiber, especially certain viscous fibers, has been associated with lowering of postprandial blood glucose levels, improving blood lipid profiles, lowering markers of inflammation, increasing insulin sensitivity, and changing the gut microbiome. Therefore, adequate dietary fiber intake is recommended (GI = 63) for the treatment of diabetes (165–167). In a cross-sectional study of 640 diabetics, higher intake of dietary fiber was associated with lower risk of elevated fasting serum glucose, but not with lower risk of elevated HbA1c (160). An analysis of RCTs showed that high-fiber diets (up to 42.5 g/day), including foods rich in dietary fiber and dietary fiber supplements containing soluble fiber (up to 15.0 g/day), reduced glycated hemoglobin and fasting plasma glucose (168).

There is no agreement concerning an optimal amount of dietary fiber intake for improvement of blood glucose control. Although some recommendations suggest at least 25 g/day, studies have shown that as much as 50 g/day may be needed to improve blood glucose control (169,170). In response, some argue that such dietary fiber intakes are so far above levels regularly ingested as to be unrealistic. Supporting this position, two systematic reviews found little evidence that dietary fiber significantly improves glycemic control at levels usually ingested (116,171). However, other studies have shown some lowering of preprandial glucose and HbA1c with dietary fiber intakes under 50 g/day, especially if the diets were plant based (172,173). Despite the ongoing controversy, various health professional organizations recommend that people with diabetes consume at least the amount of dietary fiber and whole grain recommended for the general public, especially because dietary fiber intakes are associated with lower all-cause mortality in people with diabetes (174,175).

There is general agreement that various cereal fibers in the diets of those with T2DM are beneficial and that consumption of a mix of fiber types appears to be advantageous (176). In an intervention study using cereal fibers, the insulin sensitivity of those assigned to follow a diet with 52% of energy from CHO and 43 g of cereal fiber/day was 25% better than the insulin sensitivity of those assigned to follow diets with lower fiber (14 g/day) or more protein intake (177).

Whole Grains. Results of a meta-analysis of 45 epidemiological studies and 21 RCTs show that fasting glucose was lower in subjects consuming between 48 and 80 g of whole grain/day compared with consumers who rarely if ever ate whole grains (178). T2DM subjects with a gene polymorphism putting them at high risk showed a decrease in fasting glucose, insulin resistance, and triglyceride with the substitution of whole grains and legumes for refined rice in a high-CHO diet ($\approx 65\%$ of energy) (179).

Several whole grain components, likely acting simultaneously, promote beneficial effects in the diets of diabetics. Lowered blood glucose is attributed to several mechanisms, which include the following:

- 1) Formation of a barrier that prohibits amylases from accessing the starch
- 2) Formation of a gel that reduces the rate of amylase penetration into the

starch granules, causing a decreased rate of glucose entry into the bloodstream

- 3) Changes in the rate of gastrointestinal transit
- 4) Acting as a substrate for gut microbiota that produce fermentation products and that impact blood lipids, glucose swings, and inflammation, which helps reduce complications of diabetes

CHOs, Grains, Whole Grains, and T1DM. Diets recommended for treating T1DM are often the same as those recommended for treating T2DM. Recent data from continuous glucose monitoring highlight the complexity of postprandial glucose patterns in individuals with T1DM, showing that fat slows gastric emptying and reduces glucose in the first 2–3 hr after eating (180). Such monitoring shows that meals that are high in fat and protein require more insulin than meals that are lower in fat and protein but that have identical CHO contents. Such studies indicate that meal composition rather than total CHO content or GI must be considered. In many cases the mechanisms of food effects are the same despite the very different etiologies of T1DM and T2DM.

Specific Grain-Based Foods and Treatment of Diabetes

Breads. A number of small studies have shown that substitution of breads that have a lower GIs and more cereal fiber improve one or more factors associated with diabetes, such as insulin economy (181). Some, but not all, studies show improvements in fasting glucose and other measures of glucose response (182). For example, low-GI chapatti prepared with bran had a lower postprandial glucose and insulin response compared with chapatti prepared with refined flour (183). The response was more pronounced in diabetic subjects than in normal subjects. In several studies whole grain rye breads or breads with added fibers resulted in various improvements in markers associated with diabetes risk, including significantly lower blood glucose levels and improved glycemic parameters compared with those observed with other whole grain or refined grain breads (183).

When compared with regular white (refined) bread, breads with added guar (184) or 3 g of β -glucan (185) improved lipid profiles and insulin resistance in patients with T2DM. The type of fiber in whole grains impacts diabetes factors, and

oat β -glucan helps to modulate blood glucose. The degree of impact of β -glucan depends on properties in oat-based foods that affect the viscosity and molecular weight of the glucan when eaten (186).

Dietary Patterns. Dietary patterns have been linked not only to the prevention of T2DM, they have been studied for management of T1DM and T2DM in a variety of populations. A study of the subset of individuals with diabetes in the Korean NHANES survey revealed the importance of dietary patterns (187). The “Korean healthy pattern,” including whole grains, legumes, vegetables, and fruits, improved lipid profiles over other diets. Total CHO intake was lower in the Korean healthy pattern (69%) than in the “rice pattern,” but not as low as the 61.2% in the higher fat “bread and meat and alcohol pattern.”

A comparison of diets with low-GI, low-CHO, and Mediterranean patterns in a meta-analysis of 20 RCTs ($n = 3,073$) showed that all diets led to greater improvement in glycated hemoglobin compared with control diets (188). However, the Mediterranean diet resulted not only in slightly greater weight loss than the other diets, but also better HbA1c than the other two diets studied. A recent review suggested that patterns with overall diet quality should be emphasized to lower risk of complications and improve management of diabetes (189). Diets that promote weight loss are particularly advantageous. A 2016 meta-analysis (190) showed that the Mediterranean diet reduced the risk of MetS and diabetes and was beneficial for those with diabetes.

Two recent reviews showed that a few studies suggest intermittent fasting and ketosis are advantageous both in preventing and treating diabetes and abnormal glucose tolerance, especially for those who need to lose weight (191,192). However, many more robust clinical trials testing this hypothesis are needed before this controversial approach is adopted.

Healthy, nutrient-dense foods that provide the correct balance of nutrients, dietary fiber, and bioactive components in dietary patterns similar to the Mediterranean diet are needed. Such diets positively impact the microbiome and various metabolic pathways and reduce inflammation, elevated blood pressure, impaired glucose tolerance, symptoms of diabetes and cardiometabolic disease (193). Further, balanced diets have been shown to be effective in multiethnic cohorts, such as those in the Women’s Health Initiative, for both the prevention and management

of these disorders (194). These findings emphasize that it is a healthy pattern and not one nutrient versus another that provides the most benefit.

Conclusions

Body weight, elevated blood pressure, MetS, and diabetes appear to be best addressed and prevented by diets that enable weight maintenance and loss when necessary, that focus not on the elimination of CHOs and grains, but rather on the ingestion of foods and nutrients within tested, balanced dietary patterns. These diets would contain from 45 to 65% CHO, including high levels of the dietary fiber and phytochemicals present in whole grains. Both are associated with a lower risk of elevated body weight (4) and lower risk of hypertension, MetS, and diabetes.

Consumption of an optimal number of grains and optimal balance of whole and refined grains—and the fibers and phytochemicals they contain—as part of a balanced diet can help reduce markers of inflammation; modulate blood glucose; and positively impact factors associated with insulin resistance, risk of hyperten-

sion, MetS, diabetes, and inflammation. Although there is no universal agreement concerning a dietary strategy to prevent or delay the onset of these conditions, the data do align to suggest there are preferred dietary patterns that reduce the risk and others that increase the risk for developing these conditions. All of the preferred dietary patterns include an optimal balance of CHO, dietary fiber, whole grains, and refined grains. They are characterized by a higher intake of food groups that are generally recommended for health promotion, including protein in appropriate quantities and varieties (e.g., meat, fish, poultry, and legumes); recommended servings of fruits and vegetables; optimal sources of calcium or amounts of dairy products; an optimal mix of fats, including beneficial fats from nuts and seeds; and, finally, the enjoyment of small amounts of indulgent foods.

Patterns such as the DASH, Mediterranean, and New Nordic diets and the USDA MyPlate recommendations, as well as many others, that include balanced amounts of all macronutrients, vitamins, minerals, and phytonutrients do not eschew any food groups, including grains

and breads, meet this balance (195). Sadly, only 3–8% of Americans eat according to such patterns. Less than 4% of Americans meet the dietary fiber intake requirement, and less than 1% meet the whole grain intake requirement. Data from many other countries also show a large gap between recommended patterns and actual intakes. For many, servings are too large, and grain-based desserts and other high-calorie, low-nutrient foods provide too many calories at the expense of nutrient-rich fruits and vegetables and whole and refined grain staple foods. General diets do need improvement, but elimination of CHOs and grain-based foods will not provide the improvements needed for most individuals.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Whole Grains and Disease Prevention Part III. Cancer Risk: Overview, Breast, and Colorectal^{1,2}

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Grain-based foods, and the carbohydrates (CHOs) they contain, have been accused of promoting chronic diseases. Specifically, consumption of these foods is alleged to promote metabolic pathways that favor and enhance tumor growth. A two-part review, like those previously published in this series (1–6), will assess the roles of these foods in increasing or decreasing cancer risks. Because more than 100 types of cancer have been identified, the two-part review will assess the scientific literature with respect to the effects of consuming refined, enriched, and whole grains and the CHOs they contain, including starches, dietary fibers, and resistant starches, on the five most common cancers worldwide: breast, colon, lung, prostate, and stomach.

This first review on cancer provides an overview of the influence of diet on cancer risk and examines the roles played by CHOs and grains in breast and colorectal cancers. The second review on cancer will examine the roles played by CHOs and grains in lung, prostate, and stomach cancers. Evidence from earlier reviews in the series that addressed the roles of CHOs

and grain-based foods in inflammation, insulin resistance, and glycemic response and their effects on the microbiome (3–5) will be referenced because these factors can alter cancer risks.

OVERVIEW OF CANCER AND INFLUENCE OF DIET ON RISK

The term “cancer” describes a collection of related disorders in which cells in a specific part of the body begin to divide uncontrollably. Cancer can start in any tissue in the body and has the potential to spread (metastasize) into surrounding tissues.

Cancer incidence is increasing worldwide—a fact often cited by those who suggest that some aspects of modern lifestyles, diets, and grains, in particular, are more problematic than in the past (7–9). However, such statements, although true, do not provide a fair representation of the complete picture, because they fail to consider that both the total human population and the average human lifespan have increased greatly (Table I) (10). In actuality, age-adjusted cancer incidence rates are either flat or declining, and in developed countries, death rates due to cancer

are declining. Graphs produced by the American Cancer Society based on U.S. Mortality Volumes and Mortality Data show the trends (1930–2012) in age-adjusted cancer death rates by site for U.S. [males](#) and [females](#) (11). (Note, the graphs can be accessed online at www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2016 as part of the Cancer Facts & Figures 2016 Supplemental Data.) In the United States, overall cancer incidence trends are stable for women and declining by 3.1% per year for men (2009–2012). In addition, the cancer death rate has dropped by 23% since 1991 (11,12).

To allege that one food source or food group is the sole cause of cancers in humans seems to be an overreach because the causes of various cancers are nearly as numerous as the different types of cancers identified. For many cancers, a specific cause or causes have not yet been identified. Thirty years ago, Richard Doll and Richard Peto (13) estimated that one-third of all cancer cases could be prevented by diets that avoid overnutrition; limit the intake of red meat, animal fat, and refined sugar; and emphasize the consumption of fruits and vegetables, fish, and whole grains. Research during the intervening years has shown that these foods, as well as dietary patterns containing a balance of dietary fibers, phytochemicals, and a favorable ratio of omega-6 to omega-3 polyunsaturated fatty acids, may help protect against certain cancers (14).

Dietary patterns with consistently low intakes of fruits, vegetables, and whole grains and high intakes of alcohol and total fat may increase the risks for certain cancers (14). Despite extensive coverage in the press and some international pronouncements implicating certain foods

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Table I. Top five cancers worldwide in terms of diagnosis for both men and women^a

Rank	Cancer	New Cases Diagnosed in 2012	Percentage of All Cancers ^b
1	Lung	1,825,000	13.0
2	Breast	1,677,000	11.9
3	Colorectal	1,361,000	9.7
4	Prostate	1,112,000	7.9
5	Stomach	952,000	6.8

^a Source: World Cancer Research Fund (10).

^b Excluding nonmelanoma skin cancer.

such as red and processed meats (15) and foods high in sodium and refined CHO as sources of cancer, data linking these foods with increased risk for developing various cancers show mixed results or weak associations (16,17). A direct link between CHO intake (refined or otherwise) and cancer has been shown in some studies, but not in others (18–21). However, although studies have failed to show a consistent link between intake of grains and CHOs and obesity (4), obesity and excess calorie intake have consistently been associated with increased cancer risk (22).

Calories and Macronutrients

High blood glucose levels related to excess calorie intake and high body weight have been shown to promote inflammation and increase tumor growth rate and are associated with increased risk for a number of cancers (23,24). When looking at dietary factors associated with cancer risk using systematic reviews, assignment of a specific food, nutrient, or food group is difficult because of confounding that can occur with other components and lifestyle factors. Thus, determination of the precise relationship between the intake of specific CHO-rich foods and cancer risk must be separated from other factors impacting risk, such as excess calorie and CHO intake. Further, the metabolic state of the individual, such as insulin sensitivity and body weight, must be considered.

Body mass index (BMI) has been shown to impact cancer risk. On the lower end of the normal range, BMI can decrease or delay the onset of certain cancers. However, use of calorie restriction in human diets as both a way to prevent and treat cancer is the subject of controversy (25). Calorie restriction is thought to reduce the exposure of cells to high glucose levels, insulin, and other metabolic factors that favor tumor growth. In studies with animals, calorie restriction of 20–40% has been found to lower tumor frequency. In humans, there is evidence both from extreme deprivation diets, as seen in the Dutch “Hunger Winter” (famine experienced during the winter of 1944–1945), and from milder calorie restriction diets, as seen in Okinawa, Japan, where total energy intake averaged 20% below other Japanese diets and 40% below diets in the United States. Specifically, death rates from cancer were 30% lower among individuals living in Okinawa than in other parts of Japan (26).

While it is agreed that excess energy intake is strongly associated with the promotion of tumor growth and potential metastasis, there is neither agreement on the optimal ratio of fats to CHOs nor on the types of fats and CHOs that are beneficial. Preliminary findings suggest that diets that induce ketogenesis, such as fasting, intermittent fasting (27), or very low-CHO diets, may have antitumor activity (28). However, these diets also are linked with poor compliance and other issues.

To date, findings from epidemiological studies seem to indicate that balanced dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) or Mediterranean-type diets, may help prevent certain cancers, and balanced dietary patterns have been identified in a number of prospective cohort studies as being associated with lower risk for a variety of cancers (29,30). In terms of food groups, these balanced patterns include consumption of adequate servings of fruits and vegetables, oily fishes, legumes and nuts, and whole grain cereals and bran, with consumption of modest amounts of lean meat and poultry and low-fat dairy. The panoply of antioxidant, anti-inflammatory, and antimutagenic phytochemicals in concert with a balance of fiber and micro- and macronutrients delivered by such diets may work together to reduce cancer risk. However, the findings among studies lack consistency and often show confounding, in that those who follow healthy dietary patterns often incorporate other aspects of a healthy lifestyle that also reduce cancer risks.

CHOs, Energy, and Macronutrient Balance

CHOs and CHO-rich foods have been linked in some studies with both increasing and decreasing cancer risk. This may be due to the fact that many CHO-rich foods, especially grain-based foods, contain a variety of components—some of which can increase risk and others of which can decrease risk. For example, dietary fiber has been shown to reduce or be associated with reduced risk for some cancers (31,32). On the other hand, highly refined CHOs are associated with increased risk for some cancers. However, data supporting the latter may be significant only in cases of energy excess and obesity or when other parts of the diet are unbalanced. In instances where CHO is a major contributor to excess calorie intake, it is hard to tease out whether the resulting increase in risk is due to the calories

or to the CHOs or an interaction of the two. Because diets higher in CHO must be lower in fat, and vice versa, accurate attribution of cancer risk to either fat or CHO, rather than the ratio, remains elusive. If more studies recognized this “nutrition uncertainty principle,” health outcomes could more correctly be linked to the fat/CHO/calories ratio, especially because this background ratio potentially modifies the effects of other dietary components and also is affected by the qualities imparted by specific fats, fatty acids, and CHOs. For example, both long-chain unsaturated fatty acids and resistant starches have been associated with lower risks for many cancers.

Further, CHOs in the diet are accompanied by an array of foods, making the diet a mix of macronutrients that provide a cocktail of micronutrients and phytochemicals. This mix includes components that are carcinogens, cocarcinogens, growth promoters, and anticarcinogens, as well as an array of other components that can impact health outcomes, including cancer risk. For example, whole grains contain dietary fiber with components embedded in the grain cell walls and that have the capacity to alter metabolism and cancer growth rates (33).

Theories Regarding CHOs and Cancer Risk

The ability of available CHO to raise blood glucose is theorized as a possible mechanism by which CHO can increase cancer risk. One postulated mechanism involves the insulin pathway, whereby ingestion of readily available CHO causes a rapid rise in blood glucose, which in turn provokes insulin secretion. High fasting blood glucose and insulin increase the availability of insulin-like growth factor 1 (IGF-1), a component that can increase cell proliferation and enable tumor growth (34). Circulating IGF-1 can inhibit synthesis of hormone-binding globulin, leading to higher circulating levels of free estrogens and androgens, which can increase the risk for cancer, especially in individuals who are responsive to steroid hormones. Figure 1 shows how lowering energy intake can lower levels of circulating glucose, insulin, and IGF-1 and can lower inflammation and, thereby, decrease cancer risk and progression. Buyken et al. (35) have suggested a second possible mechanism based on data linking intake of excess CHO, especially in overweight or insulin resistant individuals, to a chronic state of low-grade inflammation. Their

review of the data found that inflammatory markers such as adipokines released by visceral adipose tissue favor tumorigenesis (35).

A third possible mechanism has been theorized to be due to changes that may occur with some types of food processing. For example, refining grain by removing the bran and dietary fiber may increase glucose availability. Further, dry-heating CHO-rich and grain-based foods can produce components such as those produced in the Maillard reaction—acrylamide and advanced glyceric endpoints (AGEs)—some of which may increase cancer risk and others of which may decrease risk (36).

A fourth possible mechanism concerns aspects of CHO quality. It has been suggested that the amount and type of dietary fiber, glycemic index (GI), and glycemic load (GL) all influence cancer risk. In some, but not all, studies dietary fiber has been associated with a lower cancer risk. Although a recent consensus statement suggests there is agreement with respect to the body of evidence regarding cancer risk and GI and GL (37), the findings are variable, and as a result, the consensus statement may not fully reflect either the state of the science on the topic or conclusions drawn by other deliberative bodies. For example, the 2010 Dietary Guidelines Advisory Committee (38) reviewed the evidence from 20 prospective longitudinal observational studies and found that only 1 study showed a weak positive association between cancer risk and GI and only 2 studies showed a positive association with GL. The committee concluded, “Abundant, strong epidemiological evidence demonstrates that there is no association between GI or GL and cancer.” These findings, as well as those from studies such as a prospective cohort of more than 500,000 people, suggest there is no association between GI and GL and any type of cancer, at least in those over 50 years of age (39).

Dietary Fiber

Dietary fiber and the phytochemicals that are part of the dietary fiber complex have long been associated with reduced risk for many types of cancer, and studies continue to indicate that high dietary fiber intake is associated with reduced risk for some cancers. For example, those in a cohort followed for 32 years who ingested diets that were consistently higher in dietary fiber, in combination with other healthy lifestyle and dietary components, had a 37% lower risk for developing can-

cer (40). A recent meta-analysis of 15 prospective cohort studies showed that those in the highest versus lowest categories of dietary fiber intake reduced their cancer risk by 14% (41).

Such findings translate into dietary guidelines from most government and health-promotion bodies that recommend consumption of diets high in dietary fiber for modulation of cancer risk, especially those of the gastrointestinal tract (38,42). However, not all fiber types have the same effects, so even within a particular food group or component the actual effects may be different. Further, the impact of a dietary fiber can be affected by processing and other dietary components and lifestyle factors (43). Components embedded in whole grains and the dietary fiber matrix also may have an impact. Many whole grains deliver a total antioxidant concentration that is comparable to fruits and vegetables (44). In some cases, cereal fibers and their components, such as β -glucan from oats and barley and resistant starches and arabinoxylans from wheat and other grains, may have special benefits, and in other cases, different dietary fiber types or a combination of fiber types are needed to provide beneficial effects. As with all components in a diet, balance is key (43).

Grains, Whole Grains, and Dietary Patterns

Consumers ingesting the highest amounts of whole grain are consistently shown to have a lower risk of developing certain cancers (45). The bulk of the evidence comes from observational studies, but there is also some evidence from interventional studies that suggests a number of potential mechanisms (46). Inverse associations occur despite the fact that the

bran and outer layers of whole grain may contain heavy metals if they are grown in soils contaminated with metals such as arsenic and cadmium (class 1 carcinogens) (47).

There is increasing evidence that balanced dietary patterns, such as Mediterranean- or DASH-type diets, are associated with reduced risk for several cancers and reduced cancer mortality (48). These diets are noted for their healthy balance of all foods groups, including fruits and vegetables, legumes, grains, and whole grains. Observational studies suggest that compliance with such diets is associated with reduced risk of overall cancer mortality, as well as a reduced risk of incidence of several cancers (especially cancers of the colorectum, upper digestive tract, breast, stomach, pancreas, prostate, liver, head, and neck) (42,49).

CHOs and Diet in Early Life

Because cancer is a disease that may take years to develop, some suggest that diet throughout life, especially during periods of rapid growth, affects risk. Thus, a mother’s diet during pregnancy and an individual’s diet during early life can be important because of the possible effects on growth hormone, IGF-1, insulin resistance, and body fatness (50). Prolonged breastfeeding and maternal diet, including vitamin intake during pregnancy, may reduce the risk of cancer for offspring (51).

Information on diets followed in early life are often constructed by asking people what they ate at an earlier age and, therefore, is subject to recall bias. The best data come from studies such as the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study on youth (ages 9–15 years), because the data

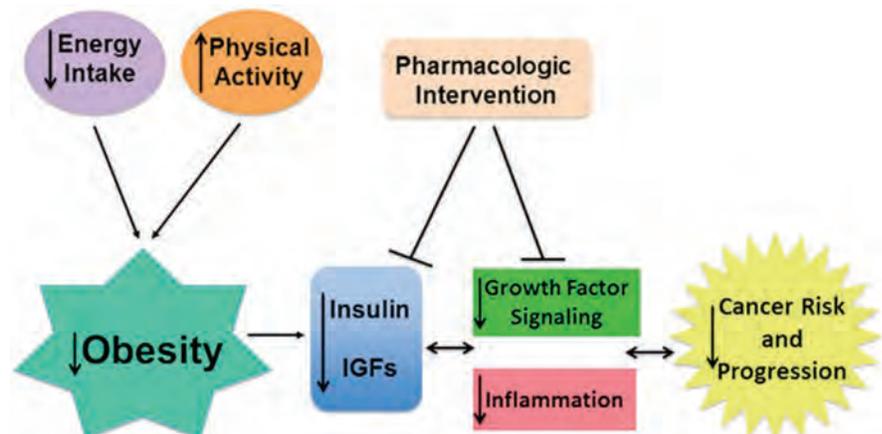


Fig. 1. Impact of calorie restriction on cancer risk and growth. IGFs = insulin-like growth factors.

are from two 3 day weighed dietary records collected during these ages. The data collected were then matched to blood samples drawn in early adulthood. Analysis showed that higher intakes of CHOs, higher dietary GL, or lower intakes of whole grain during puberty were linked to increases in some inflammatory markers during adulthood (52). Interestingly, dietary GI, added sugar, and dietary fiber intakes were not independently associated with the inflammatory marker IL-6 (52,53). Because diet may alter factors that impact cancer risk, more data and a better understanding of the effects of specific nutrients, foods, and diets consumed during various critical points in the lifecycle are needed.

Building on this background information, the next two sections will look at the role of grain-based foods and the CHOs they contain in the risk for two of the most common cancers—breast and colorectal.

BREAST CANCER AND INFLUENCE OF DIETARY COMPONENTS

Breast cancer is the most common type of cancer diagnosed in women worldwide. Body weight, obesity, alcohol intake, diabetes, and exercise all are thought to impact its risk, and diet is thought to play a role in both promoting and inhibiting its development (54–56). Total energy intake is of prime importance. However, single nutrients, macronutrient ratios, specific foods and food groups, and dietary patterns all influence breast cancer risk (57), including intakes of

- 1) Specific types of fat
- 2) Meat (due to the potential adverse effects of some heterocyclic amines formed during high-temperature cooking)
- 3) Alcohol
- 4) Iron

Several of these components are associated with increased risk because of their

role in promoting oxidative stress, DNA damage, and lipid peroxidation (48).

Intakes of vitamin D and folic acid, dietary fiber, phytoestrogen, and phytochemicals are associated with decreased risk. Except for vitamin D, grain-based foods contribute all of these protective components to the diet. However, grain-based foods also contribute dietary CHO, and excess consumption of CHOs, especially indulgent ones, can be a source of excess calories, saturated fats, and acrylamide, a carcinogenic compound produced by the interaction of CHOs and proteins, especially asparagine, during high-temperature heating (Fig. 2). Grain-based foods also are a source of iron, which may have an impact on cancer risk.

Although total CHO consumption and/or consumption of specific CHOs are thought to be associated with breast cancer risk, the reality is that most studies show either a weak or no association. In a prospective study of 12,273 postmenopausal Australian women (58), dietary factors with the potential to influence the insulin pathway and, in turn, impact breast cancer growth were assessed. None of the CHO components tested (total CHO, dietary fiber, GI, and GL) were associated with increased overall breast cancer risk. However, when these components were parsed by specific estrogen responsiveness of the cancer in this study (58) and by elevated body weight or waist circumference, low levels of physical activity, or type of CHO in other cohort studies (59–62), some of these components were significant. For example, in a cohort of more than 67,000 French women, CHO intake was associated with increased risk for breast cancer for those women with the largest waist circumference and for those with estrogen receptor-negative (ER–) cancers (62). A case-control study in Korea showed no association between breast cancer and CHO intake but did show that CHO type had an effect on breast cancer in postmenopausal, overweight women (63). The inconsistent re-

sults among studies makes an overall assessment of the role of CHO in breast cancer difficult. Nevertheless, when the data are viewed in total, both the 2013 International Agency for Research on Cancer (IARC) (64) assessment and a systematic review published in 2015 (65) found no association between dietary CHO and breast cancer risk. There are suggestions, however, that high CHO intake may interact with lifestyle factors, menopausal status, and hormone receptor status (66).

Data concerning the influence of glycemic response on breast cancer risk also show variability. In the large prospective U.S. National Institutes of Health–American Association of Retired People (NIH-AARP) cohort of more than 500,000 people aged 51–70 years, neither GI nor GL was related to breast cancer risk (39). Studies assessing the role of GI and GL in risk reconfirmed findings that total CHO intake did not influence breast cancer risk but do not provide a clear picture of the role of GI and GL. Even the results of studies conducted by the same authors and in the same country with different cohorts fail to show congruence.

In the prospective Hormones and Diet in the Etiology of Breast Tumors Study (ORDET study) of women in northern Italy, total CHO intake was not associated with increased risk of breast cancer (67). However, both consumption of foods with high GI and GL were associated with increased risk. In a study of 7,749 volunteers in the Italian cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, neither CHO by itself nor GI impacted breast cancer incidence, but consumption of high-glycemic CHO was associated with higher incidence of breast cancer (67–69). In a study of French women, dietary intake of CHO was not related to breast cancer risk, but GI and GL increased risk, although only in overweight women or those with a large waist circumference. In addition, high GL was related to increased risk for those with ER– breast cancer (62). In findings from the total EPIC cohort of more than 330,000 women throughout Europe (70), there was no association with CHO, GL, or GI. However, when the cohort was divided by menopausal status and estrogen receptivity of the tumor, there was an association. Thus, for postmenopausal women with diets high in CHO and GL there was an association with increased breast cancer risk if their cancers were

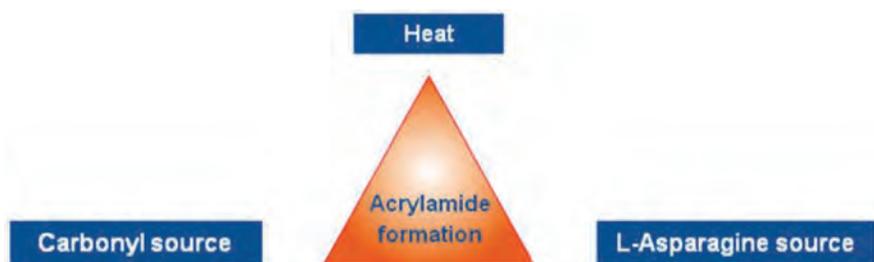


Fig. 2. Formation of acrylamide, a carcinogenic compound, by the interaction of carbohydrates and proteins during high-temperature heating.

either ER- or double hormone-receptor negative (e.g., estrogen-/progesterone-receptor negative cancer [ER-/PR-]). Similar results were reported in a Chinese case-control study (71). In addition, for the 49,613 Canadian women enrolled in the National Breast Screening Study, GI, GL, total CHO, and total sugar intakes were not associated with breast cancer risk for the cohort viewed as a whole (72). However, parsing the cohort by menopausal status revealed associations were in different directions. For premenopausal women in the highest versus the lowest quintile of GI, there was a trend toward a lower relative risk (RR = 0.78), but for postmenopausal women risk increased significantly (RR = 1.87).

Analysis of a number of studies, either as part of meta-analyses or systematic reviews, does not reduce the confusion (73,74). Meta-analysis of 10 prospective cohort studies (15,839 cases and 577,538 participants) showed GI to be significantly, albeit weakly (RR = 1.08), related to increased risk of breast cancer (72). There was no link with dietary GL, and results were not modified by variables such as menopausal status. Systematic review also yielded an RR of 1.08 for GI and breast cancer. However, the wide variability in cohorts (e.g., age, ethnicity, menopausal status, BMI, waist circumference, exercise, estrogen receptivity of tumor, and background diet, including amount of dietary fiber consumed) make it difficult to reach any firm conclusions (73, 74). A further contributing factor may be the challenge of accurately determining dietary GI and GL, especially from food frequencies (75–77).

Diet in early life is thought to influence breast cancer risk, and a link has been shown between intake of dietary fat and risk (78). However, CHO intake in early life was not associated with increased risk of breast cancer for women in the Nurses' Health Study II (79). In that cohort, estimated GI and GL of diet and insulin load in adolescence or early adulthood also were not associated with risk for breast cancer (79).

Dietary Fiber

The results of studies assessing dietary fiber and its effect on breast cancer risk are mixed. One systematic review published in 2015 found no association between dietary fiber intake and breast cancer risk (65). In analyses of data from the large EPIC cohort (80), total dietary fiber intake was inversely associated with a small

reduction in the risk of breast cancer, but the association was significant only for vegetable fiber intake, not for fibers from fruits, cereals, or legumes. In contrast, other studies found the opposite. Specifically, both total dietary fiber and cereal fiber were associated with slightly reduced risk for some types of breast cancer, in certain populations and for certain types of fiber (81–86). Parsing the fibers by solubility did not produce a clearer picture.

In a meta-analysis of 16 prospective studies, there were very weak inverse associations between intakes of total dietary fiber, soluble fiber, and insoluble fiber and breast cancer risk (84). Soluble fiber showed the strongest inverse association. Among the more than 185,000 postmenopausal women in the NIH–AARP Diet and Health Study, dietary fiber and soluble fiber intakes were inversely associated with breast cancer risk (RR = 0.87 and 0.83, respectively). For total dietary fiber, the inverse association appeared to be stronger for ER-/PR- tumors (RR = 0.56). Thus, types of dietary fiber and their source(s) may impact breast cancer risk.

It is possible that cancer risk is reduced only when dietary fiber intakes reach threshold levels or are made up of a certain mix of fiber types. For example, in a Nordic population a high intake of cereal fiber, especially from rye, was associated with a 40% reduction in breast cancer risk. This might be attributed to dietary fiber or cereal fiber, but also might be due to the antioxidants, lignans, and resorcinols found in rye and other whole grains. The resorcinols in rye and whole wheat are metabolized by the gut flora into mammalian estrogens, such as enterolactone, which are thought to protect against breast and other hormone-dependent cancers (87). Alkylresorcinols found in whole grains are good biomarkers of consumption of rye and whole grain wheat and their brans. These compounds are thought to reduce breast cancer risk because they affect the enterohepatic circulation of estrogens (88). Finnish women with breast cancer were found to have a significantly lower dietary fiber intake and lower plasma and urinary levels of metabolites of alkylresorcinols than healthy control subjects (88).

It is noteworthy that the median fiber intake in the top quintile of the Nordic cohort was 25.9 g/day, with dietary fiber ingested from a mix of rye and oats, as well as other grain and plant sources (87). Thus, the median intake for the highest quintile of consumption corresponds with

the minimum amount of dietary fiber recommended by most government and health-promotion bodies worldwide. In this population, women following diets with a combination of high-fiber and low-fat foods had the lowest breast cancer risk.

Total dietary fiber, soluble fiber, and insoluble fiber intakes during puberty and young adulthood were estimated in a retrospective food recall for women in the Nurses' Health Cohort II. For women in the quintiles with the highest fiber intakes during their early years, intake was associated with a 19–25% lower risk of invasive breast cancer later in life (89).

Cereal Foods

Despite evidence that whole grains may be associated with reduced cancer risk, some authors in the popular press and bloggers suggest that all grain-based foods, especially those made from refined grains, are associated with increased risk for a variety of cancers, including breast cancer. The scientific data, however, provide a much more mixed picture. In fact, the data suggest that refined, enriched, and whole grains, as well as grain-based foods, are both risk reducers and risk enhancers.

Charges that refined grain-based foods are associated with increased risk of breast cancer have not been substantiated by the data from many epidemiological studies. For example, intakes of bread, rice, or pasta were not associated with breast cancer risk in a prospective postmenopausal cohort ($N = 12,273$) (58). Similarly, in a French cohort ($N = 62,739$) no association was observed between intakes of white bread (baguettes) or *pain de campagne* (semi-wholemeal bread) and postmenopausal breast cancer (62). Further, in combined U.S. cohorts from the female Nurses' Health Study and Nurses' Health Study II and the male Health Professionals Follow-up Study, rice (total, white, and brown) consumption was not associated with breast cancer risk (90). For the nearly 30,000 postmenopausal women in the Iowa Women's Health Study prospective cohort and the 25,278 postmenopausal women participating in the Danish Diet, Cancer and Health cohort study, there were no relationships between the intake of total grains or whole grains and breast cancer risk (91,92). Further analysis in the Danish study also showed there was not a significant relationship between breast cancer risk and intakes of rye bread, oatmeal, and whole grain bread.

In addition to studies showing no effect, some studies have shown increased risk associated with refined grain and white bread intakes. In a case-control study with nearly 2,000 patients (nearly 6,000 control subjects) in Italy, intake of bread and pasta products was associated with increased breast cancer risk, especially among sedentary women (93). A small case-control study in Iran also showed that for those in the highest tertile of white bread and biscuit intake, there was an association with increased breast cancer risk (94). A case-control study of 438 cases in China showed that a dietary pattern high in refined grains, meat, and pickles was positively associated with breast cancer risk (90,95). It should be noted that the studies showing a positive association between consumption of grain-based foods and breast cancer risk are all case-control studies, not prospective cohort studies.

Intake of bread and other grain-based foods has also been associated with lower risk of breast cancer in both types of studies. In a case-control study in southern France, cereal intake was inversely associated with breast cancer risk (96). In the EPIC-Potsdam cohort of more than 15,000 subjects, low bread and high fat intakes were two of the factors associated with increased breast cancer risk (97).

Just as the association between intake of refined grains and breast cancer risk varies among studies, so does the association of breast cancer risk and intakes of whole grains. Whole grain consumption is often related to reduced risk of breast cancer, but the effect depends on the amount ingested. In a Greek cohort following a baseline Mediterranean-type diet, women (44–68 years of age) eating whole grains more than seven times per week had a lower risk of breast cancer than those who did not eat any whole grains (98). The association remained even after factoring in a score reflecting the degree of adherence to the Mediterranean-type diet, which could be a source of confounding. High-fiber bread intake was associated with decreased risk of breast cancer in the more than 15,000 women participating in the Malmö Diet and Cancer study (99). Higher fiber diets and increased whole grain consumption are components that may make a diet less estrogenic, and this clearly can impact breast cancer in some patients (100). Further, in the previously cited case-control study in Iran, in which there was increased risk of breast cancer for those in the high-

est tertile of white bread intake, there was reduced risk for those in the highest tertile of whole wheat bread intake (94). In another small Iranian cohort study, high-fiber and resistant starch-rich breads, as well as cereals, were associated with decreased breast cancer risk. However, the effect was dependent on the number of servings of breads and cereals consumed (101). Breast cancer risk was lower for women ingesting 3–6 servings/day but increased for those eating more than 6 servings/day. The latter finding may indicate that too many calories or CHOs were ingested or another dietary imbalance. As with many nutrients, health effects are dependent on ingesting the right balance and amount.

The effects of breads and grain-based products on breast cancer risk also can depend on individual characteristics, such as BMI and age, and the type of grain-based food eaten (102). For example, high bread intake for those with higher BMIs was positively associated with increased risk of breast cancer in an Italian case-control study of postmenopausal women. Further, the association was stronger for older women (55 and 64 years of age) in the cohort. Although there was an association for bread intake, no such association was seen with pasta. Perhaps the difference between the effects of bread and pasta intake has to do either with food structure, the amount of readily available starch and glycemic response, or differences in amounts ingested. The average Italian eats 71 g of pasta/day and 142 g of bread/day (103,104).

Relationship between Dietary Patterns and Breast Cancer Risk

Balanced dietary patterns that include grains, even with very different background diets, show a positive association between grain-based food intake and reduced risk of breast cancer. For example, in the EPIC study (105) cereals were part of a pattern that reduced the risk of hormonal receptor-defined breast cancer. In a case-control study of middle-aged Greek women (106), a dietary pattern characterized by grains and whole grains, fruits, and vegetables was favorably associated with 40% lower risk of breast cancer. For black women in the United States, the prudent diet, which included grains and other foods in the right balance, was weakly associated with lower breast cancer risk overall (107). However, for women with a BMI < 25, who were premenopausal, and those with ER-cancers, a prudent dietary pattern was as-

sociated with a significantly lower risk of breast cancer than other dietary patterns tested. In an Iranian cohort, a comparison of two dietary patterns resulted in a dramatic difference in breast cancer risk. The “healthy” food pattern incorporated a wide range of recommended foods, including whole grains (108), while the “unhealthy” food pattern was characterized by a range of indulgent foods, refined grains, and red and processed meats. Compared with women in the lowest tertile for following the “healthy” dietary pattern, those in the highest tertile had a 75% lower risk of breast cancer. In a case-control study of Asian American women adherence to a Mediterranean-type diet was inversely associated with reduced risk of breast cancer, but other dietary patterns (i.e., Western-meat/starch; ethnic-meat/starch; and vegetables/soy) were not (109). One case-control study showed that cereal foods as part of certain dietary patterns were associated with increased risk of breast cancer. In a study of Argentinian women (110), breast cancer patients consumed more cereals, as well as more calories, meat and eggs, fat and starchy vegetables, beverages, alcohol, and confections, and lower quantities of vegetables and fruits than control subjects.

These findings fit with those from a review looking at dietary patterns and associations with breast cancer (111). Among the studies reviewed, increased consumption of grains, cereals, vegetables, and fruits was significantly inversely associated with breast cancer in 10 studies. One study found no association, and two studies found a positive association (111). The authors conclude that there is much heterogeneity but suggest that traditional or Mediterranean-type balanced dietary patterns generally reduce the risk of breast cancer. Studies on dietary patterns labeled as “refined grains/meat” could also be labeled “low fruit and vegetable” or “unbalanced.” Thus, although grains may be implicated, it is not about grains per se. Although dietary pattern research can both implicate and exonerate grains, it rarely identifies a “guilty” food group and cannot reveal a cause. What dietary pattern research does do is identify unbalanced patterns as risk factors for disease: diets with a pattern of inadequate fruit and vegetable intakes and excess meat, fat, and refined and indulgent grain intakes increase disease risk. This suggests the focus needs to be on achieving balance rather than on pillorying grains or any other specific dietary component.

COLORECTAL CANCER AND INFLUENCE OF DIETARY COMPONENTS

CHOs, Grains, and Grain-Based Foods

Colorectal cancer is the third most common cancer worldwide (112). In Western countries, it is the third most common cancer in men and the second most common cancer in women. Similar to breast cancer, diet and lifestyle factors, such as obesity, lack of physical activity, tobacco use, alcohol intake, and sleep deprivation, increase the risk for colorectal cancer (113). Obesity increases the risk for colon cancer by 19%; however, regular exercise reduces the risk by 24% (32).

Poor overall dietary patterns characterized by high meat (especially if cooked at high temperatures) intake; low fruit, vegetable, and whole grain intakes; and low dietary fiber intake may be responsible for the high incidence of this cancer in Western countries (114). Intakes of more than 20 g of dietary fiber/day are associated with a 25% reduction of colorectal cancer risk. The 4th edition of the European Code against Cancer (115) recommends eating plenty of whole grains and limiting high-salt and high-calorie foods (i.e., foods high in sugar or fat).

Some studies suggest that consumption of refined grains may increase the risk for colorectal cancer (114). It is true that overconsumption of high-calorie foods of any type may result in excess insulin and IGF, which can stimulate proliferation of colorectal cells. Such findings may explain the higher colorectal cancer risk observed among overweight or inactive individuals (116). Further, CHOs, when ingested in excess, are among dietary factors that influence insulin levels, inflammation, and markers of oxidative stress, all of which can interact with various signaling genes to alter the risk for colorectal cancer (117). Diets with a higher GI could stimulate IGF-1 receptors or reduce IGF-binding protein, thereby increasing the bioavailability of IGF-1. IGF-1 may encourage cancer growth by increasing mitosis and decreasing natural cell death (apoptosis) in cancer cells (118).

However, no studies have revealed a preferred macronutrient balance or an optimal CHO intake for preventing colorectal cancer. For example, in a case-control study in Jordan, CHO intake was associated with increased risk, but intake of all other macronutrients also was associated with increased risk. Among the macronutrients, CHO had the lowest odds ratio (OR) at

1.40 compared to saturated fat at 5.40 (119). Findings showing an association of colorectal cancer risk with macronutrient intakes may simply be a reflection of total energy intake. High total energy intake is associated with a higher risk for developing colorectal cancer. A Japanese study suggests that those in the highest quartile of CHO intake had an increased risk of colorectal cancer, and the association was higher for women (120).

Despite some data implicating CHOs in colorectal cancer risk, prospective cohort studies have not confirmed this and actually show either no association or reduced risk. A meta-analysis conducted by Aune et al. (20), which included 14 large prospective cohort studies, found no association. In two cohort studies, CHO intake was inversely associated with colon cancer in more than 45,000 women in the U.S. Breast Cancer Detection Demonstration Project (BCDDP) and Japanese subjects (121,122).

Findings regarding the impact of GI and GL are mixed. The lack of association between GI and GL and colorectal cancer risk observed in a recent meta-analysis by Aune et al. (20) and earlier analysis of pooled cohort data by Mulholland et al. (123) reflect those of four other recent large cohort studies, including the U.S. NIH-AARP study (39), the Harvard Nurses' Health Study (116), 61,000 women in the Swedish Mammography Cohort (124), and the U.S. BCDDP cohort (121). In the U.S. BCDDP cohort, dietary GL was unrelated to colon cancer risk, and diets with a high GI were associated with reduced risk (121). In the Japan Public Health Center (JPHC) study, neither GI nor GL was related to colorectal cancer risk (125). GL tended to be inversely related to proximal colon cancer in Japanese men, but positively associated with risk of rectal cancer in Japanese women for those following diets with a high GL.

A few studies have found a positive association between dietary GL and increased colon or rectal cancer risk. In the Male Health Professionals Follow-up Study, high dietary GL was associated with a small increase in risk in men; the association was slightly stronger among men whose BMI was $>25 \text{ kg/m}^2$ (116). In the Canadian Cancer Registries Epidemiology Research Group registry analysis studies, Hu et al. (126) found an association between dietary GI and GL and risk for colorectal cancer. However, these findings differ from those of prospective cohort studies. In summary, research find-

ings do not clearly show a positive association for either GI or GL with colorectal cancer risk.

Dietary Fiber

Dietary fiber has been identified in animal studies as consistently reducing colon cancer risk. In a number of prospective cohort studies, lower risk of colorectal cancer has been shown, and several epidemiological studies indicate this relationship as well. The EPIC study ($N = 519,978$ adults) found that the quintile ingesting the most dietary or cereal fiber had a 25% reduction in risk of large bowel cancer (127). In a subsequent analysis of the same cohort published nine years later, the original findings were corroborated, and a dose response was established (128). Dietary fiber from cereals and from fruits and vegetables was similarly associated with reduced risk for colon cancer, but for rectal cancer, an inverse association was evident only for dietary fiber from cereals. In the Malmö Diet and Cancer Study cohort of nearly 28,000 Swedish men and women, dietary fiber and cereal fiber-rich food intakes were inversely associated with colon cancer risk (129). For the more than 190,000 subjects in the Multi-ethnic Cohort Study, dietary fiber intake was inversely associated with colorectal cancer risk (130,131). Initial analysis indicated that the relationship was significant only for men. However, follow-up analysis after several years increased statistical power and showed a significant inverse relationship for both sexes. High intakes of dietary fiber were associated with reduced risk of colon cancer in a meta-analysis of 20 studies involving 10,948 subjects (132). A significant inverse association was observed, however, only in case-control studies and not in cohort studies. Cereal fiber was associated with greater reductions in risk than was dietary fiber from fruits or vegetables. An Australian study suggested that 18% of colorectal cancers in that population were attributable to insufficient fiber intake (133).

A number of large U.S. cohort studies published around the year 2000 found no protective effect of cereal fiber (134,135). It is likely that dietary fiber and cereal fiber intakes in these U.S. cohorts did not reach the intake thresholds required to impact colorectal cancer risk. The lack of effect was seen in the Pooling Project of Prospective Studies of Diet and Cancer, which included 13 prospective cohort studies and a total of 725,628 men and

women (136). Total dietary fiber intake was not related to colorectal cancer risk overall but was inversely associated with a significantly reduced risk for incident distal colorectal adenoma (137). One recent meta-review showed a risk reduction of 16% as a result of dietary fiber intake, but the association was attenuated and no longer statistically significant after adjusting for other risk factors. However, another recent meta-analysis of 25 prospective studies with data from North American, European, and Asian cohorts showed that the relative risk of developing colorectal cancer was reduced by higher dietary fiber intake (138). All fiber types were associated with reduced risk, but legume fiber had the greatest influence.

Dietary Fiber and Colon Cancer Risk: Potential Mechanisms

Fermentation of dietary fiber and the production of short-chain fatty acids promote the growth of healthy colonic cells and apoptosis of aberrant cells. The release of many nutrients and antioxidants that are part of the dietary fiber complex also favors growth of healthy colonic cells and fosters beneficial colonic fermentation. Dietary fiber further provides fecal bulking and encourages faster transit times, so if there are carcinogens in the contents they are expelled more quickly, and any metabolic conversions to carcinogens have less time to occur.

Different types of dietary fiber have different impacts, even within a particular food grouping or component (43). In some cases, the impact is greater when the dietary fiber is in its matrix and there is synergy with antioxidants and other components, such as those found in grains or whole grains. In other cases, purified fiber may have a greater impact. In any event, both soluble and insoluble cereal fibers and some dietary fibers added to grain-based foods have the potential, along with other dietary and lifestyle factors, to reduce the risk for colorectal cancer.

Refined and Whole Grains

In several studies grains either were not associated with colorectal cancer risk or were associated with decreased risk (122, 130,139). In the Male Health Professionals Study and the Japanese cohort, the latter with half the energy intake coming from cereals, risks actually decreased with higher intakes of refined grain cereals (122,139).

In other studies, mostly case-control studies, refined grains were associated with increased risk of colorectal cancer. In the North Carolina Colon Cancer Study–Phase II (biracial) cohort, a cohort from northern Italy, and a sample of patients from the Kaiser Permanente Medical Care Program, higher intakes of refined grain products were associated with an increased risk for rectal cancer (140,141) or colon cancer (142). One study from Chile indicates that folate-enriched grains might be associated with increased colon cancer risk (143). Refined grains, when part of a Western diet that is low in fruit and vegetable intakes or other nonprudent dietary patterns, were associated in several studies with increased colon cancer risk (110,144,145).

Whole grains, on the other hand, have more consistently been associated with reduced risk for colorectal cancer. Early epidemiological studies flagged an inverse association between whole grain intake and colorectal cancer (100,146,147). However, even the data associating whole grains with cancers of the colon and rectum show inconsistencies. For women in the Swedish Mammography Cohort ($N = 61,433$), those reporting the greatest consumption of whole grains (≥ 4.5 servings/day) versus those eating much less (< 1.5 servings/day) had a lower risk for colon cancer, but not for rectal cancer (148). In direct contrast, a case-control study with subjects from the western United States showed that rectal cancer risk was reduced by 31% for the quintile eating the most whole grains, but the same effect was not observed for colon cancer (141). In the prospective NIH-AARP Diet and Health Study with nearly 500,000 people 50–71 years of age (149), there was a 21% decrease in risk of colorectal cancer for the highest versus the lowest quintiles of whole grain intake, with a greater impact on rectal cancer than on colon cancer. An analysis of 25 prospective studies from 3 continents found that 3 servings of whole grain/day was associated with a 17% decrease in risk of colorectal cancer. Another recent meta-analysis of 11 cohort studies found that consumption of whole grains was inversely associated with the risk of developing colorectal cancer; however, multivariate analysis showed that the decrease in risk was very small (150).

Bread, Pasta, and Rice

Three case-control studies, two conducted in regions of Italy and the other in two Belgian provinces, indicated that

excess energy intake—particularly from starch or refined bread and pasta—may increase the risk for colorectal cancer. The effect was especially pronounced for sedentary individuals (142,151,152). Another Italian study indicated that those with the highest intakes of bread and cereal had a 1.7 times higher risk for colorectal cancer, and the effect was more marked in women (153). In both French (154) and Italian case-control studies, epidemiologists found strong associations between colorectal cancer and pasta, rice, and pastry intake (154) and pasta, rice, and cereal intake (153). The association was greater among women and stronger than for most other foods.

The results from other studies show either reduced risk of or no association between these grain-based foods and colorectal cancer. In an Egyptian case-control study, consumption of high-fiber bread offered protection against colorectal cancer (112). In southeastern Siberia, where many foods and alcohol intake have been identified as increasing the risk for colon cancer, the consumption of both rye and wheat breads was associated with significantly reduced risk of colon cancer (155). Similarly, in a Swedish study higher intakes of crisp bread were associated with a trend toward decreased risk of colorectal cancer (156). However, in a large Norwegian study no bread types were associated with colon cancer risk. The authors of the study suggest that the inability of respondents to clearly distinguish among “refined,” “partly refined,” and “whole grain” breads may have affected the findings (157). Further, rice (total, white, and brown) consumption was unrelated to colon cancer risk in the combined cohorts of the Nurses’ Health Study, Nurses’ Health Study II, and Male Health Professionals’ Study (90).

In summary, case-control studies, which are weaker in the evidence schema than prospective cohort studies, are more likely to show an association between refined grain consumption and increased colon cancer risk. In addition, other dietary constituents and patterns may be more important than any individual constituent, which is discussed in the next section.

Influence of Dietary Patterns on Colorectal Cancer Risk

Adherence to recommended dietary patterns is associated with a lower risk for colorectal cancer. The effects of healthy eating patterns on colorectal cancer have been measured in various analyses, including a meta-analysis of 12 studies, which

found an association of healthy eating patterns with decreased colorectal adenoma risk (158). Overall, higher adherence to healthy dietary patterns was inversely associated with risk of colorectal adenomas (RR = 0.81), whereas unhealthy dietary patterns increased risk (RR = 1.24). The review (158) includes analysis of DASH- and Mediterranean-type dietary patterns and a dietary pattern adhering to U.S. Department of Agriculture (USDA) Food Guide recommendations in North American and European (EPIC and Nordic diet) cohorts (159–163). Another 2016 study of postmenopausal women (164) found that only those with high adherence to Healthy Eating Index-2010 and DASH patterns had an associated lower risk of colorectal cancer. No association was observed with other dietary patterns, and no pattern was associated with colorectal cancer mortality (164). Another study showed weaker impacts for women than for men who complied most closely with the USDA Food Guide recommendations, revealing protective associations only for current smokers or normal-weight women (161). The findings regarding this type of diet demonstrate that the inclusion of grains and whole grains when they are part of a balanced dietary pattern may reduce the risk of colorectal cancer. Similar findings with different types of grains and foods in the Nordic pattern, including berries, many rye and oatmeal products, and other whole grains and seeds, showed a lower risk for colorectal cancer (163). This indicates there are a variety of ways to construct a healthy dietary pattern and that grains are part of the pattern.

Several reviews suggest that less healthy dietary patterns characterized by higher intakes of red and processed meats (15) and refined CHOs may increase the risk of colon cancer. Thus, refined grains or high-glycemic CHOs are part of what is described as a Western dietary pattern and are often named as part of a dietary pattern that increases the risk for colorectal cancer (69,114). The question that must be asked is whether increased risk is due to specific foods, such as refined grains, included in these patterns; foods that have been omitted; or overall dietary imbalance. The difficulty with interpreting these findings not only involves food combinations, but also various lifestyle factors that may be associated with a particular food pattern.

Studies of dietary patterns suggest that overall diet quality is important. Various healthy patterns have been associated with

lower risk of colorectal cancer, and some typical diets that deviate widely from recommended patterns by being high in meat and fat, especially saturated fat, and low in whole grains, dairy, fruits, vegetables, legumes, nuts, and dietary fiber appear to increase risk. Thus, there is a role for balanced intake of grains and whole grains in the context of a healthy diet to promote colon health and reduce colon cancer risk.

CONCLUSIONS ON THE ROLE OF CHOS, GRAINS, AND WHOLE GRAINS IN CANCERS

Many health-promotion groups, such as the American Cancer Society (165), the Cancer Council of Australia (166), and the European Cancer Organization (167), recommend eating whole grain breads, pastas, and cereals in place of refined grain products as an overall strategy for preventing cancer. IARC (168) also recommends eating a healthy diet that includes “plenty of whole grains, pulses, vegetables and fruits” and to “limit high-calorie foods (foods high in sugar or fat).”

The totality of the data from most large prospective cohorts indicates that total CHO intake is not related to breast or colorectal cancers, although some studies, especially case-control studies, show a weak association with increased risk and others show a slightly decreased risk. In some instances a specific population, such as those with a certain breast cancer gene or body weight, might be affected differently than the general population. Studies on GI and GL show mixed results for most cancers, so it is hard to draw any firm conclusions.

Regarding the role of dietary fiber in risk, the most convincing and strongest data exist for colon cancer. Dietary fiber intake appears to be inversely related to colon cancer, and a number of mechanisms, some with strong evidentiary support, have been proposed. Studies of breast cancer show either no or an inverse association with dietary fiber intake.

For refined grain or specific grain-based food consumption, such as bread, the data provide a mixed picture. With regard to breast and colon cancers, case-control studies show that refined grain intake was associated with increased risk, although in many studies the increase was slight. For breast cancer, low bread intake increased risk in the large EPIC cohort, and high-fiber bread intake decreased risk, especially when BMI was high. For colon

cancer, large cohort studies indicate that refined grain intake might reduce risk, but the decrease was small. Further, some studies show a decrease in colon cancer and others rectal cancer, but the data from different cohorts seem to conflict. Some studies show no impact on risk for type of rice or whole grain bread consumed. Thus, the effects of these foods on colorectal cancer risk do not reveal a clear picture.

Cancers can take many years to develop, and dietary patterns always involve a combination of foods, in which over-selection of one food or food group may mean under-selection of another. As a result, attribution of cancer causes based on the assessment of a specific dietary component is difficult. Dietary pattern research may provide a clearer picture and does show that when there are dietary imbalances, there is a greater risk for developing several types of cancer. The elevation of risk may be more pronounced with excess calorie intake, higher BMI, or certain gene-specific types of cancer. Excess insulin and IGF-1 levels and diets with excess CHO, fat, or total energy can raise insulin levels. Whole grains, and the dietary fibers they contain, may lower insulin levels and, in turn, may reduce or slow cancer proliferation.

When the available evidence is considered as a whole, there appears to be support for the following general dietary recommendations. Diets in which calorie intake matches energy needs, in which food groups are represented in recommended amounts, and in which there is a mix of whole and refined staple grains, there seems to be less risk for developing certain cancers. Such a diet is rich in inflammation-reducing and cancer-preventing dietary components (169). Adequate dietary fiber from this balance of foods, including those from brans and whole grains, positively impact the immune system, microbiome, gut transit, and colonic fermentation, which significantly contributes to general health and decreased cancer risk. Thus, adequate intake of grains, especially whole grains, and their many phytonutrients, may help inhibit the growth of various cancers.

There is only weak data suggesting that consumption of refined grains or specific refined grain-based foods, such as bread or rice, is associated with an increased risk for developing certain cancers. There is clear data from intervention trials, such as those associated with the DASH diet, that whole and refined grains eaten as part of a balanced dietary pattern are as-

sociated with decreased risk for developing a wide variety of cancers. Large cohort studies that look at dietary patterns, such as the Mediterranean diet, report similar results.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates, Grains, and Whole Grains and Disease Prevention Part IV. Cancer Risk: Lung, Prostate, and Stomach^{1,2}

Julie M. Jones, Roberto J. Peña, Renee Korczak, and Hans J. Braun³
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Grain-based foods, and the carbohydrates (CHOs) they contain, have been accused of promoting chronic diseases. Specifically, consumption of these foods is alleged to promote metabolic pathways that favor and enhance tumor growth. A two-part review, like those previously published in this series (1–6), will assess the roles of these foods in increasing or decreasing cancer risks. Because more than 100 types of cancer have been identified, the two-part review will assess the scientific literature with respect to the effects of consuming refined, enriched, and whole grains and the CHOs they contain, including starches, dietary fibers, and resistant starches, on the five most common cancers worldwide: breast, colon, lung, prostate, and stomach.

The first review on cancer provided an overview of the influence of diet on cancer risk and examined the roles played by CHOs and grains in breast and colorectal cancers (7). This second review on cancer will examine the roles played by CHOs and grains in lung, prostate, and stomach cancers. Evidence from earlier reviews in the series that addressed the roles of CHOs and grain-based foods in inflammation,

insulin resistance, and glycemic response and their effects on the microbiome (3–5) will be referenced because these factors can alter cancer risks.

LUNG CANCER AND INFLUENCE OF DIETARY COMPONENTS

CHO, Grains, and Whole Grains

In 2015, lung cancer overtook breast cancer as the leading cause of cancer deaths among European women (8). Among both men and women, lung cancer is the leading cause of cancer deaths in the United States and most other countries worldwide. Smoking is the predominant risk factor for lung cancer, and risk increases markedly in the presence of high alcohol intake (9). Although they are less important factors in lung cancer risk, both diet and lifestyle appear to play roles. Poor diets, especially those low in fruit and vegetable intakes, and excess calorie intake have been shown to increase risk (10). Although some studies have shown an association between diets rich in antioxidant vitamins and phytochemicals and reduced risk, others have shown an association with increased risk (11).

Dietary bioactives seem to reduce lung cancer risk (12,13), and many fruits and vegetables and grain-based, CHO-rich foods contain beneficial bioactive components. However, even for fruits, vegetables, and foods containing beneficial compounds, the research results are inconsistent. In the Netherlands Cohort Study on Diet and Cancer, ingestion of cooked vegetables was not associated with reduced risk (14). Diets including adequate fruit, but not vegetable, intakes were identified in the European Prospective Investigation into Cancer and Nutri-

tion (EPIC) cohort as reducing the risk for lung cancer. In a Polish study with subjects whose jobs put them at high risk for lung cancer, frequent consumption of carrots (at least five times a week) combined with a daily intake of other vegetables significantly lowered the risk for lung cancer (15). In contrast, large trials, such as the widely published α -tocopherol and β -carotene study of Finnish smokers, have shown that antioxidant vitamin supplements actually had an adverse effect on lung cancer in individuals who previously smoked (16,17). Although most studies on healthy dietary patterns that include an optimal balance of grain-based foods have shown an association with a 20% lower risk for lung cancer, the roles of bioactives from grains remain unclear (18).

CHOs, Glycemic Index, and Glycemic Load

Few studies have specifically assessed the role of CHOs in lung cancer risk. However, in a small case-control study of Uruguayan men ($n > 800$ per group), CHO intake was not related to risk (19). Conversely, antioxidant intake, including antioxidants that might be found in CHO sources such as whole grains, was associated with reduced risk (odds ratio [OR] = 0.69). In addition, diets low in CHO and dietary fiber and high in meat, protein, and animal fat (termed “unhealthy” diets) were found to increase lung cancer risk more than diets high in dietary fiber and CHO and low in protein and animal fat (19,20). There seems to be an interaction between genetics and diet, in that the effects were more marked for those who carried certain SNPs (single nucleotide polymorphisms) associated with higher risk (20).

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The precise impact of dietary glycemic index (GI) and glycemic load (GL) with respect to lung cancer risk remains elusive. Neither GI nor GL was related to lung cancer risk when data from the Canadian Cancer Registries Epidemiology Research Group were analyzed to assess the association (21). Similarly, for the more than 500,000 older subjects participating in the U.S. National Institutes of Health–American Association of Retired People (NIH-AARP) cohort no relationship was found between GI or GL and lung cancer risk (22). In a case-control study in Poland, intake of high-GI cereal foods was not significantly different for the case and control subjects (23). However, intake of low-GI cereal foods was greater for the control than for the case subjects, suggesting a beneficial role for these foods. In a Texas cross-sectional study that included non-Hispanic white subjects, GL was not related to lung cancer risk in either smokers or nonsmokers, but GI was (24). There are, however, several caveats to these findings:

- 1) Diets were assessed at the time of diagnosis, which might not be representative of a lifetime eating pattern.
- 2) The same risk was observed in the second, third, and fourth quintiles, thereby not showing the expected increase in risk as intake of high-GI food increased.
- 3) The increase in risk was greatest for nonsmokers.
- 4) Low-GI cereals and foods may contain higher levels of dietary fiber and antioxidant components that can modulate risk.
- 5) Case subjects had other risk factors not seen for the control subjects that could have impacted the outcome, such as lower educational and socioeconomic status. A number of these factors influence diet and lifestyle choices.

Dietary Fiber, Refined and Whole Grains, and Grain-Based Foods

Because smoking is the major modifiable risk factor for lung cancer, dietary impacts are often overshadowed, although interactions do appear to be possible. Two large studies failed to show an association between dietary fiber intake and lower risk for lung cancer. One was the large EPIC cohort study (25), and the other was the U.K. cohort study of 1.2 million women smokers and nonsmokers (26). How-

ever, those who smoke are documented as having dietary habits that increase the risk for cancer, including lower intakes of fruits, vegetables, and rice and intake of fewer nutrients and less dietary fiber. In a case-control study of Chinese women, dietary patterns high in dietary fiber and vitamin C were associated with reduced risk of lung cancer in a dose-dependent manner in both smokers and nonsmokers (27). In a study of more than 4,000 heavy smokers in Italy, food frequencies were matched with lung scans. Those classified as following the high “vitamins and fiber” pattern were associated with a >40% reduction in lung cancer risk (28).

There are only a few studies that have assessed the impact of whole and refined grains and grain-based foods on lung cancer risk, but these studies have not yielded results that point in the same direction. In the Netherlands Cohort Study on Diet and Cancer ($N = 58,279$) intakes of brown bread or white bread had no impact on lung cancer risk (14). In a U.S. cohort, a sample of 20,195 food intake records from the U.S. National Health Interview Survey were linked with death records. In this cohort, high consumption of breakfast cereal and other starches was associated with reduced lung cancer mortality (29). In a Polish study, women who frequently ate margarine and bread were associated with having a significantly reduced risk of lung cancer ($OR = 0.14$) (15). In short, one large study found no association, and one large and one small study identified inverse associations.

The following small case-control studies identified an association between grain-based food intake and increased risk for lung cancer. One Iranian study found an association between traditional clay-oven baked bread and increased risk of lung cancer (30). However, in this study bread comprised an average of 70% of calories consumed, making the CHO and refined grain portions of the diet very high and leaving few calories for other needed dietary components. Also, these types of bread production methods potentially can produce smoke and char, which may be associated with increased risk of lung cancer. Another small Iranian case-control study found that those who were in the upper tertiles of bread and rice intakes were associated with an increased risk of lung cancer (31). The authors suggest that all bread eaten in Iran is made with refined flour that contains no bran, indicating a lack of dietary fiber might be a factor in increased risk. However, the data from this

study also suggest a number of potential confounders (31). First, those with lung cancer ate fewer fruits and vegetables than control subjects. Second, those in the middle third of rice intake were associated with a higher risk of lung cancer, and those in the upper third were not, so in multivariate analyses rice was no longer significantly associated with risk. Whether CHOs and grain-based foods are problematic, the nongraded dose response is hard to explain. As was observed in the Texas study, case subjects in Iran ate fewer fruits and vegetables and were more likely to smoke and to be less educated. Rice and pasta as part of a dietary pattern labeled as the “salad pattern” in a Dutch dietary study were associated with lower risk of lung cancer (14). In contrast, pasta was found to be related to lung cancer risk in a case-control study in Brazil (32). However, the rise in relative risk related to diet was dwarfed by the association of lung cancer risk with smoking. In a Dutch cohort, the dietary pattern labeled “sweet foods” was inversely associated with lung cancer risk, possibly due to higher intakes of fruit and lower intakes of alcohol (14).

Dietary Patterns and Lung Cancer Risk

Examination of dietary patterns appears to offer a better assessment of diet–cancer associations than assessment of the roles of individual foods or nutrients. For lung cancer risk, it may also be important to assess the interaction of diet with smoking patterns. In fact, one study showed that a “healthy eating” pattern that included vegetables, fruits, and low-fat foods was associated with a significant reduction in lung cancer risk among those who never smoked (33). Assessment of diet quality in the NIH-AARP Diet and Health study ($N = 460,770$) by scoring compliance with any of four common indices (Healthy Eating Index-2010, Alternative Healthy Eating Index-2010, alternative Mediterranean Diet score, and DASH Diet) yielded very similar results (34). Each type of diet offered similar reductions in risk; high dietary adherence to any of the four diet plans was associated with a 14–17% reduction in lung cancer risk (34). Higher consumption of whole grains was among the individual components that were significantly inversely associated with lung cancer risk. A study looking at lung cancer risk in more than 35,000 Australians showed that following a Mediterranean dietary pattern reduced lung cancer risk, especially for

current smokers (35). The lower risk was partly due to an overall low inflammatory diet score. However, a high dietary inflammatory score was not significantly related to risk in nonsmokers.

PROSTATE CANCER AND INFLUENCE OF DIETARY COMPONENTS

Grains and Whole Grains

Prostate cancer is the fourth most common cause of cancer worldwide and is the second most common cancer, after lung cancer, for males. It is found at higher rates in industrialized countries than in developing countries, but rates are rising in developing countries.

Many factors have been identified as contributing to prostate cancer risk, including obesity, increased waist-to-hip ratio, metabolic syndrome, and lack of exercise (36,37). Serum insulin and insulin resistance, and factors that affect them, appear to impact risk as well. High insulin sensitivity is associated with lower risk, whereas high insulin resistance is associated with elevated risk (38). The combination of greater waist circumference and high insulin resistance markedly increases risk.

Diet is thought to modulate prostate cancer risk and growth (39). However, the scientific literature does not agree on all aspects of diet and, at times, seems to show diametrically opposed results (40). Commonly accepted theory holds that a Western-type diet high in red meat and dietary fat (especially saturated fat) and low in dietary fiber and anti-inflammatory components is associated with an increased risk of prostate cancer. Inclusion of fruits and vegetables and many plant components in the diet may help reduce the risk of prostate cancer (39). Further, published analyses of prostate cancer risk in large cohorts, such as the EPIC cohort, have not identified foods or food components that increase risk (25). These data not only fail to identify meat, fish, fruits, vegetables, dietary fiber, fat, or alcohol as potential causative agents, they also fail to yield suggestions regarding the optimal balance of fat and CHO intakes needed to reduce risk of prostate cancer.

Macronutrients and CHOs

Although some studies suggest that high-fat diets may be associated with increased prostate cancer growth rates and low-fat, high-CHO diets with slower cancer growth rates (41), the totality of stud-

ies assessing the association between fat and CHO intakes and prostate cancer risk provide a fuzzy picture. Some studies show no association of prostate cancer risk with CHO intake, including the following:

- 1) A recent meta-analysis of 13 case-control and 5 cohort ($N = 74,115$) studies (42)
- 2) A systematic review of 27 epidemiological studies (18 case-control studies and 9 cohort studies) (43)
- 3) The Malmö Diet and Cancer cohort of 8,128 men aged 45–73 years (44)
- 4) A small cohort of black veterans from North Carolina (45)

A few studies show an association between CHO intake and decreased prostate cancer risk. White men in the North Carolina veteran study in the tertile with the highest CHO intake were associated with a lower risk of prostate cancer (45). Further, findings from this study indicate that higher CHO intake might be associated with reduced risk of some aggressive forms of prostate cancer but not with others. In a systematic review of 44 randomized clinical trials conducted by Hackshaw-McGeagh et al. (46), a low-fat (higher CHO) diet compared with usual diets was associated with benefits for prostate cancer patients.

Other studies show CHOs may increase prostate cancer risk. Two Italian case-control studies, each having between 1,300 and 1,500 case subjects, found that those following starch-rich dietary patterns compared with those following patterns with the least starch had a 40–50% greater relative risk of developing prostate cancer (47,48). The authors suggest that high CHO intake, and perhaps low dietary fiber intake contributed by refined breads, pasta, rice, crackers, and cookies, might be a factor. Another Italian research group has suggested that CHOs may increase the dietary inflammatory index, which increases prostate cancer risk (49).

Yet another study found that low-CHO, high-fat diets were associated with reduced risk for prostate cancer (50). This fits with findings from a systematic review and meta-analysis of 14 cohort studies with more than 750,000 participants. This review found that high dietary fat intake was not associated with prostate cancer risk (51). In addition, animal studies suggest that very low-CHO diets (ketogenic diets) may delay prostate cancer growth relative to Western or low-fat diets

(52). In short, the role of macronutrient balance and prostate cancer risk and growth is unclear and requires further research.

GI and GL

Insulin and insulin resistance are thought to play a role in risk for prostate cancer (53). Thus, some have postulated that GI and GL may be risk factors; however, the scientific literature does not support this theory. Neither GI nor GL was related to prostate cancer risk in

- 1) A meta-analysis of 27 studies (43)
- 2) The prospective NIH-AARP cohort of more than 500,000 people aged 51–70 years (22)
- 3) The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial cohort ($N = 30,482$) (54)
- 4) The 49,934 participants in the Male Health Professionals Study (55)

In contrast, dietary GI was positively associated with the risk for prostate cancer ($OR = 1.26$ for the highest versus the lowest quartile) in the Canadian Cancer Registries Epidemiology Research Group study (21). No such relationship was shown for GL. In a systematic review assessing 75 observational studies, the relative risks for prostate cancer when comparing the highest versus the lowest GI and GL intakes were 1.06 and 1.04, respectively (56). Although these numbers are statistically significant, the additional risk was slight, showing either no or an extremely weak relationship.

Dietary Fiber

The roles of dietary fiber, whole grains, and grain-based foods in prostate cancer risk also are unclear. In terms of dietary fiber, it appears that different fibers have different impacts. Systematic reviews and meta-analyses that include a variety of U.S. and northern and southern European cohorts, all failed to show an association between dietary fiber and prostate cancer risk (43,55–59). However, three studies did show an inverse relationship. In the Supplémentation en Vitamines et Minéraux Antioxydants cohort ($N = 3,313$ French men), total dietary fiber and insoluble fiber intakes, as assessed using dietary records, were associated with reduced risk for prostate cancer (60). However, total dietary fiber intake, not cereal fiber alone, reduced risk. In a study looking at black and white men in the southeastern United States, those in the top two tertiles of di-

etary fiber intake had lower risk of developing aggressive prostate cancer than those in the lowest tertiles (61). In the Malmö Diet and Cancer cohort, those ingesting high levels of cereals with little dietary fiber were associated with having an increased risk for prostate cancer (44).

Whole Grains

A 2003 case-control study in northern Italy suggested that whole grains might reduce prostate cancer risk (62). A more recent intervention study found that ingestion of whole grain and bran from rye by 17 men resulted in significantly lower plasma serum antigen (PSA) levels compared with prostate cancer patients following a cellulose-supplemented, refined-wheat diet (63). The added fiber may have slowed cancer progression due to decreased exposure to insulin, as indicated by lower plasma insulin and urinary C-peptide excretion.

Despite studies showing a possible impact from eating whole grains and brans from rye, whole grains showed no association with prostate cancer risk in a meta-analysis of 27 studies (43). Similar findings regarding the intake of whole grain products, high-fiber breads, or oatmeal were reported in

- 1) The 26,691 men aged 50–64 years in the Danish Diet, Cancer and Health cohort study (58)
- 2) The nested case-control study with more than 1,000 participants in each arm of the Malmö Diet and Cancer Study (44)
- 3) The AGES-Reykjavik cohort study of 2,268 men, aged 67–96 years (64)

However, daily consumption of rye bread during adolescence compared with less than daily consumption was associated with a decreased risk of prostate cancer later in life (64).

Refined Grains

The scientific literature also shows mixed results concerning the relationships between refined grain or specific refined grain food intakes, such as white bread, and the risk of prostate cancer. Several studies show an association between ingestion of refined grain products and increased risk of prostate cancer, but there also are several studies that show no association and one that shows an inverse association.

Three studies showed a weak association between refined grains and prostate

cancer risk. For example, in an Italian case-control study ($N = 1,451$) frequent consumption of bread was associated with a slightly increased risk of prostate cancer, although calorie intake was the most important risk factor (65). Further analysis showed that bread had a weak positive association, but none was observed for rice, pasta, sugar, or desserts (65). However, in the Danish Diet, Cancer and Health cohort ($N = 26,691$ men aged 50–64 years), high intakes of rice and pasta showed a borderline association with increased risk of low-risk (small, slow-growing, and contained) prostate cancer (58). Similarly, in the Malmö Diet and Cancer prospective cohort those following diets containing the highest intakes of rice, pasta, or low-fiber cereals showed a borderline association with increased risk of low-risk prostate cancers and no association with high-risk prostate cancers (44). Refined grain bread intake was associated with decreased risk for prostate cancer in men from three Canadian provinces, whereas whole grain breakfast cereals, surprisingly, were associated with a higher risk (66).

Additionally, two studies showed no association between prostate cancer risk and refined CHO or specific CHO-rich food intake, such as rice. One study found an inverse association. In the Uppsala Longitudinal Study of Adult Men (ULSAM), which employed 7 day food records to assess diet intakes, there was no association between prostate cancer risk and refined CHO intake (67). In the combined Nurses' Health Study, Nurses' Health Study II, and Male Health Professionals Study cohorts, rice (total, white, and brown) consumption was unrelated to risk for prostate cancer (68). In addition, country-specific food consumption data, provided by the Food and Agricultural Organization of the United Nations for analysis by the International Agency for Research on Cancer (IARC), showed that consumption of cereal grains and rice, in particular, correlated strongly with decreasing prostate cancer mortality (69).

Based on the existing data it is hard to conclude that there is a strong relationship between consumption of CHOs, grains, and whole grains and prostate cancer risk. Some special effects of rye consumption have been noted in both human and animal experiments. Consumption of rye can cause a number of metabolic changes with the potential to impact prostate metabolism and lower the risk of prostate cancer and possibly

inhibit its growth. These include lowered insulin and leptin levels, as well as an increase in betaine (also observed with wheat intake) and ketone bodies (70).

Dietary Patterns and Prostate Cancer Risk

Studies assessing diet and prostate cancer have focused primarily on individual foods and nutrients, as opposed to examining overall dietary patterns, particularly foods eaten in combination, and risk of disease. With respect to dietary patterns, the findings are mixed regarding those that include refined and whole grains and CHOs.

Some research on dietary patterns has found that consuming refined grains or white bread as part of the food grouping has the potential to increase the risk for prostate cancer. Unfortunately, in some studies the patterns are named the “refined grain and meat” or “white bread” patterns. In many cases these patterns are unbalanced, so it is difficult to attribute increased risk simply to refined grain consumption. For example, in a case-control study of Jamaican men (71), there was nearly double the risk of prostate cancer for those in the highest tertile of adherence to the “refined CHO pattern” versus other dietary patterns. This pattern contained not only rice and pasta, but also sugar-sweetened beverages and sweet baked foods. Because it contained many CHO-rich foods, it is difficult separate grain-based staples from indulgent foods that should be eaten infrequently. Other studies show similar confounding. In a case-control Canadian study of men 50–80 years of age, with food intake assessed prior to diagnosis, the “processed pattern,” containing processed meats, red meats, organ meats, refined grains, white bread, onions and tomatoes, vegetable oil and juice, soft drinks and bottled water, was associated with a higher risk of prostate cancer, whereas the “healthy living” pattern, which contained much more fiber and a large variety of fruits and vegetables, was associated with a lower risk (72). In a case-control study in Australia, prostate cancer risk was nearly double for the “Western pattern” compared with the “vegetable” or “health-conscious” patterns (73). The “Western pattern” consisted of high intakes of red and processed meats, fried fish, hamburgers, chips, high-fat milk, and white bread and was low in vegetables. In all of the patterns that suggest refined grains may be a risk factor, there is the possibility that unbalanced consumption,

including inadequate fiber and fruit and vegetable intakes and an improper balance of whole grains, may be the real risk factor.

No association or an inverse association between refined grains or refined grain foods and prostate cancer risk was shown in a number of studies. For example, in the National Health and Nutrition Examination Survey (NHANES) Epidemiological Follow-up Study, prostate cancer risk was not associated with the “red meat-starch” pattern (74). Further, there was an inverse association with the “Southern” pattern, which was characterized by cornbread, grits, sweet potatoes, okra, beans, and rice. Socioeconomic status was a factor in a cohort of Tehranian men. Those with a higher socioeconomic status, which enabled higher intakes of meat and dairy and lower intakes of bread, vegetables, and fat, had a higher risk of prostate cancer (75).

A study in Poland that evaluated the nutritional status and eating habits of men diagnosed with prostate cancer showed that they were more likely to have elevated body mass indexes (BMIs) and waist circumference and a low intake of available CHOs, dietary fiber, and key nutrients and a high intake of total and animal protein and cholesterol (76). Countries following traditional Mediterranean dietary patterns, particularly southern European countries, have lower prostate cancer incidence and mortality compared with other European countries. However, a review of studies testing adherence to a Mediterranean-type pattern and cancer prostate cancer incidence did not find an association with either the risk of prostate cancer or its progression (77). The authors note that cereals and legumes were the main energy sources in the diet. The analysis did find that adhering to a Mediterranean-type pattern after diagnosis of non-metastatic prostate cancer was associated with lower overall mortality (77).

For men participating in the Physicians’ Health Study who were diagnosed with nonmetastatic prostate cancer, those following the “prudent” pattern, which was characterized by higher intakes of vegetables, fruits, fish, legumes, and whole grains, had lower overall and prostate-related mortality than those following a “Western” pattern, which was characterized by higher intakes of processed and red meats, high-fat dairy, and refined grains (78). In the ULSAM study, those who adhered more closely to a low-CHO, high-protein diet were associated with a lower risk of prostate cancer (67).

Although the findings are mixed, it is possible to state that the specific role of CHOs and grain-based foods with respect to prostate cancer appears to be beneficial when they are eaten as part of a diet that contains an optimal balance of dietary components.

STOMACH CANCER AND INFLUENCE OF DIETARY COMPONENTS

Stomach cancer is the fifth leading cause of cancer globally, and the third leading cause of death from cancer. It has a high rate of morbidity and mortality around the world and is characterized by an abnormal, malignant growth in any part of the stomach, usually the lining. Infection by *Helicobacter pylori*, an organism that can cause ulcers and chronic inflammation in the stomach lining, was identified 25 years ago as the main cause of gastric cancer. Fortunately, ingestion of fewer pickled foods coupled with modern treatments has reduced morbidity due to stomach cancer, and it is no longer the leading cause of cancer death worldwide.

Associations between lifestyle and stomach cancer risk have been identified, and smoking is a major risk factor. In terms of diet, the following risk factors have been identified: 1) high intakes of pickled, salted, or dried foods; 2) high intakes of meats, fat, and nitrates; 3) inadequate consumption of fruits and antioxidant vitamins; and 4) poor vitamin D status (79,80). A recent study has found that certain food and herbal components may be useful in reducing *H. pylori* infections (81). In contrast, obesity and diabetes may increase the risk of gastric cancer through the shared risk factors of insulin resistance, hyperglycemia, and hyperinsulinemia (82). All of these factors may increase inflammation and reactive oxygen species that can increase all cancers, including stomach cancer.

CHOs

The scientific literature on the role of CHO intake in stomach cancer risk provides a mixed picture. Even though elevated fasting blood glucose and diabetes are related to increased risk of stomach cancer, studies assessing the role of dietary CHO in stomach cancer risk fail to show congruence. The results of case-control studies from various parts of the world with very different dietary patterns, such as China (83), eight Canadian provinces (84), and Poland (85,86), support the theory that increasing consumption of di-

etary CHO is associated with higher risk of stomach cancer (86). Further, some studies found that the relationship was strengthened for those who were overweight, women, and current or past smokers (83,84,86). In one Polish study, there appeared to be a dose effect, in that moderate CHO intake increased stomach cancer risk somewhat, whereas high CHO intake markedly increased it (86). In addition, a small Portuguese study using data from the National Alimentary Survey coupled with disease statistics found that CHO intakes were related to increased risk (87).

Although the results of the cited studies might lead one to deduce that CHO intake is consistently associated with an increased risk for developing stomach cancer, there also are studies that show no effect or even an inverse effect. For example, some large and small studies show no association. For the 61,433 women in the Swedish Mammography Cohort, total CHO intake did not affect the risk of stomach cancer (88). Similar findings were reported in a case-control study from Uruguay (89). Further, polysaccharide intake, as measured in a small study in Belgium, was not related to gastric cancer incidence (90). Two case-control studies—one conducted in Serbia and one in Nebraska—showed that CHO intake was inversely related to gastric cancer risk (87,91,92). In fact, graded reduction in risk was observed in the Serbian study (i.e., as CHO intakes increased, stomach cancer risk was reduced) (87).

GI and GL

Although higher levels of fasting plasma glucose were related to increased risk of stomach cancer in a Japanese cohort (93), data on the role of both GI and GL in stomach cancer risk are not consistent among studies. A systematic review by cancer site did show an association, albeit small, between both dietary GI and GL and the risk for stomach cancer. However, the ORs were 1.17 and 1.10, respectively, and the authors of the review note a high degree of heterogeneity among studies (56). Two Italian case-control studies showed a positive relationship between GL and gastric cancer, but only one found a relationship with GI (94,95). The latter study identified an interaction that showed the risk was much stronger when diets were low in fruit and vegetable intakes and also had a high GI or GL (95). In contrast, neither GI nor GL was associated with increased stomach cancer risk in a small Serbian case-control study or in the large

population-based Swedish Mammography Cohort ($N = 61,433$ women) (87,91).

Dietary Fiber

Dietary fiber is inversely related to the risk of stomach cancer in many, but not all, studies. For example, in the Netherlands Cohort Study, which assessed the diets of men and women ages 55–69 years ($N = 120,852$), there was no relationship between dietary fiber and stomach cancer (96). However, in case-control studies from eight Canadian provinces, two U.S. states (Nebraska and California), and Italy, dietary fiber intakes were inversely associated with stomach cancer (21,92,97,98). In the California study, dietary fiber intake also countered adverse effects of a high-fat diet (92).

Cereal fiber may play a separate role in stomach cancer risk, but again the literature does not paint a consistent picture. In a large Swedish case-control study, a 70% reduction in cancer risk was observed when comparing the quartiles with the highest and lowest cereal fiber intakes with regard to risk of gastric cardia adenocarcinoma (99). In this case, total fiber was significant, but cereal fiber was the primary force behind the effect. In the EPIC prospective cohort with more than 500,000 subjects from 10 countries, total dietary fiber and specific fiber types were not related to stomach cancer risk, but cereal fiber intake was inversely related (100). However, the opposite was found in an Italian study: total fiber, cellulose, insoluble fiber, fruit fiber, and vegetable fiber were all associated with reduced stomach cancer risk, but cereal fiber was not (97).

Specific Grains and Grain-Based Foods

The results of studies looking at the association between specific grain-based foods or whole and refined grain foods and stomach cancer are inconsistent. De Stafani et al. (19) reported that a case-control study in Uruguay indicated there was an increased risk of stomach cancer with intake of starch and starchy foods. Rice intake was associated with increased risk for stomach cancer in a survey of food intake in Portugal (87). A case-control study in Nebraska showed that bread was associated with increased risk of stomach cancer, and a case-control study in Italy noted an association of stomach cancer with refined cereal intake (92,101,102). In the Seven Countries Research Group Study, refined grains were associated with a very slight increase in stomach cancer risk, but the authors suggest the increase

might have been due to the combination of high refined grain and low fruit consumption, because vitamins and antioxidants such as flavonols are protective against stomach cancer (103). For those with stomach cancer, in a Greek case-control study pasta intake was more frequent and “brown bread,” citrus fruit, and salad vegetable intakes were less frequent for case subjects than for the control subjects (104). In the U.S. Cancer Prevention Study (CPS) II cohort ($N > 1,200,000$), no food group was significantly associated with risk (105). However, a high overall intake of plant foods (a sum of vegetables, citrus fruits, and whole grains) was associated with a 21% reduced risk in men, but not women.

Not all studies show positive associations between stomach cancer risk and grain and refined grain food intakes. In an Italian correlational study, bread and pasta intakes were associated with reduced stomach cancer mortality rates (106). In a case-control study in Turkey, low bread and cereal intakes were associated with a higher risk of stomach cancer (107). Whole grain intake was one of the factors identified as reducing risk in a comprehensive review of foods that impact the risk of developing stomach cancer (108).

Dietary Patterns and Stomach Cancer Risk

Dietary pattern research shows that when a pattern is balanced, the risk for developing stomach cancer is lower. In the EPIC cohort, adherence to a Mediterranean-type diet, which includes grains and emphasizes whole grains, was associated with reduced risk of gastric adenocarcinoma (109). In an Italian study, the dietary pattern labeled as “refined” was not associated with an increase in risk for gastric cancer (110). A later Italian study showed that a pattern defined as “animal products” caused the greatest increase in risk, and although the “starch-rich” dietary pattern also increased risk, it included low intakes of fruits and vegetables (111). In a small Mexican case-control study, dietary patterns that were very high in refined grains and desserts, compared to either a traditional Mexican diet or a pattern including fruits and vegetables and white meat, were associated with a much higher risk of gastric cancer (112).

A meta-analysis evaluated the results of 16 studies by grouping similar dietary patterns prior to analysis. The “prudent/healthy” pattern included patterns with high intakes of fruits, vegetables, vitamin C,

and fish. It was associated with a 25% reduction in the risk of stomach cancer for those with the highest adherence to this type of pattern. The “Western/unhealthy” pattern was high in meat and often included bread, high-fat dairy foods, eggs, and/or sweets. This pattern was associated with increased risk of stomach cancer and had an OR of 1.51 (113).

The wide variance in research findings and background diets makes it difficult to determine the precise role of grain-based foods in stomach cancer risk. What is clear is that unbalanced diets and diets that lack antioxidants appear to be associated with an increased risk. Diets with meats and starchy CHO-rich foods from grains and other sources may be associated with increased stomach cancer risk when dietary fiber or antioxidant vitamins and compounds are lacking in the diet.

CONCLUSIONS ON THE ROLE OF CHOS, GRAINS, AND WHOLE GRAINS IN CANCERS

Many health-promotion groups, such as the American Cancer Society (114), the Cancer Council of Australia (115), and the European Cancer Organization (116), recommend eating whole-grain breads, pastas, and cereals in place of refined grains as an overall strategy for preventing cancer. IARC (117) also recommends eating a healthy diet that includes “plenty of whole grains, pulses, vegetables and fruits” and to “limit high-calorie foods (foods high in sugar or fat).”

The totality of the data indicates that total CHO intake is not related in most large prospective cohorts to lung, prostate, or stomach cancers, although some studies, especially case-control studies, show a weak association with increased risk and others show slightly decreased risk. In some instances a specific population, such as those with a certain cancer gene or body weight, might be affected differently than the general population. Studies on GI and GL show mixed results for most cancers, so it is hard to draw any firm conclusions.

Regarding the role of dietary fiber in risk, there are very few studies on the role of dietary fiber in lung cancer, but those that do exist show that low CHO and dietary fiber intakes may increase risk. For prostate and stomach cancers, no significant association has been shown between total fiber intake and cancer risk. However, cereal fiber intake specifically has been associated with reduced risk.

For refined grains or specific grain-based foods, such as bread, the data also provide a mixed picture. The effects of these foods on lung cancer are unclear based on the few studies available in the scientific literature. For prostate cancer there may be a weak association between increased risk and refined grain and refined bread consumption, but the effect is much weaker than that of excess calorie intake and seems to be greater for those with higher BMIs. For stomach cancer there seems to be less risk associated with whole grain intake and increased risk with diets constituted by high levels of refined grains and low levels of fruits and vegetables.

Cancers can take many years to develop, and dietary patterns always involve a combination of foods, in which over-selection of one food or food group may mean under-selection of another. As a result, attribution of cancer causes based on the assessment of a specific dietary component is difficult. Dietary pattern research may provide a clearer picture and does show that when there are dietary imbalances, there is a greater risk for developing several types of cancer. The elevation of risk may be more pronounced with excess calorie intake, higher BMI, or certain gene-specific types of cancer. Excess insulin and insulin-like growth factor 1 (IGF-1) levels and diets with excess CHO, fat, or total energy can raise insulin levels. Whole grains, and the dietary fibers they contain, may lower insulin levels and, in turn, may reduce or slow cancer proliferation.

When the available evidence is considered as a whole, there appears to be support for the following general dietary recommendations. Diets in which calorie intake matches energy needs, in which food groups are represented in recommended amounts, and in which there is a mix of whole and refined staple grains, there seems to be less risk for developing certain cancers. Such a diet is rich in inflammation-reducing and cancer-preventing dietary components (118). Adequate dietary fiber from this balance of foods, including those from brans and whole grains, positively impact the immune system, microbiome, gut transit, and colonic fermentation, which significantly contributes to general health and decreased cancer risk. Thus, adequate intake of grains, especially whole grains, and their many phytonutrients, may help inhibit the growth of various cancers.

There is only weak data suggesting that consumption of refined grains or specific

refined grain-based foods, such as bread or rice, is associated with an increased risk for developing certain cancers. There is clear data from intervention trials, such as those associated with the DASH diet, that whole and refined grains eaten as part of a balanced dietary pattern are associated with decreased risk for developing a wide variety of cancers. Large cohort studies that look at dietary patterns, such as the Mediterranean diet, report similar results.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates and Their Grain Sources: A Review on Their Relationships to Brain Health^{1,2}

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ABSTRACT

Recent claims suggesting whole and refined grain-based foods should be omitted from the diet because the carbohydrates (CHOs) they contain negatively impact the brain's long-term health and functioning need to be evaluated in light of the scientific literature. This review reveals that grain-based foods are important sources of glucose for the brain, which preferentially uses glucose as a source of energy. The lipid-rich brain is very metabolically active and, therefore, requires a lot of energy. Further, CHO-rich foods such as whole grains contain a variety of antioxidant and bioactive compounds that counter oxidative stress and inflammation, helping to prevent damage to brain tissue and maintain optimal cognitive functioning. Such compounds become more important with aging because the brain becomes more susceptible to oxidative stress and inflammation—conditions that promote the development of neurological diseases and disorders. An overview of studies on the relationship between CHO-rich, grain-based foods and many different neurological conditions is presented. The body of scientific evidence shows that whole and refined grain-based foods contribute energy and needed glucose for brain metabolism and that whole grains have the potential to offer slow glucose release and the capacity to deliver vitamins, minerals, and phytonutrients that are important for brain health. Because refined grain-based foods often deliver rapidly available glucose and may contain fewer phytochemicals and nutrients and less fiber than whole grains, results described in the scientific literature on the effects of refined grains on cognitive health are mixed. For example, studies have found that too much refined grain, as well as too many calories or too much fat, in the diet can have adverse health effects. However, refined grains consumed as part of a balanced diet, including the minerals and vitamins contained in enriched and fortified grains, appear to contribute positively to cognitive capacity and brain health. The roles whole and refined grains and their CHOs play in brain metabolism and various neurological diseases and disorders when consumed as part of balanced dietary patterns (e.g., Mediterranean-style diets) and as part of unbalanced dietary patterns (e.g., typical Western diets) that include too many calories and grain-based desserts and too few fruits, vegetables, and whole grains are examined.

In the previous review articles in this series, carbohydrates (CHOs) and grains were introduced and established as important contributors of nutrition in the human diet and as promoters of a vast array of health benefits (1–3), such as reduced risk of cardiovascular disease (CVD), weight gain (4), type 2 diabetes (5), and both specific-cause and all-cause mortality (6–9). The relationship between

different types of CHOs and the development of neurological diseases and disorders is another area of interest, especially due to the links between oxidative stress and inflammation in the aging brain (10). Various bioactive, antioxidant, and fiber components found in refined and whole grains can aid in combatting inflammation and oxidative stress and regulating blood glucose response; all of which are beneficial for brain health. Refined grains contain less fiber and fewer vitamins than whole grains but often are enriched or fortified to provide key micronutrients, such as zinc, folic acid, and B vitamins, that are necessary to maintain a healthy brain. In prospective cohort studies, dietary intake scores that show high compliance with Mediterranean and DASH (Dietary Approaches to Stop Hypertension) style dietary patterns that include optimal amounts and types of grain products are associated with higher scores for cognitive function (11,12).

Despite the positive association between brain health and inclusion of grains as part of a balanced diet, many claims from authors and the media discourage the consumption of CHOs from grains, with specific accusations like “whole grain bread can slowly impinge on your brain's long-term health and functionality” (13). These sources further claim that consumption of carbohydrates, including those found in grains such as wheat, cause cognitive decline and numerous neurological disorders.

The purpose of this review is to provide an overview of common neurological disorders, evaluate the scientific literature on the important role of CHOs as fuel for the brain, and discuss existing evidence concerning the roles of CHOs and grains in the development and course of some common neurological diseases and disorders. An overview of the scientific evidence regarding common sources of CHOs and their relationships to different neurological outcomes will be provided.

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Overview of Common Neurological Diseases and Disorders

More than 600 neurologic diseases and disorders have been identified. These neurologic conditions can lead to problems with movement, speech, breathing, learning, memory, sensory perception, mood, and behavior. There are nearly as many causes as there are diseases and disorders. These include gene-related conditions such as Huntington's disease and muscular dystrophy; nervous system growth impairment and developmental conditions such as spina bifida; abnormal growths or injuries that impair the brain and spinal cord or other parts of the nervous system; infections such as meningitis; impaired blood supply to the brain, such as occurs with stroke; disordered chemical or electrical balances in the brain, such as those associated with depression, epilepsy, mental illness, and attention deficit hyperactivity disorder (ADHD); and degenerative diseases that are progressive and affect the nervous system, such as Parkinson's disease, or that cause irreversible changes in the brain, such as Alzheimer's disease.

Some common neurological disorders and diseases are listed in Table I. Some of these conditions, although minor in many forms or episodic, affect many people across the globe. According to data from the World Health Organization (WHO), depression is ranked as the fourth leading cause of disability worldwide, and the top four neurological disorders worldwide are migraine, epilepsy, dementia, and Parkinson's disease (23). The incidence of headache is likely underreported, but studies from North America, Europe, and Central America suggest that the percentage of the population experiencing tension headaches may be as high as 80%. These studies also suggest that severe headaches such as migraines affect 6–8% of men and 15–18% of women (18).

Depression affects nearly 16 million adults in the United States (24), whereas epilepsy and schizophrenia affect 2.9 and 3.5 million Americans, respectively (17). Some disorders are more common in children, such as ADHD, which affects 9% of American children 13–18 years of age, with boys at four times higher risk compared with girls (15). A number of conditions listed in Table I, such as Alzheimer's disease and dementia, occur more frequently as people age. Although Alzheimer's disease and other dementias can occur in younger adults, they are most prevalent in people over the age of 60.

The root causes of these conditions are still unknown.

Disorders such as mild cognitive impairment (MCI) cause some degree of decline in cognitive ability, including memory and thinking skills. Individuals with MCI have an increased risk of developing Alzheimer's disease or other dementias. Of the diseases and disorders listed in Table I, degenerative diseases such as Parkinson's and Alzheimer's are especially concerning because they are characterized by massive neuronal loss, loss of memory, and cognitive dysfunction (25). As these diseases progress, they lead to the inability to complete activities of daily living, which ultimately places a huge burden on their families and care givers.

MCI, Parkinson's disease, Alzheimer's disease, and dementia are recognized as common consequences of the aging process (25). In the United States alone, about 5.3 million people have Alzheimer's disease, and about 10–20% of those 65 years of age and older have MCI (16,26,27). Globally, nearly 44 million people have Alzheimer's disease or a related dementia

(16,26), while Parkinson's disease affects 1 million Americans and 7–10 million individuals worldwide (27). Unfortunately, these numbers will continue to grow as the global population continues to age (28). A recent survey from the WHO projects that between one in four and one in six people in most countries will meet the criteria for a mental disorder during their lifetime (29).

Other less serious conditions have also been described. Some are controversial, including "brain fog," which is a reportedly frustrating disorder because those who suffer from it lose mental clarity and are unable to think coherently. Unfortunately, there is no general consensus as to whether brain fog is an actual condition, nor are there statistics to describe its prevalence. However, cancer patients undergoing certain treatments and celiac patients prior to following a gluten-free diet can experience a cognitive deficit referred to as "brain fog" (30,31). Although brain fog is a term commonly used in the popular press, unlike other neurological diseases and disorders scientific evidence

does not exist that relates it to changes in the brain that occur during aging.

The Brain and Aging

Senescence or "aging" is a natural physiological process that takes place over time. Eventually it can result in changes in metabolism, errors in DNA replication, loss of function, disease processes, and progressive deterioration of organs. As the brain ages, learning becomes more difficult, and memory impairment can lead to a decline in cognitive function.

Progressive changes in the brain with increasing age contribute to the decline in cognitive function. The first change generally is a decreased rate of neurogenesis that occurs because of reduced production of new neural cells with increasing age (10). The second change is decreased neuroplasticity of the cortex and hippocampus—the two regions that are most susceptible to the aging process (25). Neuroplasticity is defined as the brain's ability to reorganize itself by forming new neural connections throughout life. Neuroplasticity allows the neurons in the brain

Table I. An overview of some common neurological disorders and diseases^a

Disease or Disorder (Reference)	Definition
Alzheimer's disease (14)	A type of dementia that causes problems with memory, thinking, and behavior. Symptoms usually develop slowly and progress over time, becoming severe enough to interfere with activities of daily living. Alzheimer's disease is characterized by the presence of plaques and tangles that spread through the cortex as the disease progresses.
Attention deficit hyperactivity disorder (15)	Attention deficit hyperactivity disorder (ADHD) is most commonly diagnosed in children but can be diagnosed in adolescents and adults. Symptoms of ADHD include difficulty in staying focused and paying attention, difficulty controlling behavior, and hyperactivity (overactivity).
Dementia (16)	A group of disorders that cause cognitive decline as a result of death or damage to brain cells. Dementias cause a decline in at least two of four essential cognitive functions: 1) memory; 2) ability to speak or understand language; 3) capacity to plan, make sound judgments, and carry out complex tasks; and 4) ability to process and interpret visual information.
Epilepsy (17)	A central nervous system disorder in which nerve cell activity in the brain is impaired, causing seizures or periods of unusual behavior, sensations, and sometimes loss of consciousness. Epilepsies are a group of conditions characterized by recurring seizures, sometimes called seizure disorder.
Headache (18)	A pain in any part of the neck or head characterized by a dull ache, sharp pain, or throbbing sensation. The pain may be located in a specific area, occur on one or both sides of the head, radiate, or feel vice-like. Migraines, tension-type headaches, and cluster headaches are among the types of primary headaches whose incidence is unrelated to an identifiable cause, such as infection or trauma to the head and/or neck. Headaches caused by the latter are termed secondary headache disorders. Altogether headaches are among the most common disorders of the nervous system.
Major depressive disorder (19)	Depression is a catchall term for feelings of sadness. Major depressive disorder is a serious illness that involves a persistent feeling of sadness and loss of interest. It involves the body, mood, and thoughts and affects the way a person eats, sleeps, feels about themselves, and thinks about things. Depression alters brain chemistry. Major depressive disorders can be mild, moderate, or severe and include persistent depressive disorder and bipolar disorder.
Mild cognitive impairment (20)	Mild cognitive impairment is characterized by cognitive changes that are serious enough to be noticed by the individuals experiencing them or by other people but that are not severe enough to interfere with daily life or independent function. These are distinguishable from the cognitive changes of normal aging and other dementias.
Parkinson's disease (21)	A chronic, neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and a deficiency of dopamine in the structures of the basal ganglia. This loss results in the slow and progressive loss of motor and nonmotor functioning.
Schizophrenia (22)	A long-term, disabling mental disorder involving a breakdown in the relationship between thought, emotion, and behavior, causing disordered or delusional thinking, inappropriate actions and feelings, withdrawal from reality and personal relationships, and an inability to sense what is real and what is not.

^a This table provides an overview of the most common neurological disorders and diseases discussed in this review; it does not provide a comprehensive review of all neurological disorders.

to compensate for injury and disease and to adjust their activities in response to new situations or changes in their environment. The cortex and hippocampus are two regions of the brain that are critical because they play important roles in both short- and long-term memory, as well as attention, perception, thought, and language.

Finally, with aging there is a decrease in the expression of specific neurotrophic factors that play important roles in synaptic and neuronal growth (25): brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-derived neurotrophic factor (GDNF). BDNF, a small dimeric protein (structurally related to NGF) that is abundant in the adult mammalian brain, is responsible for regulating long-term potentiation (the ability of the brain to determine how frequently it sends signals to other brain cells), synaptic plasticity (the ability of the synapses to strengthen or weaken over time), axonal sprouting (the process in which fine nerve sprouts grow out from intact axons to reinnervate denervated muscle fibers), and differentiation of neuronal cells (32).

Studies have shown that levels of BDNF are low in Alzheimer's disease patients compared with healthy individuals (33–35), which suggests that neurotrophic factors also are affected in the aging process and may be associated with cognitive decline. Furthermore, there is evidence that aging is associated with impairment in episodic (i.e., working) and spatial memory (Table II). Spatial and working memory are largely dependent on the hippocampus, and Leal and Yassa (10) have de-

scribed how with aging the hippocampal network and its input pathways are altered. Collectively the changes associated with the brain and aging are multifaceted. To summarize, neurogenesis decreases with age, and the regions of the brain responsible for learning and memory decline in functionality (10,25). A lifetime of oxidative stress and inflammation also contributes to problems with neurological functioning and to diseases such as Alzheimer's and Parkinson's (36).

Oxidative Stress and Inflammation: Two Pathways Common to Neurodegenerative Diseases and Disorders

Oxidative stress is the result of an imbalance between reactive oxygen species, such as superoxide, hydrogen peroxide, and the hydroxyl radical, and a biological system's ability to detoxify them. The end result is damage to proteins, fat, DNA, and RNA and the release of transcription factors such as nuclear factor kappa B (NF- κ B) (44). The activation of NF- κ B activates pro-inflammatory cytokines, which include interleukin 1 (IL-1), tumor necrosis factor alpha (TNF α), and chemokines such as cyclooxygenase 2. Although all promote inflammation (44), TNF α has been shown to be overexpressed in Alzheimer's and Parkinson's disease patients (45,46).

The lipid-rich brain is highly susceptible to oxidative stress and inflammation compared with the rest of the body (44,47–50) because there is only a limited antioxidant defense system for this very metabolically active organ (51). As a result, the brain is vulnerable to lipid peroxidation, which

ultimately decreases cell membrane fluidity and can damage membrane proteins, enzymes, and ion channels (51). Patients with Alzheimer's or Parkinson's disease, when compared with the normal population, have impaired mitochondrial function and ATP generation, a lower antioxidant status, and greater oxidative damage to lipids, proteins, DNA, and RNA (52,53). Oxidative stress and inflammation are not the only aberrations found in neurological disorders—impaired glucose metabolism and insulin resistance also are common.

Fueling the Brain

Glucose Metabolism. Glucose is the main source of energy utilized by the brain (54–56). The human brain accounts for about 2% of body weight, but it consumes 20% of the energy and 25% of the body's glucose supply (57,58). Of all the cells in the adult body, brain neurons have the highest energy demand. They require a constant supply of glucose because they rely almost exclusively on glucose metabolism for energy generation. The demand for glucose is absolute, and while it cannot be replaced, it can be supplemented, as during periods of starvation, with ketone bodies. The average minimum amount of glucose utilized by the brain is 130 g/day (59).

The breakdown of glucose not only provides fuel for brain functions through the generation of adenosine triphosphate (ATP), but also yields metabolites that are used by the brain, including glycoproteins, glycolipids, amino acids, and one-carbon donors, for methylation reactions (57). Further, glucose metabolism is involved

Table II. Some terms used to describe or measure brain function^a

Term (Reference)	Definition
Attention (37)	The behavioral and cognitive process of selectively concentrating on a discrete aspect of information, whether subjective or objective, while ignoring other perceivable information.
Cognition (38)	The set of all mental abilities and processes related to knowledge, attention, memory and working memory, judgment, evaluation, reasoning, decision making, comprehension, and production of language.
Episodic (working) memory (39)	The ability to learn and retain new information. Episodic memory typically declines throughout life, and impairment is consistent with normal, healthy aging decline.
Executive functioning (40)	The ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behavior.
Foggy brain or brain fog (41)	A state of mental confusion or lack of mental clarity. Brain fog may cause a person to become forgetful, detached, and often discouraged and depressed. Currently, brain fog is not recognized as a clinical diagnosis because there is no agreed upon medical test, it is highly subjective, and it is affected by a variety of things, including lack of sleep.
Mental energy (42)	Mental energy consists of mood, motivation, and cognition. Optimal mental energy is characterized by an enthusiastic outlook, abundant energy, clear thinking, and a sharp memory.
Mini-mental state exam (43)	A widely used tool implemented by physicians to test for problems with memory or other mental abilities. The mini-mental state exam (MMSE) is used to test a number of different mental abilities, such as memory, language, and attention.
Spatial memory (10)	The part of memory that is responsible for recording information about an individual's environment and its spatial orientation.

^a This table provides an overview of some of the most common terms used to describe the aspects of neuroanatomy discussed in this review; it does not provide a comprehensive review of all terms.

in the formation of neurotransmitters such as acetylcholine and plays a critical part in the formation of memories, verbal and logical reasoning, and the ability to concentrate (54). Because the blood-brain barrier controls the entry of critical neuroactive compounds (e.g., glutamate, aspartate, glycine, D-serine) into the brain, these compounds must be synthesized from glucose within the brain.

Ketone Bodies as Alternative Fuel Sources. Dietary patterns that are very low in CHO, such as the paleo diet or periods of prolonged starvation, do not provide enough glucose to meet the energy needs of the brain, and the brain is unable to utilize fatty acids without breakdown products from CHO to enable metabolism through the Krebs cycle. Ketone bodies produced by the liver are able to fuel the brain when CHO is not available. The two main ketone bodies are acetoacetate and β -hydroxybutyrate; acetone is the least abundant ketone body (60). An overview of ketone bodies is provided in the text box below.

The long-term use of ketone bodies as an energy source for the brain in healthy individuals has been questioned. In a recent publication, Schönfeld and Reiser (61) describe multiple problems stemming from this scenario. The first is that the ATP generated from β -oxidation of fatty acids requires more oxygen compared with glucose, and the additional oxygen increases the risk of neurons becoming hypoxic (61). Second, harmful free radicals such as superoxide are generated from the β -oxidation of fatty acids, which causes severe oxidative stress. Finally, the rate of ATP generation is much slower for fatty

Overview of Ketone Bodies

Ketone bodies include acetone, acetoacetate, and β -hydroxybutyrate and are produced by the liver from fatty acids during periods of low food intake. Of the three, acetone is the least abundant and is produced from the decarboxylation of acetoacetate. Acetone is slowly excreted via the lungs and generates the distinct smell on the breath of patients with diabetic ketoacidosis. Acetoacetate and β -hydroxybutyrate serve as an energy source for peripheral tissues, such as skeletal muscle, cardiac muscle, the renal cortex, and the brain.

acids compared with glucose (61). Therefore, during periods of rapid neuron firing in the brain, the oxidation of fatty acids cannot guarantee ATP is generated quickly enough to be used by the neural cells. Collectively, all of this can lead to a decrease in brain function. In contrast, the metabolism of glucose generates more than twice as much ATP in the same amount of time as fat does (61).

In some cases, a ketogenic diet is used to treat specific medical conditions, such as epilepsy, especially epilepsy in children. This is because $\approx 30\%$ of epilepsies fail to respond to anticonvulsant drugs (62). A ketogenic dietary pattern is high in fat, adequate in protein, but low in CHO. The mechanism by which it helps control seizures is complex and largely still unknown, but it has been reported to lower blood glucose levels through the inhibition of glycolysis (63). This is helpful for those who are deficient in GLUT1—a transporter that facilitates the transport of glucose across the plasma membranes of cells (64,65). Statistics show that more than 10% of early-onset epilepsies and up to 1% of common idiopathic epilepsies are ascribed to a GLUT1 deficiency. Because glucose delivery to the brain is restricted in epileptic patients due to GLUT1 deficiency, the ketogenic diet is well suited for this population; however, vitamin and dietary fiber intakes must be monitored for potential deficiencies. Adverse effects can include acidosis, constipation, gastroesophageal reflux disease and other gut disorders, poor linear growth, renal calculi, changes in gut microbiota, and other metabolic abnormalities (66–68).

Some preliminary studies, mainly with rodents, have caused some researchers to hypothesize that intermittent fasting and other methods of inducing ketosis may be useful for maintaining hippocampus size, addressing some neurological conditions, and delaying impacts of aging in many tissues, especially the brain. However, several points must be noted. First, because the data are from animal studies direct extrapolation of the findings is limited due to metabolic differences. Second, energy-restricted diets or intermittent fasting plans reduce all types of calories, not just those from CHO and grains. Third, the few human studies conducted have had small sample sizes and limitations in design and tended to include subjects with a specific disorder, further restricting their applicability. Most data from low-CHO diets are based on diets

with much higher levels of CHO than those found in either therapeutic ketogenic diets or those used in animal studies, so these may not be directly applicable. Nevertheless, the findings all emphasize that diets with excess calories or that are unbalanced nutritionally are not ideal for the general health and functioning of the body and brain (58,69–73).

Effects of Excess Energy Intake and Insulin Resistance on Brain Function

The body responds to intake of macronutrients, especially CHO and protein, by causing the pancreas to secrete insulin in order to utilize the ingested macronutrients. Under normal conditions, insulin binds the resulting blood glucose and delivers it to cells needing energy. However, if energy needs have been met, insulin activates metabolic machinery that promotes the synthesis of the excess glucose into triglycerides. In conditions such as chronic hyperglycemia and excess circulating insulin, which can occur with excess body weight or insulin resistance, insulin does not bind with the glucose effectively, and excess circulating glucose is not removed from the bloodstream. Any impairment of glucose entry into cells is concerning, and its impact is greater as insulin resistance increases. Excess circulating glucose can trigger an inflammatory response, lead to glycosylation of proteins, impair the functioning of all tissues (74), and lead to a variety of chronic conditions such as diabetes. The brain, like the rest of the body, is adversely affected by excess circulating glucose (1), and the aging brain is even less able to deal with excess glucose and conditions that impair glucose entry into cells (75).

Excess CHO intake in individuals with impaired glucose tolerance and insulin resistance has been shown to be problematic, but CHO intake is not the sole cause (1). Excess intake of fat or calories and inadequate intake of nutrients and phytonutrients also are known causes of inflammation, insulin resistance, and their attendant adverse effects (76–78). However, intake of the right balance of available CHO and dietary fiber, especially some dietary fibers from whole grains and other CHOs, has the ability to attenuate glucose and insulin response (79). Thus, consumption of cereal fibers and whole grains is recommended to the public in dietary guidance (80). These dietary components are important not only because they can help achieve the right balance of available CHO, but they also con-

tain many components in their matrices that may also be important for brain health. Whole and enriched grains are examples of CHO sources that contain additional nutrients and bioactive components that are beneficial for brain health.

Optimal Fuel for Brain Health: Whole and Enriched Grains

Antioxidants and Anti-inflammatory Agents. Whole and enriched grains contain nutrients that provide protection to the brain through different mechanisms

Nuclear Factor Kappa B

Nuclear factor kappa B (NF- κ B) is a protein complex that controls DNA transcription and cytokine production. It is produced in response to infections, stress, cytokines, free radicals, oxidized metabolites (including oxidized LDL), and bacterial or viral antigens. Its full name is nuclear factor kappa light-chain enhancer of activated B cells, in which the kappa light chains are critical components of immunoglobulins. Overexpression of NF- κ B has been linked to cancer and other autoimmune diseases. NF- κ B has also been implicated in synaptic plasticity and memory processes.

(Tables III and IV). Further, many whole grains are rich sources of phenolics that function as antioxidants and anti-inflammatory agents that have the potential to mediate oxidative stress throughout the body and combat pro-inflammatory proteins (81,82). For example, akyresorcinols, a class of phenolic lipids that act as plant estrogens, have high antioxidant activity (83,84). Both rye and wheat contain akyresorcinols, but they are found in higher quantities in rye. Akyresorcinols are used in some studies as markers of whole grain intake. In addition, lignans are changed by bacteria in the gut to enterolactone, which in animal experiments has been found in various parts of the body, including the brain, after eating grains (83).

Bioactives. While certain bioactives are found to some degree in nearly all grains, others are unique to only a few grains. For example, most grains contain some phenolics. Highly colored grains such as purple corn and red rice are very rich in these compounds, and antioxidant potential is correlated with total phenolic content (84). Various yellow or orange grains such as corn (maize) and wheat contain carotenoids, which also act as antioxidants. Because few of the carotenoids found in grains are vitamin A precursors, grains contribute only slightly to vitamin A status. Many whole grains are rich in tocopherols and tocotrienols, with wheat germ containing particularly high levels of

these components (82,85). Rice is one of the few grains that contain oryzanol. Oats, on the other hand, are rich in avenanthramides, tocopherols, tocotrienols, β -glucan, and phenolic compounds (85–87). Avenanthramides are polyphenol compounds that can decrease inflammation and block the activity of NF- κ B. The role of NF- κ B is discussed in the text box to the left.

The benefits of these grain bioactives depend on their bioaccessibility, absorption in the gastrointestinal tract, bioavailability, and overall impacts on oxidation throughout the body and in nervous system tissue. Bioactives such as betaine and choline are found in the bran and germ of most grains. In fact, cereal grains are the main source of betaine in the diet, providing 60–67% of the betaine in the typical Western diet (88). Betaine, a methyl derivative of glycine, functions as an osmolyte and methyl donor, functions in the brain as part of the γ -amino butyric acid (GABA) metabolic pathway, has antidepressant and other effects, and is a precursor to choline (89). As an osmolyte, betaine helps maintain water balance and protects cells from dehydration. As a methyl donor, betaine, like choline, provides the one-carbon units for DNA methylation reactions. Although choline participates in DNA methylation reactions, it also is required for the synthesis of the neurotransmitter acetylcholine and

Table III. Bioactive compounds found in whole grains and their health-protective mechanisms^a

Bioactive Compound(s)	Grain(s) High in Bioactive Compound(s)	Potential Protective Mechanisms	Health Benefits
Polyunsaturated fatty acids (PUFAs)	Whole grain wheat, rice, oats, maize, and most grains	Regulate neurotransmission, cell survival, and inflammation	Improve mood and cognition
Alkyresorcinols	Whole grain wheat, rice, rye, and oats	Function as antioxidants	Antioxidants and estrogenic
Anthocyanins	Colored rices (including brown rice) and colored maize	Suppress iNOS (inducible nitric oxide synthase) expression and scavenge free radicals	Antioxidants and anti-inflammatories
Avenanthramide	Oats	Decreases inflammation-related cytokine production	Antioxidant and anti-inflammatory
Choline	Whole grain wheat, rice, quinoa, most cereal grains, and oats	Supports intracellular signaling, methyl donor for DNA methylation, epigenetic regulator of gene expression, and accelerates synthesis and release of acetylcholine	Aids brain development and normal learning and memory functions
Ferulic acid	Whole grain wheat, rye, oats, maize, and rice	Scavenges free radicals and decreases inflammatory cytokines	Antioxidant and anti-inflammatory
Methionine	Whole grain wheat, rice, and oats	Functions as an antioxidant, precursor to S-adenosyl methionine, and methyl and glutathione donor	Prevents neural tube defects and cognitive impairment
Tocotrienols	Whole grain wheat, wheat germ, rice, maize, and oats	Function mainly as antioxidants, act directly to inhibit formation of carcinogenic compounds, and act as anti-inflammatories	Protect neurons and prevent neurodegeneration
Oryzanol	Brown rice, Korean rice, and rice bran oil	Functions as an antioxidant that prevents cell death in neuronal cells	Helps lower cholesterol, anti-inflammatory, and possesses anticancer and antidiabetic properties

^a Adapted from Fardet, "A New Hypothesis for the Health-Protective Mechanisms of Whole-Grain Cereals: What Is Beyond Fiber?" *Nutr. Res. Rev.* 23:65, 2010.

an array of phospholipids, which are components of brain lipids and membranes such as the myelin sheath (90). In addition, choline plays a critical role during periods of neonatal development and can have a long-term effect on memory (90). Fetal development of the hippocampus (the memory center of the brain) requires choline, and the presence of betaine may reduce the impact of alcohol exposure during fetal development (91,92). Rodent studies have shown that lack of choline in the diet causes detrimental changes to brain structure and function at all stages of life (93).

Because choline plays diverse roles, from formation of cell structure to neurotransmitter synthesis, adequate choline in the diet is critical for prevention of neurological disorders (94). Choline, in tandem with folate and the essential amino acid methionine, is critical for DNA methylation and gene expression. These are critical processes throughout the body, as well as for proper brain and nervous system functioning (91). Alzheimer's disease is associated with acetylcholine neuronal deficit (93). In the Framingham cohort, better verbal and visual memory were associated with higher choline. Furthermore, an inverse association was observed between

past choline intakes and the presence of greater white-matter hyperintensity, measures associated with impaired cognitive function and Alzheimer's disease (95). Sadly, recent research shows that only 1–3% of females in the United States over 14 years of age and 2–13% of males meet the AI (adequate intake) guideline for choline (96).

Vitamins. A healthy nervous system relies on the closely interrelated functions of the eight B vitamins working together. They function as coenzymes throughout the body in various key cycles, such as the Krebs cycle, which is crucial for utilizing energy provided to the brain. They also are involved in antioxidant generation, tissue repair, methylation of DNA and RNA and other components, and synthesis of neurochemicals and other signaling molecules. Their importance is underscored by the fact that a specific carrier for crossing the blood-brain barrier has been found for each of these vitamins. Serious neurological complications ensue when these vitamins are lacking, including peripheral neuropathy, cognitive impairment, dementia, and depression.

For example, thiamin (vitamin B1) plays an essential role in maintaining the func-

tional integrity of neuronal cells, including neuroglia. It also plays a key role as a cofactor for enzymes that are critical for brain functioning. Thiamin-dependent transketolase helps synthesize the antioxidant glutathione, which provides protection for cells, including brain cells. Two other thiamin-dependent enzymes are involved in the synthesis of neurotransmitters, including acetylcholine. Thiamin also is necessary for production and maintenance of the myelin sheath, which must function properly to carry electrical impulses (97). Lack of thiamin leads to mitochondrial dysfunction in regions of the brain and other impairments, such as increased oxidative stress and inflammation, decreased neurogenesis, and blood-brain barrier disruption (97). An animal study has shown that short-term depletion of thiamin drastically affects plasma, liver, and cerebellum concentrations, whereas repletion of thiamin from consumption of whole wheat bread or white (refined) bread restores thiamin levels in the cerebellum and kidneys (98). Data from human studies reveal that the brains and peripheral tissues of patients with Alzheimer's disease have reduced thiamin levels and thiamin-dependent enzyme activity (99).

Table IV. Vitamins and minerals found in whole grains and their health-protective mechanisms^a

Vitamin or Mineral	Grains High in Vitamin or Mineral	Potential Protective Mechanisms	Health Benefits
Biotin	Whole grain wheat, rice, barley, and oats	Functions as a coenzyme in bicarbonate-dependent carboxylation reactions, necessary for cell growth and production of fatty acids, and helps maintain a steady blood sugar level	Mental and nervous system health (helps prevent certain neurological disorders)
Copper	Whole grain wheat, rice, and oats	Serves as a cofactor for superoxide dismutase and functions as an antioxidant	Brain and mental health (helps prevent central nervous system dysfunction)
Folate	Whole grain wheat, rice, and oats; quinoa; wild rice; and many enriched or fortified flours, cereal grains, and meals	Functions as a coenzyme in single-carbon transfers in metabolism of nucleic amino acids and prevents depletion of brain membrane phosphatidylcholine	Prevents neural tube defects and promotes mental health (reduces risk of cognitive impairment and depression)
Iron	Whole, enriched, and fortified cereal grains	Functions as an antioxidant in prevention of diseases arising from increased oxidative stress	Brain health (helps prevent development of certain neurodegenerative diseases and disorders)
Magnesium	Whole grain wheat, rice, oats, flours, cereal grains, and meals	Improves glucose uptake and clearance, can act as an antioxidant against lipid peroxidation, and plays a role in neurotransmission	Mental health (helps prevent fatigue, stress, and anxiety)
Riboflavin	Whole grain wheat, rice, and oats; quinoa; and many enriched or fortified flours, cereal grains, and meals	Participates as a coenzyme in numerous redox reactions in metabolic pathways and energy production via respiratory chain and assists fat, protein, and carbohydrate metabolism	Mental health (helps prevent neurodegeneration and peripheral neuropathy)
Thiamin	Whole grain wheat, rice, and oats and many enriched or fortified flours, cereal grains, and meals	Involved in glucose metabolism and Krebs cycle through thiamin-dependent enzymes and promotes healthy nerves (i.e., neuromodulation in brain and involvement in neurotransmitter synthesis)	Helps prevent alcohol-induced Wernicke-Korsakoff syndrome and beriberi; low levels are associated with diseases such as Alzheimer's
Zinc	Whole grain wheat, rice, and oats and many enriched or fortified flours, cereal grains, and meals	Antioxidant effect mainly as a cofactor for superoxide dismutase, role in neurotransmission and DNA stabilization, and regulates mechanisms of inflammatory disease pathologies	Mental health

^a Adapted from Fardet, "A New Hypothesis for the Health-Protective Mechanisms of Whole-Grain Cereals: What Is Beyond Fiber?" *Nutr. Res. Rev.* 23:65, 2010.

Other B vitamins, such as riboflavin (vitamin B2), also play essential roles in the brain. Riboflavin is a precursor for flavin coenzymes, which are involved in generation of energy. Not only is it critical for the metabolism of other B vitamins, it is involved in the synthesis of heme proteins, which carry oxygen, generate energy through electron transport to the brain's energy-demanding cells, and detoxify xenobiotics and active oxygen species. Dysregulation of any of these processes due to riboflavin deficiency has adverse effects on brain and nervous tissue functioning. A recent review described the role of riboflavin in iron absorption, tryptophan metabolism, mitochondrial dysfunction, and brain dysfunction (100). Further research is needed to gain a deeper understanding of its role and potential for nutrition therapy and brain dysfunction in the future (100).

Niacin (vitamin B3) plays a role in brain health as well, mirroring the role of riboflavin in the niacin-derived processes and enzymes that are involved in a vast array of brain and nervous tissue reactions. Niacin receptors are downregulated in people with schizophrenia and upregulated in the substantia nigra of people with Parkinson's disease, in which niacin levels are generally low. Other B vitamins, such as B6 (pyridoxine), are involved in the folate cycle. Vitamin B6 is a rate-limiting cofactor in the synthesis of neurotransmitters such as dopamine, serotonin, GABA, and noradrenaline.

Many other vitamins are found in grains as well. While some are lost in milling, others are added to refined grains to replace these losses. The important contribution of grain-based foods is shown in the Multiethnic Cohort Study of U.S. adults 45–75 years of age. In the study, whole and refined grain-based foods contributed one-third to one-half of the thiamin; one-fourth of the riboflavin, vitamin B6, and folic acid (vitamin B12); and about one-third of the niacin in the diets consumed (101). Because the interaction of these B vitamins is important for nervous system tissue integrity and functioning, the vitamin contribution of grain-based foods is critical (102). Low levels of these B vitamins can impact neural functioning and result in decreased cognitive functioning. Poor dietary choices in developed countries can result in marginal intake of many B vitamins, which may cause mild learning or other neurological and brain function issues. Because grain-based foods are an important source of B vitamins, elim-

ination of whole and refined grains from the diet can have a negative impact on the intake of these and other vitamins.

Minerals. Whole and refined grains are also a source of minerals. Although whole grains contain more minerals, in some cases absorption from refined grains is better than from whole grains. Minerals such as magnesium and zinc play a vital role in synaptic plasticity, learning, and memory (103,104). Animal studies have shown that zinc is involved in enabling communication between neurons and the hippocampus and, therefore, plays a role in memory. Supplementation of magnesium and zinc in rats with Alzheimer's disease reversed impairments in synaptic proteins and dendrites (103–105). Low levels of magnesium are associated with a variety of neurological problems, including migraine headaches, Alzheimer's disease, and cerebrovascular accident (stroke) (105).

Zinc is important not only for prevention of low-level inflammation throughout the body and nervous system associated with its deficiency, but also as a cofactor in a variety of neurological functions (106). It is found in the presynaptic vesicles and is needed for neuronal signaling and proper synaptic functioning. Throughout the lifespan, starting with fetal development, zinc is involved in neuronal plasticity. At the cellular level, zinc modulates synaptic activity. Alterations in brain zinc status are implicated in a wide range of neurological disorders, including impaired brain development and neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and prion diseases, as well as mood disorders, including depression. In addition, zinc has been implicated in neuronal damage associated with traumatic brain injury, stroke, and seizure. Because of differences in bioavailability due to grain type and processing, it is difficult to accurately quantify the contribution of bread and cereal products to the nutritive value of these minerals. However, their contribution is thought to be important (107,108).

Fatty Acids. Polyunsaturated fatty acids (PUFAs) found in the germ of most cereal grains are important for cell membrane and brain functioning (109). Throughout the body they function as anti-inflammatories. Both arachidonic acid and the n-3 family of long-chain fatty acids from fish and seeds are esterified and found in nerve cell membranes as phospholipids. Either directly or after conversion these compounds participate in signal transduction

compounds and regulate several processes within the brain, such as neurotransmission, cell survival and inflammation, and, thereby, mood and cognition. PUFA levels and the signaling pathways they regulate are altered in various neurological disorders, including Alzheimer's disease and major depression. As a result, they appear to be important for the prevention and treatment of brain disorders (110).

Finally, tocotrienols are antioxidants with neuroprotective effects, as shown in a recent trial. Volunteers with risk factors for CVD received 200 mg of mixed tocotrienols twice a day for 2 years. The results showed that mixed tocotrienols attenuated progression of white-matter lesions compared with a placebo treatment (111).

CHOs, Grain Intake, and Brain Health

Grains provide a large portion of dietary CHO, and they enter the diet in many ways. Although CHOs, as mentioned earlier, are critical for brain functioning, it has to be emphasized that diets high in CHOs and sugars in general represent a higher risk for Alzheimer's disease (112). This is because excess circulating glucose, particularly when connected to insulin resistance and impaired glucose tolerance conditions, may create underlying patterns of inflammation and play havoc with brain and cognitive functioning. In fact, poor glucose regulation is an established risk factor for impaired cognitive function in patients with diabetes (113). A recent systematic review concluded that poor glucose tolerance affects several domains of cognitive function, such as verbal memory, working memory, vigilance, and attention. These functions are most vulnerable to the adverse impacts of hyperglycemia and insulin resistance conditions (114).

Some suggest that the glycemic index (GI) or glycemic load (GL) of CHOs is a good way to predict their impact on the body and brain. However, attempts to associate either GI or GL with cognitive or other outcomes have often produced mixed results. For example, one review concludes that studies assessing the effect of GI on domains of cognitive function are inconsistent (113). The authors further conclude that although a low-GI meal may favor cognitive function in adults, the findings collectively are inconclusive (114).

Another area in which data are inconclusive is the long-term effect of ketosis on cognitive health. Some studies have suggested that dietary ketosis can enhance memory in individuals with MCI

(115); however, they were short-term (6 weeks) studies and did not test the effects of long-term ketosis. Proving that dietary ketosis is effective for cognitive health will require longer interventions and a better understanding of the metabolic changes and neurocognitive effects that occur during ketosis over the long term (115).

Effects of CHOs and Grains on Cognitive Performance and Mental Health. CHOs and grains have recently been attacked by some bloggers, media personalities, book authors, and health professionals who claim that all grains and most CHOs should be removed from the diet. Statements such as these that target CHOs and cereal grains need to be evaluated in light of the available scientific evidence. Other statements have attacked specific whole grain food sources, such as bread. For example, one author states, “Whole grain breads and favorite comfort foods are slowly impinging on your brain’s long-term health and functionality” (13). Such controversial assertions need to be scrutinized and supported with scientific evidence. The Whole Grains Council (part of the Harvard Oldways Trust) recently reviewed popular arguments made for avoiding grains in the diet and stated, “There is no evidence for the idea that we should avoid all grains in the diet” (116). Grains have been a staple in the human diet for thousands of years, and claims that “all grains are injurious to brain health” (13) are not substantiated by the scientific evidence (116).

Furthermore, scientific evidence supporting the health benefits of whole grains has been discussed in the previously published reviews in this series (1–5) with regard to lowering the risks for CVD, overweight, type 2 diabetes, and specific and all-cause mortality (6–9). Whole grains have also been shown to decrease markers of inflammation (i.e., TNF α) in a randomized trial in which participants were asked to replace portions of refined wheat with whole grain wheat or refined wheat products for 8 weeks (117). New evidence also confirms that whole grains were important to the evolution of the human brain (118). More specifically, Hardy et al. (118) looked at the role of diet in the development of early humans and found that CHOs, including whole grains, other starchy plant foods, and certain root vegetables, were necessary to accommodate the increased metabolic demands of the growing brain and that cooking of CHO-rich and other foods in-

creased their digestibility and palatability, allowing for increases in brain size (118).

Relationship between Breakfast Consumption and Cognitive Performance and Mental Health. Cognitive performance during the day has been associated with consumption of breakfast, including ready-to-eat cereals (RTEC), especially in school-aged children. Studies have been conducted to assess the effects of consuming breakfast on cognition and academic performance, as well as the effects of breakfasts differing in energy and macronutrient composition. However, the scientific evidence on this subject is not conclusive for either children or adults.

In a systematic review conducted by Hoyland et al. (119), the majority of the evidence demonstrates positive effects of eating breakfast on certain measures of cognitive performance in school-aged children compared with not eating breakfast. These include positive associations between some aspects of memory and attention, although not verbal memory. For spatial memory, some studies show a benefit of breakfast consumption, whereas other studies show no difference. The review concludes that it is difficult to recommend an optimal breakfast for cognitive function based on current research findings (119).

Another review looking at the relationship between cognitive and academic performance and energy intake at breakfast and breakfast composition found little consistency (120). Even though some of the evidence indicates that a lower glycemic response is beneficial for cognitive performance in children, this finding needs to be substantiated by further trials.

Consumption of RTECs and other cereals at breakfast compared with no breakfast was associated in one study with improvements in some areas of cognition, including spatial memory in both boys and girls and short-term memory in children 6–11 years of age (121). Compared with children who did not eat breakfast younger children in the cohort (6–8 years old) showed improved spatial memory and better auditory attention after consuming oatmeal. Girls also displayed better short-term memory skills after consuming oatmeal (121). In addition, deportment was improved in those children who ate a nutritionally balanced breakfast.

In another study, compared with those who skipped breakfast children who had eaten a high-quality breakfast consisting of milk and fortified breakfast cereal or bread showed better scores on the child

behavior checklist (122). However, RTEC consumption for those over 65 years of age was not associated with improved measures of cognitive functioning as assessed by the MMSE (123). In fact, in this 11 year prospective cohort of 3,381 men and women in the Cache County Study on Memory, Health and Aging (CCMS) (123), daily RTEC consumption resulted in better micronutrient intake compared with more or less frequent consumption but was associated with poorer cognitive performance both at baseline and after the 11 years of follow-up (123). This finding is puzzling, because both higher and lower consumption levels were associated with better cognitive performance. Further analyses are needed before a conclusion can be drawn.

Some studies, however, have shown that breakfast and breakfast cereal consumption positively impact mental health in adults (124,125). One study divided adults ($N = 126$), 20–79 years of age, into irregular breakfast consumers, low breakfast cereal consumers, and high breakfast cereal consumers (124). Individuals who were high breakfast cereal consumers were less depressed and less emotionally distressed and had a lower level of perceived stress than irregular breakfast consumers (124). These findings were replicated in another study of similar design using a larger sample size ($N = 262$) and a slightly older population (21–85 years of age) (125). In another study examining the dietary habits of 1,252 men and 4,991 women (40–60 years of age), those with poor mental health were less likely than their healthier counterparts to report consuming fresh fruits, vegetables, low-fat milk, cheese, and cereals, including porridge (126). Thus, most studies confirm that the inclusion of breakfast and cereals generally results in better cognitive performance and mental health in both children and adults, especially when they are consumed as part of a balanced dietary pattern.

Impact of Balanced Dietary Patterns on Brain Health. Adherence to balanced dietary patterns, especially those that emphasize inclusion of a variety of grains and whole grains, such as Mediterranean, DASH, or New Nordic diets, has been associated in epidemiological studies with improved cognitive performance and positive impacts on brain health and functioning (127). For example, for the 1,393 U.S. adults who participated in a 4.5 year multiethnic community study, those individuals in the middle and high-

est tertiles of adherence to the Mediterranean Diet, when compared with those in the lowest tertile, over the study period had a 17 and 28% lower risk, respectively, of developing MCI (127). Similar findings were reported in a cross-sectional study of 806 Korean older adults (>60 years of age), in which a “prudent” pattern incorporating a mix of grains and foods was not associated with cognitive impairment and a “bread, egg, and dairy” pattern was inversely related to risk for cognitive impairment. In contrast the “white rice only” pattern (high consumption of white rice, low consumption of multigrain rice, and little dietary diversity) was positively associated with risk for cognitive impairment (128).

Balanced dietary patterns, such as DASH- and Mediterranean-style diets, are replete with adequate intakes of fruits, vegetables, grains, and whole grains that provide antioxidants and other components that are likely to support brain health (129) and are associated with better cognitive function (11). Another balanced pattern, the New Nordic Diet, is based on common Scandinavian food items such as fruits, rapeseed oil, berries, vegetables, fish, and whole grain products, including oats, barley, and rye, and a low to moderate intake of alcohol and meat (130). Like the Mediterranean Diet, the measures of cognitive functioning assessed by MMSE and other tests for more than 1,000 men and women in Scandinavia between the ages of 57 and 78 years show that dietary pattern alignment with the New Nordic Diet at baseline was positively associated with verbal fluency and word list learning (130). Further, in those cognitively normal at baseline, the New Nordic Diet also was positively associated with better performance on MMSE and neuropsychological tests (130).

Finally, a recent study published on the MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) Diet, a hybrid of the Mediterranean and DASH diets, found that the risk for Alzheimer’s disease was reduced by ≈50% in participants who strictly adhered to the diet compared with a 35% reduction in Alzheimer’s disease risk for those who followed the diet moderately (131). The MIND Diet recommends consumption of at least 3 servings of whole grains daily, along with green leafy vegetables, nuts, beans, fish, poultry, olive oil, and wine.

Effects of Grain-Based Food Intake on Mental Health. A few studies have focused on grain-based food intake and mental health. For example, a Japanese

study looked at the association between dietary patterns and depressive symptoms among 791 individuals (132). Patterns that included bread and pasta or high intake of noodles did not differ in their depression scores (132). Data from a larger cohort, such as the Women’s Health Initiative, indicate an association between diets that are high GI and risk for incident depression (133). More specifically, those women who consumed diets high in lactose, fiber, fruit, and vegetables had significantly lower risk for depression, whereas those who consumed diets high in refined grain from sweets, cookies, and cake had increased risk for depression (133). Determining the difference between refined and whole grains and their relationship to cognitive health is difficult, however, because most of the evidence in this area is epidemiological and focuses on subsets of cognitive and mental health issues, such as stress and depression (133). The type of grain-based food, frequency of selection, amount of fiber, and glyce-mic response may, in fact, all be related to one or more aspects of mood and mental health. Further research is needed to clarify the relationships.

Conclusions

Grain-based foods and the CHOs they contain are critical to supporting overall health when included in the proper amounts as part of a balanced diet such as DASH- or Mediterranean-style dietary patterns. It is clear that overconsumption of calories or macronutrients, including those from grains, especially in a diet in which other essential components are lacking, can be problematic for brain health, especially for those with impaired glucose tolerance and insulin resistance. In fact, CHO and/or calorie restrictions are being used clinically to treat certain conditions.

Recent claims that CHOs should be removed from the diet and that whole grain bread and comfort foods negatively impact the long-term health and functioning of the brain run counter to the evidence reported in the scientific literature. Such claims fail to consider data documenting that the brain preferentially uses glucose as its primary source of fuel and that CHOs are best suited to provide this fuel (59). Although alternative sources of energy, such as ketone bodies, can be used by the brain, these are most beneficial for those who suffer from GLUT1 deficiencies, such as those with epilepsy (64,65). Furthermore, the long-term efficacy of dietary ketosis for maintaining

brain health are largely unknown because research in this area is focused on acute intervention studies in people with various brain disorders (115). In short, the elimination of CHO foods and the many nutritional advantages they provide the body and brain could have unintended negative consequences. The nutrients and phytonutrients in whole and enriched grains can help counter the oxidative stress and inflammation that occurs in aging and contributes to many neurological diseases and disorders (36).

Whole grains are a key contributor of dietary fiber, and some, such as oatmeal, are particularly good sources of soluble fiber, which works to attenuate blood glucose and insulin levels. This is important because elevated blood glucose and insulin resistance are contributors of inflammation in the body and impair glucose entry into the brain (134). Refined grains contain lower amounts of fiber because much of it is removed during processing, and they are, therefore, not associated with a blood glucose and insulin benefit. However, enriched and fortified refined grains provide key micronutrients such as minerals, folic acid, and B vitamins—nutrients that are essential for brain health. There is a gap in the literature, however, and it is unclear whether the CHOs from refined or enriched grains have an effect on cognitive health. Diets with too many calories and too many refined CHOs from all sources, including those from grains, together with low dietary fiber, phytochemical, and micronutrient intakes, are problematic for a variety of health endpoints.

The scientific evidence linking various grains and cognitive health outcomes is mostly epidemiological, with the exception of a few randomized trials (11,12,59,117,121–128,130–136). Although epidemiological data do not prove cause and effect, they are the best data currently available. Studies continue to show that grains consumed as part of healthy, balanced dietary patterns that are culturally appropriate are beneficial for cognitive health as well. In an upcoming review, the health benefits of grains as part of these specific dietary patterns will be described.

For all of the reasons discussed in this review, there should be a continued effort to incorporate healthy CHO-rich foods, including grain-based foods, as part of a balanced diet, as well as continued efforts to combat false claims concerning CHOs and cereal grains made in the media.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Carbohydrates and Vitamins from Grains and Their Relationships to Mild Cognitive Impairment, Alzheimer's Disease, and Parkinson's Disease^{1,2}

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ABSTRACT

Grain-based foods are alleged in the popular media to cause various neurodegenerative conditions, such as mild cognitive impairment (MCI), Alzheimer's disease, and Parkinson's disease. The scientific literature shows that diets containing the right balance of foods, including grain-based foods with an optimal mix of whole and enriched (or fortified) grains, are associated with lower risk for developing a number of neurological conditions. This article, the first of a two-part review, examines the literature on the role of macronutrients, particularly carbohydrates (CHOs), dietary fiber, and vitamins provided by grain-based foods, in the development of various dementias. Studies suggest that grain-based foods and their CHOs and vitamins when incorporated in diets that meet calorie and nutrient needs are important for maintaining brain health and reducing the risk for various dementias. In contrast, excess CHO, fat, or calorie intake from any source, including grain-based foods, may lead to impairment of glucose tolerance, increased inflammation, and production of advanced glycation end products, which are all risk factors for these dementias. The dietary fiber and vitamins found in whole and enriched grain-based foods are associated with normal cognitive functioning. Despite the fact that intake of many B vitamins is low in many elderly people and MCI, Alzheimer's disease, and Parkinson's disease sufferers, the benefits of high-dose supplements, much less lower intakes from grain-based foods, are unclear. It is known, however, that these components play key roles in reactions that reduce oxidation in the brain and promote healthy brain function and that grain-based foods provide one-third to one-half of the required intake of many B vitamins. Although the contribution of these foods to meeting dietary requirements for these vitamins is without question, their role in preventing or treating these disorders is not clear. However, it is clear that grains and the macronutrients and vitamins they contain, when consumed in recommended amounts, do not increase the risk for MCI, Alzheimer's disease, or Parkinson's disease. The companion review will assess the roles of minerals and phytonutrients from grain-based foods, specific grain-based foods, and dietary patterns that contain recommended amounts of grains (e.g., Mediterranean, DASH, and Mind diets), compared to unbalanced patterns, in altering the risk and course of MCI, Alzheimer's disease, and Parkinson's disease.

The relationship between grain-based foods and brain health was introduced in a previous article (1) as part of the CIMMYT series on the role of grains in health (2–8). This article focuses on the role of macronutrients, particularly carbohydrates (CHOs), dietary fiber, and vitamins provided by grain-based foods, in the development of the most common dementias—mild cognitive impairment (MCI), Alzheimer's disease, and Parkinson's

disease (1). Although these disorders are characterized by certain unique symptoms, they all share commonalities in their development and progression. For example, the incidence of each increases with age, especially in individuals who are 60 years of age or older (9–12). In addition, all are made worse by impaired glucose utilization, oxidative stress, and inflammation.

Both the causes and cures for these conditions are elusive, so the role of lifestyle and nutrition is being scrutinized to determine whether they play a role in prevention and therapy. This article reviews the existing scientific literature on the relationship between macronutrients and vitamins from grains and these disorders. First, the impact of diet and CHOs from grains in the context of total calories and overall macronutrient balance on these disorders will be addressed. Then, the vitamin contributions of enriched, fortified, and whole grains and their impact on these disorders will be addressed. In the forthcoming companion article, the role of min-

erals and phytonutrients from grain-based foods, specific grain-based foods, and the overall place of grain-based foods in optimal and unbalanced diets will be assessed with respect to the incidence and course of these neurological disorders.

MACRONUTRIENTS FROM GRAINS: THE ROLE OF DIET AND CHOs IN BRAIN HEALTH

Diet and CHO

Grain-based foods and their CHOs and vitamins, when incorporated in diets that meet calorie and nutrient needs, are important for maintaining brain health and reducing the risk for various dementias (Table I). Excess calorie intake from all food groups, including grain-based foods, and overweight are associated with many health risks, including impaired cognition (14). High saturated fat intake, high scores for cardiovascular risk, and impaired glucose tolerance are all associated with MCI and other cognitive decrements (15–17).

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Table I. Contribution of cereal grains and their products to daily intakes of carbohydrate, dietary fiber, and vitamins

Nutrient ^a	% Daily Intake
Carbohydrate ^b	21
Dietary fiber	23
Total fat	7
Thiamin	31
Riboflavin	17
Niacin	23
Folate	31
Vitamin B ₆	17
Vitamin B ₁₂	13
Vitamin A	12
Vitamin D	8
Vitamin E ^b	9

^a Data source for nutrients other than carbohydrate and vitamin E: U.S. Department of Agriculture.

^b Data source: NHANES 2005–2010 (13).

Although some authors pillory certain foods, food groups, or macronutrients as causes of dementia (18–20), high calorie intake from any combination of foods, macronutrients, or dietary imbalance, especially in older individuals, can increase the risk of cognitive impairment (21).

Moderate calorie intake appears to be associated with improved memory and cognition (22), whereas excess calorie intake results in overweight. This can lead to inflammation and impairment of insulin function and blood flow to areas in the cortex involved in executive functioning and reasoning (21). Disturbances in insulin signaling and insulin resistance impair glucose delivery and utilization by brain and nerve cells, which decreases function. All this can result in structural changes in the hippocampus associated with cognitive dysfunction and memory impairment (23–26).

Type 2 diabetes mellitus and metabolic syndrome are both major risk factors for cognitive decline and Alzheimer's disease (27). High fasting glucose, impaired glucose regulation, and hypoglycemia result in lower scores on executive function tests, information processing speed, and selective attention (28,29). Findings from various cohorts show that those with diabetes, prediabetes, and impaired glucose tolerance are at significant risk for MCI and have a substantially accelerated progression from MCI to dementia (16,20,30–32).

Findings regarding the role of dietary CHOs, including those from grains, in the development of MCI, Alzheimer's disease, and Parkinson's disease do not present a clear picture, despite evidence showing the impact of impaired glucose utilization. For example, in a study of institu-

tionalized elderly individuals in Madrid, Spain, greater intakes of CHOs and cereals (as well as eggs and polyunsaturated fatty acids) were associated with fewer errors on cognitive tests (33). On the other hand, for cognitively normal elderly individuals (mean age ~80 years; $N > 900$) the combination of high CHO and low fat and protein intakes was associated with nearly twice the risk for developing MCI (20). The authors note that the association could be caused by too little intake of the fat needed for optimal brain function or too much intake of CHO.

Some authors suggest that ketogenic diets may be beneficial for treating MCI, Alzheimer's disease, and Parkinson's disease (17,18,34). This is based on studies with victims of severe brain injury or mouse models. The latter show that ketogenic diets impact the tau protein associated with Alzheimer's disease plaques, in some but not all studies, and improve motor activity, but not cognition (17,18, 35,36). Such studies also show that excess calorie intake or high-CHO diets impair not only the formation of brain-derived neurotrophic factor, but also its signaling in the hippocampus, which is critical for memory (37).

Several studies have linked glycemic index (GI) and glycemic load (GL) to cognition. In older cohorts in Naples, Italy (a segment of the EPIC prospective cohort) and Ireland consumption of a high-GL diet was one factor associated with poorer scores on cognitive tests and with MCI (38, 39). However, a systematic review showed that the quality of the studies was wanting, and the findings were too variable to suggest that dietary GL has a consistent impact on cognitive functioning (40). The following examples demonstrate such variability as well. In subjects with impaired glucose tolerance and central adiposity, a low-GL breakfast, relative to a high-GL breakfast, attenuated verbal memory impairment (41). However, such changes were not seen in subjects with diabetes or those with normal glucose tolerance and waist circumference (41,42). In another study, high-GI evening meals, compared to low, resulted in better verbal recall and memory performance the next day, suggesting a second-meal cognitive effect (43). In a study with older veterans (mean age ~70 years; $N = 49$) (44), the effect of dietary CHO and GI depended on the presence or absence of cognitive impairment. A low-fat, high-CHO, low-GI diet (25% fat; <7% saturated fat; 55–60% CHO; GI < 55) compared to a high-fat, low-CHO,

high-GI diet (45% fat; >25% saturated fat; 35–40% CHO; GI > 70) improved memory measures for subjects with and without cognitive deficits, but changes in amyloid and other measures differed by cognitive status. Dietary GI, GL, and CHO intakes were not significantly associated with successful aging in a 10 year study of middle-aged adults ($N = 1,609$) in which measures of cognitive functioning were assessed as one aspect of successful aging (45). In the 15% of subjects who were deemed to be aging successfully, those with the highest total fiber intake and fiber from fruits, breads, and cereals fared better.

The dietary fiber components and contents of CHO- and grain-based foods may impact dietary GI and GL and can add to variability in outcomes. In general, dietary fiber is associated with better health and cognitive outcomes. In a French cohort of more than 4,800 women (46), habitual low intakes of dietary fiber were associated with higher risk of recent cognitive decline. In contrast, higher intakes of dietary fiber and n-3 fatty acids were associated with lower risk. The authors of the study suggest there is a possible long-term neuroprotective effect of dietary fiber-containing foods. Thus, intake of high-fiber foods, including grains, are suggested as a strategy for successfully maintaining cognitive functioning throughout the aging process (42).

Diets high in CHOs, especially simple CHOs, and low in fiber, fat, and cholesterol may contribute to cognitive decline. Levels of fat and cholesterol that are inadequate for neuronal membrane function have been suggested as causes of decline (47). High intakes of simple CHOs, such as fructose, have been shown to create cognitive problems in mice (48). However, adequate n-3 fatty acids have been shown to minimize CHO-associated decrements in cognition (45). Although higher intakes of foods that are high in sugar, such as cakes and pies, were associated in a French cohort with slightly lower risk of cognitive impairment (43), such diets also may promote the formation of advanced glycation end products (AGEs), which are associated with impaired cognition and Alzheimer's disease (49). Higher serum AGEs and C-reactive protein were found in elderly diabetic subjects with cognitive deficits than in those without them (49). Animal data suggest that high-GI diets, compared to low-GI diets, increase accumulation of AGEs in the brain, whereas low-GI diets reduce AGEs (50). However, if the B vitamin-dependent gluta-

thione pathway is functioning properly, CHO- and AGE-induced hippocampal changes associated with decreased cognition are prevented (51).

Parkinson's Disease. An association between CHO intake and Parkinson's disease has been observed in some studies. In a Swedish cohort of patients newly diagnosed with Parkinson's disease (52) and the 30 year Honolulu-Asia Aging Study ($N > 8,000$), high CHO intake was associated with the development of Parkinson's disease (53). In such cases, hyperglycemia and impaired glucose utilization or excessive CHO catabolism has been suggested as resulting in high levels of methylglyoxal, an AGE precursor associated with the mitochondrial dysfunction observed in Parkinson's disease (54,55). The net result in patients with Parkinson's disease and dementia is hypometabolism of glucose in the brain (56).

Alzheimer's Disease. The role of dietary macronutrients in MCI and Alzheimer's disease is not clear; however, imbalances in macronutrients, especially too much fat or excess calories, are problematic, particularly if diets are poor or genetic risk is high. In a small case-control study, patients with Alzheimer's disease, compared to controls, were more likely to ingest excess energy. Their major sources of energy were grains and animal fats, and this was coupled with low intakes of B vitamins (57). In a four year study of nearly 1,000 elderly individuals free of dementia at baseline, high calorie intake was associated with increased risk of Alzheimer's disease. Among individuals who did not have the high-risk apolipoprotein E (*APOE*) $\epsilon 4$ allele, the combination of high calorie and fat intakes had no impact on risk, but for those had the allele the combination more than doubled the risk of Alzheimer's disease (58).

Summary. Excess calories, impaired glucose tolerance, elevated waist circumference, diabetes, and inflammation all increase the risk for MCI, Alzheimer's disease, and Parkinson's disease. It appears that individuals who have alleles that increase genetic risk for Alzheimer's disease may be more deeply impacted by high levels of fat and calories in the diet than those who do not have these alleles. Excess CHO is associated with risk for Parkinson's disease, but this may be due to excess inflammation and hypometabolism of glucose. An imbalanced macronutrient profile with low levels of dietary fiber, B vitamins, and phytonutrients can contribute to risk. Calorie restriction has been shown in some

models to help prevent cognitive deficits, and ketosis has been suggested as a treatment modality. However, data on humans are very limited. Dietary patterns that include an optimal balance of grains and CHOs and other macronutrients are associated with decreased risk for MCI, Alzheimer's disease, and Parkinson's disease and will be examined in the forthcoming companion review.

MICRONUTRIENTS FROM GRAINS: THE ROLE OF VITAMINS IN BRAIN HEALTH

Grains, the vitamins they contain, and neurological functioning have been intertwined since the discovery of vitamins because behavioral changes, learning impairments, and cognitive deficits are hallmarks of most B vitamin deficiencies (59). In this section, the scientific literature on vitamins provided by enriched, fortified, and whole grain foods is reviewed, and their impact on MCI, Alzheimer's disease, and Parkinson's disease is assessed.

Thiamin

The search for a cure for beri beri, a neurological condition that is endemic in many countries in which rice is a dietary staple, led to the discovery and naming of one of the first vitamins—thiamin (vitamin B_1). Studies conducted in Jakarta, Indonesia, proved that rice bran added to diets high in polished rice prevented beri beri. In the more than 100 years since its discovery and characterization, many of roles of thiamin in normal brain functioning and neurogenesis (the formation of new neural cells) have been delineated. The active form of thiamin, thiamin pyrophosphate, is a cofactor for more than 20 enzymes. Many of these enzymes are involved in neurological functioning:

- 1) Catalyzing glucose breakdown and delivering energy to the energy-hungry brain
- 2) Facilitating production of the neurotransmitters acetylcholine and γ -amino butyric acid (GABA), which are compounds necessary for normal cognitive functioning
- 3) Helping with nerve transduction
- 4) Reducing oxidative stress

Impairment of cerebral glucose metabolism is not only a salient feature of thiamin deficiency, but also of MCI and Alzheimer's disease. Further, it precedes the onset of clinical symptoms of MCI and Alzheimer's disease (60–62). Glucose hypometabolism

leads to a reduction in glutathione and other antioxidant metabolites that are critical for brain health (61–64). In animal models and preclinical human trials, thiamin deficiency results in excess phosphorylation of tau protein, which encourages the aggregation of brain fibers associated with memory deficits and accumulation of brain plaques characteristic of Alzheimer's disease (61). These plaques occur particularly in the cortex, hippocampus, and thalamus, which are all areas critical to memory and processing (65). In some cases high doses of thiamin have been shown to reduce Alzheimer's disease-like pathologies and levels of Alzheimer's disease-associated carbonyl proteins, a possible marker for neurodegenerative disease (65). So critical is the role of thiamin in providing glucose to the brain that only a few weeks of deficiency result in neurological and cognitive deficits (61,62).

MCI and Alzheimer's Disease. A review of both cross-sectional and case-control studies supports the thesis that higher thiamin intakes support better cognition but still leaves many unanswered questions (66). For example, in the 1999–2000 Nutrition and Health Survey of elderly individuals in Taiwan ($N = 1,412$) inadequate intakes of thiamin, as well as of B_6 and B_{12} , accounted, in part, for cognitive impairment (67). Similarly, other studies have shown that thiamin status was lower in those with cognitive impairment than in normal control subjects (66, 68,69). Further, several scores on the Mini-Mental State Examination (MMSE) were weakly correlated with blood thiamin metabolites in the elderly (70). In addition, 13% of patients admitted to a geriatric psychiatric unit who presented with behavioral disturbances and cognitive impairment were thiamin deficient (71). For deficient patients, thiamin therapy improved their MMSE scores (70) or decreased the frequency and severity of behavioral disturbances (71). After two months of supplementation, MCI patients 61–87 years of age ($N = 42$) showed improved blood levels of thiamin and other B vitamins, which were attendant with some measures of improved quality of life and self-perception (9,70). In other studies, thiamin supplementation was either of marginal or little help for patients with Alzheimer's disease and did not stop the progression of MCI to Alzheimer's disease (72,73).

Thiamin deficiency and decreased thiamin-dependent enzyme activity have been documented in some patients with

Alzheimer's disease (61,74,75). However, other studies have found no difference in thiamin status for those with Alzheimer's disease or MCI (76). Nevertheless, some suggest that management of thiamin and other deficiencies is important in the treatment of MCI and Alzheimer's disease (77). Blood thiamin pyrophosphate levels could be a possible diagnostic tool for Alzheimer's disease (77,78), but more studies are needed (73,79). Further, research that helps to determine the mechanisms of thiamin deficiency in Alzheimer's disease and under what circumstances thiamin might be useful as an adjunct in treating Alzheimer's disease patients is needed (62).

Parkinson's Disease. Although the role of thiamin in Parkinson's disease is unclear, low levels of thiamin have been documented in the serum and cerebrospinal fluid of those with Parkinson's disease (10,80,81). In such patients, high-dose parenteral or oral thiamin administration improved both motor and nonmotor symptoms of Parkinson's disease (11,12,14,81–83). Thus, preliminary findings suggest that thiamin supplementation is of benefit for patients with Parkinson's disease (80); however, evidence from large-scale randomized trials is needed to endorse its use therapeutically. Further, low dietary thiamin intakes might predict greater risk of Parkinson's disease because a low thiamin/calorie ratio for up to 8 years before Parkinson's disease diagnoses was associated with olfactory dysfunction at the time of Parkinson's disease diagnosis (84).

Summary. Long-term chronic thiamin inadequacy has been shown to contribute to cognitive impairment (85); however, data are mixed regarding the role of thiamin in either the development or course of Alzheimer's disease and Parkinson's disease (53) and whether supplementation may hold promise for treatment.

Data from diet surveys of older adults in Western countries not living in institutions suggest that 39% of women and 50% of men have thiamin intakes that are below the estimated adequate requirement (EAR) (86). These numbers are likely higher in parts of Southeast Asia (87). Although U.S. NHANES surveys indicate that the median intake of thiamin for people over the age of 65 is at the recommended level, it is also thought that 20–30% of these individuals are at risk for deficiency (88,89).

Enriched and whole grains are important contributors of thiamin. In fact, approximately half of the dietary thiamin intake in the United States comes from

foods that naturally contain thiamin; the remainder comes from foods enriched or fortified with thiamin (90). Grain-based foods contribute one-third to nearly one-half of the thiamin in the U.S. diet (88,91), and enriched and fortified grain-based foods make an important contribution (92). Enriched, fortified, and whole grains are relatively inexpensive staples, and their low cost makes them readily available sources of thiamin for individuals in all socioeconomic strata. These foods also are important to those who exclude other important sources of thiamin, such as meat and fish, especially where grain enrichment is not customary and dairy is not used.

Riboflavin

Epidemiological studies indicate riboflavin status impacts cognitive function from birth through old age. Surveys of healthy elderly subjects (mean age 71 years) showed that riboflavin blood levels were related to cognitive function (93). However, it only accounted for 2–3% of the variance in cognitive function. It is logical that riboflavin would have an impact on cognitive function because homocysteine (Hcy) metabolism and one-carbon metabolism rely on it. Any reduction in the activity of enzymes in these pathways due to insufficient riboflavin, or other B vitamins, results in high Hcy, metabolic disorders, and accelerated brain cell death and is associated with cognitive decline, Alzheimer's disease, and Parkinson's disease (94–99).

An association between riboflavin intake and cognition has been observed in some, but not all, studies. This was true in the study of a Korean elderly cohort (mean age 74.5 years) in which dietary riboflavin intake was positively associated with several measures of cognitive functioning (100). Both dietary and total riboflavin intakes in subjects diagnosed with MCI and Alzheimer's disease were associated with a number of cognitive measures (101, 102). Better cognitive functioning in institutionalized elderly individuals in Madrid, Spain, and lower odds of cognitive decline were associated with adequate intakes of vitamins B₆, B₁₂, and riboflavin (33,45). In contrast, lifelong riboflavin intake in a Scottish cohort was not related to cognitive functioning at age 70 (103).

Parkinson's Disease. In the Honolulu-Asia Aging Study riboflavin intake was not related to development of Parkinson's disease, and riboflavin supplementation had no observable impact (53). A similar outcome was observed in a Japanese case-control study in which riboflavin intake

was not associated with risk for Parkinson's disease (99). A few small trials indicate that very high doses of riboflavin, as an adjunct to the usual medications, improved motor capacity (104); however, more trials are needed to demonstrate the effectiveness of riboflavin supplementation for patients with Parkinson's disease (90).

Grain-based foods provide ≈25–30% of dietary riboflavin; in the United States and Canada some riboflavin is provided by enriched and fortified grain-based foods (91, 92). For the United States population as a whole, inadequate riboflavin intake is rare. NHANES data (2003–2006) show that <6% of the total U.S. population has riboflavin intakes from foods and supplements that are below the EAR.

Data from other regions suggest that higher percentages of populations do not to meet the EAR for riboflavin. For example, the Korean NHANES data suggest that 28% of adults 19–64 years of age fail to meet the EAR (105). A systematic review of community-dwelling older adults in developed Western countries ($N > 28,000$; some in countries that do not enrich refined grains) found that 31–41% have riboflavin intakes below the EAR. This raises the possibility that chronic low intakes could have a potentially negative impact on cognition (86).

In Western diets, whole and enriched grains are a major source of riboflavin—second only to dairy products. Inadequate intake of grain-based foods and the B vitamins they contain might be a factor in cognitive health, but the specific role of lifelong intake of grain-based foods and their thiamin and riboflavin contributions in MCI, Parkinson's disease, and Alzheimer's disease is not known.

Folate

Folate is a crucial cofactor for DNA synthesis, methylation reactions, and Hcy metabolism and is important during early life development for the prevention of neural tube and other birth defects, demonstrating its necessity for brain development.

MCI. Low folate status in aging is associated with cognitive dysfunction, which ranges from mild to severe (86). In a Chinese randomized trial with MCI patients, several measures of cognitive performance improved in the group given 400 IU of folic acid/day compared with the un-supplemented group (106). Combinations of folate and vitamin B₁₂ are often employed in treating MCI. Over 12 weeks of supplementation of institutionalized patients with MCI (65 years of age or older; $N = 48$) with

folate and vitamins B₆ and B₁₂, scores on a number of cognitive measures improved (107).

Alzheimer's Disease. In case-control studies in countries with different dietary patterns (India and Italy), older adults with low plasma levels of folate, as well as vitamin B₁₂, were associated with higher risk for Alzheimer's disease (108,109). Those with genetically lower levels of an enzyme necessary for folate metabolism (methylene tetrahydrofolate reductase) were more prone to develop Alzheimer's disease than were individuals with adequate enzyme activity (108). Supplements with a combination of vitamins show promise for treating Alzheimer's disease (110,111), but confirmation with well-constructed randomized clinical trials is needed (73,79).

Parkinson's Disease. Animal models suggest that folate supplementation might reduce mitochondrial dysfunction and oxidative stress, which play a role in the pathogenesis of Parkinson's disease (112). In fact, folate intake eight years prior to diagnosis of Parkinson's disease was associated with olfactory dysfunction and disease risk in Swedish patients (52,84). In contrast, the Honolulu-Asia Aging Study cohort and case-control studies from three regions in China ($N > 6,000$) found no relationship between folate or vitamin B₁₂ intake or status and risk for Parkinson's disease (53,113,114). However, a recent meta-analysis of 14 studies found that elevated plasma Hcy was an independent risk factor for Parkinson's disease (96,115,116).

Low dietary intakes of folate were found in about one-third of community-dwelling older adults in developed Western countries ($N > 28,000$) (86). These folate intakes were coupled with inadequate intakes of many B vitamins, especially those needed for proper functioning of the Hcy pathway (86). Pronounced folate deficiency has been estimated to affect 9–12% of older people in the United Kingdom (117,118), and the most common cause is low dietary intake.

Flour-enrichment programs and a mandate for folate fortification of grain products affect the number of individuals who are low in folate. For example, U.S. NHANES data show that 90% of the population would be below the EAR for folate if they relied solely on food sources. However, with flour fortification, only 13% fall below the EAR (90). It has even been suggested that folate should be added to whole grains on a par with fortified grains in North America, where the public health

benefits of fortification have been documented (119).

Vitamin B₁₂

MCI. Impaired cognitive function due to pernicious anemia and low vitamin B₁₂ availability is well established (120). Because B₁₂ utilization in the elderly may be impaired due to inadequate stomach acidity (achlorhydria), decrements in kidney function, and other metabolic disorders, results of studies on intake and serum levels may seem contradictory (121,122). A cross-sectional analysis of 100 older MCI patients (50–80 years of age) revealed poorer scores for several measures of cognitive ability in those with low, compared to high, vitamin B₁₂ status (123). Supplementation with vitamin B₁₂ alone has produced disappointing results. For example, an intervention trial showed that vitamin B₁₂ supplementation did not prevent cognitive decline in older diabetic patients with borderline vitamin B₁₂ status (124). However, some studies have shown that vitamin combinations improved cognitive performance and memory in some patients. Apolipoprotein E (apoE) status and other aspects of subjects' health must be examined in clinical trials to establish the role of vitamin B₁₂ in cognitive functioning (125). Differences in the ability to absorb B₁₂ may explain some differences.

Parkinson's Disease and Alzheimer's Disease. Hyperhomocysteinemia is related to cognitive impairment in Parkinson's disease patients (115). Lower folate and vitamin B₁₂ levels and higher Hcy levels were found in a meta-analysis of 15 studies of Parkinson's disease patients with cognitive dysfunction (115). Further, as Parkinson's disease progressed levels of vitamin B₁₂ decreased, and low B₁₂ was associated with greater disease severity (113,116). However, no clear relationship between vitamin B₁₂ intake and the risk of Parkinson's disease has been demonstrated (53,113,114,116).

Numerous population surveys show vitamin B₁₂ deficiency is prevalent in older people globally (126). Vitamin B₁₂ deficiency or suboptimal status has been documented in older people from Western nations, and higher prevalence rates have been observed in countries like India. Because vitamin B₁₂ is found mostly in animal products, 11–90% of elderly vegetarians are deficient (127). Grain-based foods such as ready-to-eat (RTE) breakfast cereals that are fortified with vitamin B₁₂ can be an important source of this vitamin for this group.

Because the functions of vitamin B₁₂ are closely related to those of folate and other B vitamins, especially for Hcy metabolism, interventions often involve supplementation with combinations of vitamins. Although grain-based foods may offer a combination of vitamins and their lifelong intake may play a positive role in maintaining brain health and cognition, doses used in many intervention studies suggest that the amounts of vitamins delivered by grain-based foods may provide a baseline but have little clinical impact for reducing or treating high Hcy levels and, thus, the ultimate impact on Alzheimer's disease or Parkinson's disease (73,79,128). Documented poor dietary intakes and impaired utilization of these vitamins, especially among older adults, may play an exacerbating role in these diseases, and grain-based foods could help address this deficit. Combination of B vitamins in supplements added to a balanced diet may be of value for neurocognitive function, but the evidence is inconclusive (123).

Vitamin E

More relationships have been documented between water-soluble vitamins and cognitive functioning than have been documented for fat-soluble vitamins. Although grains do contain vitamin E, different grains contain different isomers in differing amounts.

The antioxidant activity of vitamin E is thought to protect the lipid-rich brain cells from oxidation and, thereby, help maintain cognitive status (129). Vitamin E also plays a role in maintaining hippocampal plasticity and may affect the generation and clearance of amyloid- β (A β) peptides, which is the main component of the amyloid plaques found in Alzheimer's patients (130,131).

Vitamin E obtained from foods or supplements in a prospective study of free-living elderly individuals (65–102 years of age) was associated with less cognitive decline over 3 years (132). Similarly, adequate vitamin E and cereal intakes, as part of an overall health-promoting diet, were two of the factors associated with better cognitive functioning in Spanish institutionalized elderly subjects (33). A review of 51 studies revealed that cognitive impairment, along with other age-related morbidities, was associated with low serum levels and intakes of vitamin E (tocopherols) and its isomers (tocotrienols) (133). Those with plasma levels of total tocopherols, total tocotrienols, or total

vitamin E in the highest tertile, compared to the lowest, had a reduced risk of developing Alzheimer's disease over time (134). Of the isomers, high plasma levels of β -tocopherol were associated with the greatest neuroprotection (135).

Intervention studies testing pharmacological doses have shown some impact on cognitive function (136). Vitamin E supplements (800 IU/day), compared to a placebo, were shown to reduce markers of oxidative stress in patients with cognitive impairment. However, there was no difference in MMSE scores. Another study testing extremely high doses of vitamin E (2,000 IU/day) failed to show any difference between supplemented and non-supplemented groups in the progression from MCI to Alzheimer's disease (137). In contrast, in a randomized controlled trial spanning 2 years, α -tocopherol supplementation (2,000 IU/day) was found to significantly delay cognitive decline, slow disease progression, and increase median survival in individuals with moderately severe Alzheimer's disease (54). In a smaller, longer case-control study there was no effect of the same dosage of vitamin E on MCI or the progression from MCI to Alzheimer's disease (55).

Because the data are mixed, evidence confirming that vitamin E provides benefits in the treatment of either MCI or Alzheimer's disease is lacking. A meeting of experts from the British Association for Psychopharmacology reviewed the data in 2016 and concluded that the evidence to date is not strong enough to suggest vitamin E (or any other nutritional supplements) be used for the treatment or prevention of Alzheimer's disease. Similar results were reported in a 2017 Cochrane Review that found no evidence that the α -tocopherol form of vitamin E given to people with MCI prevents progression to dementia or that it improves cognitive function in people with MCI or dementia due to Alzheimer's disease. The review did note, however, that there is moderate evidence from a single study that α -tocopherol may slow functional decline in Alzheimer's disease. There is some indication that the variability in the data may be due to inadequate characterization of the different vitamin E isomers. The data on various isomers suggest that future trials should attempt to characterize the various isomers and that interventions should not be restricted to α -tocopherol.

The major form of vitamin E in U.S. diets, γ -tocopherol, has received little attention compared with the more extensively

studied α -tocopherol (138). Clinical trials suggests α -tocopherol supplements may reduce serum γ -tocopherol and impact the bioavailability of other forms of tocopherols and tocotrienols. This might account for the null effects of α -tocopherol supplementation on MCI and Alzheimer's disease observed in some studies.

Wheat germ and wheat germ oil are among some of the best dietary sources of vitamin E (135). Whole grains, although they are less concentrated sources, may provide as much as 14–17% of the vitamin E requirement in some parts of Europe. Further, all grains provide more tocotrienols than other food sources (139). Despite the fact that 85% of the vitamin E content is removed during grain milling and processing (139,140), a study of elderly Hispanic and non-Hispanic Puerto Ricans found that white bread provided 3% of vitamin E intake, but only for non-Hispanic individuals who consumed more breads and RTE breakfast cereals (141). For non-Hispanic individuals, RTE breakfast cereals provided another 11.5% of vitamin E intake (141). Although RTE breakfast cereals may be fortified with vitamin E, it is not added back as a standard enrichment measure. Deliberations concerning addition of this vitamin to the enrichment mixture might be warranted but would need to consider the biological activity of various tocopherol isomers that some processing methods, such as extrusion and baking, can decrease (142,143).

CONCLUSIONS

Most of the scientific data show that grain-based foods, when consumed in recommended amounts, do not increase the risk for MCI, Alzheimer's disease, or Parkinson's disease. Although these foods often provide around 50% of dietary CHOs and between 20 and 25% of calories in Western diets, many studies show they are not associated with increased risk for MCI, Alzheimer's disease, or Parkinson's disease. When studies do show a decrement in cognitive functioning, it is usually when either the diet is out of balance, containing excess calories from either fat or CHO, or an individual has impaired glucose tolerance or insulin resistance. Disturbances in glucose delivery to the brain and nerve cells can result in structural changes in the memory center of the hippocampus. Some data show that calorie restriction may be beneficial, but data on the benefits

of ketosis for cognitive functioning are limited and mixed.

The quality of CHO consumed may have an impact on MCI, Alzheimer's disease, or Parkinson's disease, but the effect of GL and GI on these disorders is so variable among published studies as to preclude any conclusions regarding their impact. Findings appear to be impacted by insulin and glucose sensitivity, waist circumference, genetic differences (such as the presence of the *APOE* ϵ 4 allele), other dietary components, and difficulty with obtaining accurate GI and GL assessments from food frequency surveys. In contrast, low intakes of dietary fiber are consistently associated with poor performance on various cognitive measures.

Vitamins are important for proper structure and function of nerve tissue, so adequate levels of many are associated with cognitive health. Grain-based foods are important sources of key vitamins. For example, thiamin is critical for generating the glucose that is needed to fuel the brain. What is not clear is whether adequate thiamin intake throughout life helps prevent MCI, Alzheimer's disease, or Parkinson's disease or whether it may act therapeutically for those with these cognitive diseases. Enriched, fortified, and whole grains are important sources of this vitamin, providing approximately one-third of thiamin in the diet. Riboflavin, folate, and vitamin B₁₂ all are involved in pathways that metabolize Hcy—a risk factor for the three cognitive disorders discussed. Cereals and cereal products provide more than 30% of the folate in the diets of elderly individuals in the United States and United Kingdom (144).

Studies assessing the role of these vitamins in preventing or treating MCI, Alzheimer's disease, or Parkinson's disease report mixed results—some studies suggest they might be useful, especially at high levels; however, other studies show little or no effect. What is clear is that low intakes of many of these vitamins occur in elderly populations, and grain-based foods are an economical way to address these inadequacies. Vitamin E is also low in the general population as a whole and in the elderly, and different isomers may have different impacts on cognitive function. Whole grains, especially those rich in tocotrienols, are good sources of this vitamin. The antioxidant activity of vitamin E may also be helpful in protecting nerve tissue.

Thus, the scientific evidence supports the role of grains and grain-based foods in maintaining brain structure and func-

tion. Allegations that they destroy the brain have little data to support them, especially when such foods are eaten in recommended amounts and as part of a balanced diet. Diets with an excess of calories, fats, and CHOs and inadequate levels of fiber and antioxidants, especially when ingested by those with impaired glucose tolerance and high waist circumference, can be problematic for both general health and brain health and may contribute to development of MCI, Parkinson's disease, and Alzheimer's disease. Further, such diets would be contraindicated for those with these conditions.

The second part of this review will look at minerals and phytochemicals in grain-based foods and the role of grains in balanced dietary patterns. As with this portion of the review on the role of CHOs and vitamins from grains, it will show that grains are not the cause of MCI, Alzheimer's disease, and Parkinson's disease, and, in fact, when eaten in recommended amounts are part of the solution.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Impact of Minerals, Phytochemicals, Specific Grain-Based Foods, and Dietary Patterns on Mild Cognitive Impairment, Alzheimer's Disease, and Parkinson's Disease^{1,2}

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ABSTRACT

Incidence of mild cognitive impairment (MCI), Alzheimer's disease, and Parkinson's disease is increasing as the mean age of Western populations rises. This article, the second article of a two-part review, assesses the existing scientific literature addressing the role of minerals, phytochemicals, specific grain-based foods, and dietary patterns, with and without grains, to determine whether these foods and their constituents affect the onset or course of these common dementias, as has been alleged in various books, blogs, and other media. Intakes and serum markers of mineral and phytonutrient intakes in many cases have been documented as low or below recommended levels in elderly individuals and patients with MCI, Alzheimer's disease, or Parkinson's disease. However, it is not clear whether adequate intake of these minerals and phytonutrients from all sources, including grains, can impact the onset or course of these dementias. There are few published studies on specific grain-based foods and their relationships to common dementias, and the results have been mixed or shown a dose or total diet effect. Studies have shown an association between whole grain, cereal, and high-fiber grain-based food intakes and lower risk of cognitive impairment and dementias. Results of studies on specific grain-based foods indicate that higher bread intakes, especially high-fiber breads, are associated with better cognitive performance and lower rates of dementia; however, higher than recommended levels are associated with poorer performance and greater risk of impairment. Other studies have shown that high rice intake may be associated with poor cognitive performance but that this may be due to the lack of important components in the diet, rather than solely to rice intake, or to an interaction of the two factors. Studies have also shown an increased risk associated with excess white bread, rice, or indulgent grain intakes when the overall diet is out of balance. The results of most, but not all, studies show that grain-based foods that are eaten as part of a balanced dietary pattern do not increase the risk for developing MCI, Alzheimer's disease, or Parkinson's disease and, in fact, may reduce the risk.

The relationship between grain-based foods and brain health was introduced in a previous article (1) as part of the CIMMYT series on the role of grains in health (2–8). This is the second article in a two-part review on the impact of nutrients from grains and grain-based foods on mild cognitive impairment (MCI), Alzheimer's disease, and Parkinson's disease. Because both the causes and cures for these conditions are elusive, lifestyle and nutrition are being scrutinized to

determine whether they play roles in prevention and therapy for these common dementias.

This article reviews the existing scientific literature on the impact of minerals, phytochemicals, specific grain-based foods, and grain-based foods in balanced and unbalanced dietary patterns on these disorders. The companion article to this review focused on the impact of macronutrients (CHOs) and vitamins from grains on MCI, Alzheimer's disease, and Parkinson's disease (9).

nesium enables neurons to pass electrical and chemical signals to other neurons (neurotransmission) and is critical for learning and memory functions (10–14). Excess or inadequate levels of one or more of these metals upsets the overall balance of minerals, which may have a number of impacts, including altering the absorption or utilization of minerals, initiating changes in brain structure and function, changing the oxidative state of certain minerals, creating toxicity, and causing cell death. The net result can be diminished cognition and neurodegenerative disorders (15,16).

Alzheimer's Disease and Parkinson's Disease

Disordered mineral transport and tissue distribution can be markers of dementias and cognitive disorders. For example, zinc homeostasis is regulated, in part, by the zinc transporter mechanism. Abnormalities in this mechanism have been documented in the brains of mice and humans with Alzheimer's disease.

MINERALS FROM GRAINS: IMPACT ON BRAIN HEALTH

Mineral balance is crucial not only for overall health, but also for brain health. Copper, zinc, and iron, and to a lesser extent manganese and magnesium, are naturally abundant in the brain, where they play key roles in the activities of various enzymes, stabilization of DNA, and maintenance of synapse function, density, and plasticity. In addition, mag-

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Alzheimer's disease patients, compared to individuals without dementia, have elevated levels of iron, copper, aluminum, and zinc in their brains, as well as amyloid plaques (17). Patients with Parkinson's disease, compared to healthy controls, have lower levels of serum zinc and iron transport proteins and higher levels of iron deposited in the substantia nigra (18), the area of the midbrain where the loss of cells results in a deficit of dopamine, which is characteristic of Parkinson's disease. Lower plasma selenium and iron levels are associated with reduced risk for Parkinson's disease (15,18). In addition, the brains of patients with Parkinson's disease have higher levels of copper, zinc, and manganese (12,16,17,19). Excess zinc favors formation of zinc- $A\beta$ (β -amyloid) complexes, β -amyloid precursor protein expression, and plaque burden (10,11,17). Furthermore, zinc deposition in amyloid in the brain appears to deplete zinc from other body systems, resulting in low hair and serum levels (10,11,16,17,20–23). Studies have also shown that copper and manganese levels in hair are higher and selenium level is lower in patients with Alzheimer's disease than in healthy controls (21,22), and magnesium levels in cerebrospinal fluid in patients with Alzheimer's disease is lower than in healthy controls (22).

Redox-active minerals such as copper and iron can promote oxidation, which is thought to occur early in the process of neurodegeneration and is a hallmark of both Alzheimer's disease and Parkinson's disease (15–17,24,25). This not only impairs function, but also decreases the number of neurons and can catalyze aggregation and hyperphosphorylation of tau protein, the main component of the neurofibrillary tangles associated with Alzheimer's disease (26). In addition, the mineral-amyloid complex formed is active and furthers oxidation (1,26,27). For both Alzheimer's and Parkinson's disease, it is unclear whether the effects of minerals are due to altered utilization, caused by disease processes, or result from a combination of low intakes or changed metabolism.

MCI

Proper mineral nutrition throughout life appears to be important for cognitive health, especially because magnesium can counter insulin resistance and reduce the risk of type 2 diabetes, which are known risk factors for dementia and poorer cognition (28). Studies have specifically iden-

tified the association of higher magnesium intakes with reduced risk for developing MCI and low magnesium levels with increased risk (29–31). In a Japanese cohort, those who had the highest magnesium intakes showed nearly a 75% reduction in risk for vascular dementia, including MCI and Alzheimer's disease (30). The 17 year Personality and Total Health (PATH) Through Life Project also showed that adequate dietary mineral intake by cognitively healthy individuals was associated with a lower risk for developing MCI (31).

Mineral Status and Grain-Based Foods

Because adequate mineral status may impact cognitive functioning, appraisal of mineral intakes is important. Data from food intake surveys in the United States, Canada, and Europe show that iron intakes are adequate for most individuals, even the elderly (32–35). For example, the European Nutrition and Health Report II showed that the mean prevalence of iron inadequacy was below 11% (35). Yet, there are minerals for which intake by elderly individuals may be low. This was shown in a small Polish cohort of postmenopausal women (36), and in India, where only 59% of male and 43% of female elderly individuals, mostly vegetarians, had adequate intakes of iron (37). Further, iron absorption studies on Indian diets have shown that a much smaller portion of iron is available from a mixed cereal–pulse vegetarian diet. Among different types of cereal grains, iron was better absorbed from rice than from wheat, and absorption from both of these grains was better than absorption from millet.

Zinc. Elderly individuals are particularly prone to zinc deficiency because of the lower energy requirements and physiological vulnerabilities associated with aging (38). About 25% of older U.S. males and females (51–70 years of age) failed to meet the EAR (estimated average requirement) for zinc from food alone; however, with the addition of supplements the number was reduced to <5% (32). Similar data were reported for Canadians (33), whereas European data showed only 10% prevalence of inadequate zinc intake (35).

The overall European intake data may hide inadequate intakes in the elderly populations in certain countries, however. In a sample of free-living elderly Spanish individuals (mean age ~79 years) inadequate intakes of zinc were observed, with men having lower intakes than women (39). Intake data for elderly Irish individuals

showed a similar pattern (40). Among older Polish adults 44% had deficits in zinc, and a small study of Polish postmenopausal women found that nearly 70% of the women had inadequate intakes (36). Among elderly Indian adults (mostly vegetarians), only 39% of the males and 26% of the females had adequate zinc intakes (37,41). In parts of Southeast Asia and South Africa, more than 70% of elderly adults are at high risk of developing zinc deficiency (38,42). In a random national survey of Australian adults, daily intakes of zinc were marginal, with intake for 67% of men and 85% of women below recommended levels (43). To add to the problem of inadequate intake, some elderly individuals have a reduced capacity to absorb or utilize zinc due to drugs or disease, which exacerbates the effects of low intakes (44). Low zinc levels in serum were correlated with oxidative stress and cellular aging (45).

Magnesium. Magnesium intake seems to be low in most surveys. Surveys in North America show that a significant portion of the population failed to meet the EAR through food intake (32,33). More than 85% of adults in the United States over the age of 70 failed to meet the EAR for magnesium through diet alone; however, that percentage was reduced in supplement users to around 40% for males and 30% for females (32). In Canada for those 51 years of age and older, 61% of males and 46% of females had inadequate magnesium intakes from their diet alone. Supplementation brought these percentages down to levels similar to those seen in the United States (33). The prevalence of obesity is a complicating factor as well (46). Compared with normal weight adults in NHANES data, obese adults had lower intakes of micronutrients (about 5–12%) and a higher prevalence of nutrient inadequacy, especially for men (46). In an elderly population in India (mostly vegetarian), 88% of the males and 76% of the females had adequate intakes (37).

For young adults in Poland, magnesium intakes from food were below recommended levels (47), and nearly 70% of postmenopausal women had inadequate intake levels (36). Low intake levels were also found among elderly adults in Ireland (40) and free-living elderly adults in Spain (mean age ~79 years) (39). Of the elderly Spanish adults more than 90% did not meet 80% of the European Food Safety Authority (EFSA) magnesium intake requirements (48).

Copper. The European Nutrition and Health Report II showed that the mean prevalence of inadequacy for copper intake was 11–20% for adult and elderly populations (35). Once again, however, the overall means fail to tell the whole story for some specific regions. For example, among Polish postmenopausal women, more than 85% had inadequate copper intakes (36).

Selenium. The European Nutrition and Health Report II showed that the mean prevalence of inadequacy for selenium was higher than 20% (35). In a systematic review of free-living older adults, intakes of selenium were low enough to be considered a public health concern (49). Grain-based foods can be important sources of selenium, depending on the selenium content of the soil in which the crop is grown. Selenium content is high in shale soils; thus, it is naturally high in wheat-growing regions of North America, such as Kansas and North and South Dakota (50). Soil biofortification with selenium, which is done in parts of Europe and elsewhere, has proven to be a successful method for addressing mineral inadequacies, including selenium (51).

Role of Grain-Based Foods in Brain Function

Consumers of breakfast cereals ($n = 3,728$, aged 2 years and older) in the U.K. Low Income Diet and Nutrition Survey (2003–2005) had higher intakes of iron and zinc than nonconsumers (52). Cereals and grain products also were the major dietary contributor of magnesium (22.6%) in a cohort of elderly Spanish adults (48).

Adequate intakes of a variety of grain-based foods are very helpful for maintaining a healthy mineral status, with whole grains providing higher levels of minerals and enriched grains allowing easier absorption of minerals. A systematic review found that zinc intakes were higher among consumers of exclusively whole grain and high-fiber breakfast cereals compared with consumers of other breakfast cereals (53). Enriched, fortified, and whole grains contribute 31% of the iron, 16% of the zinc, 14% of the magnesium, 13% of the phosphorus, and 7% of the potassium in a balanced diet (54).

The outer layers of whole grains can also be a source of heavy metals if they are present in the environment (55). Adequate intake of other minerals and nutrients is the best defense against absorption and the negative impacts of many of these toxic

sumption of grain-based foods helps to maintain proper neurological functioning and delay onset of MCI, Alzheimer's disease, or Parkinson's disease (74).

IMPACT OF SPECIFIC GRAIN-BASED FOODS ON COGNITION AND BRAIN HEALTH

Only a few studies have looked at grain-based foods, collectively or individually, and their impact on cognition, brain health, and MCI, Alzheimer's disease, and Parkinson's disease. There are a number of studies that have examined these foods as part of dietary pattern research, and these will be reviewed after looking at the impact of specific foods.

Breads and Cereals

Studies on the impact of breads and cereals on cognition and cognitive decline in elderly adults suggest that the outcome depends on the types and amounts of bread eaten and the background dietary pattern. However, the results from most of these studies indicate that these staple grain-based foods, especially those containing dietary fiber, are associated with improved cognition and lower risk for developing MCI and other dementias. Several studies of elderly populations indicate that cognitive function is related to higher intakes of grain-based foods. In more than 2,000 elderly Norwegian subjects (70–74 years of age), those who had the highest intakes of grain products (as well as fruits, vegetables, and mushrooms) performed significantly better on cognitive tests than those with very low or no intake (75).

Institutionalized elderly Spanish subjects ($N = 178$) with higher cereal and dietary fiber intakes had fewer errors on memory tests and showed improved cognition (76). The results of a statewide survey of elderly adults in Alabama ($n = 1,056$) showed bread/cereal intake was inversely associated with cognitive impairment, whereas dessert intake was positively associated with cognitive impairment (77). Cereals were one of the foods associated with lower risk for Alzheimer's disease in populations from Europe and North America (75).

The amount and type of bread consumed may also have an impact on cognition. For example, cognitive test scores for the elderly Norwegian Hordaland Health Study cohort were highest after consumption of certain foods, one of which was high-fiber bread (75), whereas very high intakes of

white bread were associated with lower scores. However, this study showed that there was an optimal intake level for grain-based foods. Cognitive scores increased as intakes of grain products (and potatoes) increased to between 100 and 150 g/day and then plateaued or decreased at higher intake levels. The study showed that consumption of excess amounts of grain and white bread products and inadequate amounts of dietary fiber were problematic, underscoring the need for dietary balance (75). The benefits of dietary balance were also demonstrated in a study of 4,000 elderly adults in the 12 year Cache County (Utah) Study on Memory Health and Aging (78). Cognitive scores were higher, both at baseline and subsequently, for those consuming ready-to-eat (RTE) cereals more frequently than weekly but less frequently than daily. Daily and non-consumers of RTE cereals had lower scores (78). In the Women's Health Study, higher whole grain intake (2.2 servings/day) was associated with higher average cognition scores compared with women whose daily intake of whole grains was lower (0.8 servings/day) (79). In a European cohort, higher whole grain bread and cereal intakes provided higher mineral intakes from the diet (80). Findings such as these suggest that when eaten in the right balance grain-based foods are associated with better cognitive functioning (75,81).

The literature on the impact of grain-based foods on Parkinson's disease is limited. In Sweden, intake of Swedish white and French breads in a small case-control study was associated with lower risk for Parkinson's disease. In contrast, a U.S. study conducted in Washington State found that neither bread nor cereal intake was associated with risk for Parkinson's disease (82,83). In a case-control study, Parkinson's disease patients reported eating significantly larger quantities of sweet foods and eating more snacks than control subjects (84). (Studies with Alzheimer's disease patients point to similar trends.) The authors suggest that the findings may be the result of illness-related changes in dietary habits and perhaps were not causal (84).

Rice

Study findings on rice intake and its impact on MCI, Alzheimer's disease, and Parkinson's disease show mixed results. Higher total cereal (primarily rice) and carbohydrate (CHO) intakes among older Korean women ($n = 239$) were positively associated with higher scores on cognitive

tests, whereas lower cereal intake was associated with lower scores for cognitive functioning (85).

In contrast, two Japanese studies implicate rice in increased risk for Alzheimer's disease. One study showed that total energy, meat, and rice intakes were associated with risk for Alzheimer's disease (86). Further, in more than 1,000 Japanese subjects, a balanced dietary pattern that included a mix of soybean-based foods and vegetables and lower intakes of rice was associated with lower risks for Alzheimer's disease and cognitive decline (87). However, the authors of the paper stress that the association between rice intake and Alzheimer's disease and cognitive decline might be the result of unbalanced dietary patterns (i.e., high rice intake might mean that foods that could help prevent dementia were lacking) rather than any harmful effects of the rice itself (87).

GRAIN-BASED FOODS AS PART OF HEALTHY DIETARY PATTERNS

The impact of a specific grain-based food or group of foods on brain health is often difficult to determine because grains are not (nor should they be) eaten in isolation. Healthy dietary patterns such as the Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH) Diet, and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet all include grain-based foods as part of a balanced pattern (88,89). The basic components and recommended servings for each of these diets are provided in Table I. Study findings have shown that these diets are associated with lower risks for cognitive impairment, cognitive decline, and dementia or Alzheimer's disease compared with typical "Western" diets that are high in red meat, dairy products, and sweets; are low in foods that provide key nutrients; and have minimal intakes of fruits, vegetables, fish, legumes, and whole grains (88,90). The Mediterranean, DASH, and Mind Diets, as well as other patterns that focus on dietary balance and diversity, are thought to promote general health because they include nutrients and phytonutrients in beneficial proportions. In a study on dietary quality, an association between dietary diversity and higher cognitive scores was shown for elderly Taiwanese adults (91).

This review focuses primarily on the Mediterranean and DASH Diets, but their similarity to other health-promoting diets suggests they are all likely to have similar

impacts. The MIND Diet is also discussed. The Mediterranean Diet was recognized more than 50 years ago by Ancel Keys and colleagues (92) as being associated with heart health and longevity. More recently, an association between the diet and lower risk for cognitive decline has been shown. The DASH Diet was developed by the U.S. National Heart, Lung, and Blood Institute to determine whether healthy eating patterns could have positive impacts on blood pressure. Subsequent research has shown that the diet can improve not only blood pressure but many health outcomes, including cognition (93). Such diets emphasize inclusion of vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, beans, and healthy oils and recommend moderate consumption of foods that are high in saturated fat, red meat, and wine (79,88). There are a few differences between the two diets. The DASH Diet limits sodium and the Mediterranean Diet emphasizes olive oil and nuts; however, they both recognize the role of cereal grains (both refined and whole in balanced amounts) as part of a balanced diet. The MIND Diet is a blend of these two diets, but recommends consumption of only whole grains and fewer servings of grain. The diet was designed to specifically address cognitive functioning and delay dementia.

In contrast with these balanced dietary patterns, unbalanced patterns often include excess saturated fat and very inadequate fruit, vegetable, and fiber consumption.

Unbalanced patterns may also include a high proportion of refined sugars and snack foods with low nutritional value. There are many names for unbalanced diets, such as “Western,” “meat and potatoes,” and “red meat and white bread” patterns. They are not only linked with higher risks for obesity, heart disease, and diabetes, but also with higher risk for Alzheimer’s disease (77,79,88–90,94–97). In contrast, balanced dietary patterns that include lower intakes of white bread, sugars, and red meat and higher intakes of fruits, vegetables, fish, and whole grains are termed “prudent” diets.

Results of studies from several countries show that lower cognitive scores and greater risk of Alzheimer’s disease occur with diets that are high in meat, fat, and white bread and low in vegetables and grains. In a Polish case-control study ($n = 71$ patients and matched controls), patients with Alzheimer’s disease had high intakes of meat, butter, eggs, refined sugar, and high-fat dairy products, whereas the control group had high intakes of grains, cereals, bread, and vegetables (95). In a study of more than 1,000 elderly British adults over 85 years of age, dietary patterns high in meat, butter, gravy and potatoes were associated with poorer cognitive scores than other dietary patterns (98–100). However, the pattern was not associated with cognitive decline. Further, intake of whole and refined grains differed little among the dietary patterns and had little impact on outcomes despite the fact that

cereals and cereal products were the top contributors to energy and CHO intakes. In elderly Irish subjects following “prudent” dietary patterns, which specifically were noted as being low in red meat and white bread, had higher cognitive function scores than those following “Western” dietary patterns described as high in red meat and white bread and low in fruits and vegetables (96).

In Asian cultures unbalanced dietary patterns are sometimes characterized by very high intakes of white rice and low intakes of other foods. Among more than 750 older Korean adults, those following a “multigrain rice, fish, dairy products, fruits and fruit juices” pattern, compared to those following a pattern with higher intakes of “white rice, noodles, and coffee,” had lower risk for cognitive impairment (85).

Dietary pattern research does contain some degree of confounding. Those who follow a Western pattern may ingest excess calories and have sedentary lifestyles, which are associated with a number of adverse health conditions, such as diabetes, that contribute to cognitive impairment (101–105). On the other hand, those following a “prudent” diet often have a number of dietary and lifestyle patterns that may lower disease risk, making the attribution of risk to a specific food, nutrient, food group, or combination of nutrients difficult.

Since the first published studies showing the cognitive benefits of adherence to

Table I. Dietary patterns associated with cognitive health: Dietary components and recommended servings for the DASH, Mediterranean, and MIND Diets^a

DASH Diet ^b		Mediterranean Diet		MIND Diet	
Food Group	No. of Servings	Food Group	Frequency or Amount	Food Group	Frequency or Amount
Grains (mostly whole) per day	6–8	Grains/cereals (mostly whole)	Every meal	Whole grains	≥3/day
Meat, poultry, and fish per day	≤2	Meats and sweets	Less often	Green leafy vegetables	≥6/week
				Other vegetables	≥1/day
Vegetables per day	4–5	Poultry, eggs, cheese, and yogurt	Moderate portions, daily to weekly	Berries	≥2/week
Fruits per day	4–5	Fish and seafood	Often, ≥2/week	Red meat	<4/week
				Fish	≥1/week
Low-fat or fat-free dairy products per day	2–3	Fruits, vegetables, nuts, legumes, and seeds	Base every meal on these foods	Poultry	≥2/week
Nuts, seeds, legumes per week	4–5			Beans	>3/week
Fats and oils per day	2–3	Fats (i.e., olive oil)	Replace butter with olive oil at each meal	Nuts	≥5/week
				Fast/fried foods	<1/week
				Olive oil	<1 Tbsp/day
				Butter/margarine	<1/week
				Cheese	<5/week
Sodium per day	2,300 mg	Herbs and spices	Use to flavor foods	Pastries and sweets	<5/week
				Alcohol/wine	1 glass/day

^a DASH = Dietary Approaches to Stop Hypertension; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay. Other similar dietary patterns include the French National Nutrition and Health Programme (Programme National Nutrition Santé [PNNS]); Recommended Food Score (RFS); Healthy Eating Index (HEI); and Alternate Healthy Eating Index (AHEI) (88).

^b Based on a 2,000 calorie/day diet.

the Mediterranean Diet, studies from New York, rural Utah, and Australia have shown that greater compliance with such dietary patterns from the middle decades of life and beyond is associated with reduced risk for MCI and Alzheimer's disease and slower progression of the disease (89,90,93,97,106–117). Similarly, high adherence to DASH and other balanced dietary patterns that emphasize intake of fruits, vegetables, cereals, and whole grains have also been associated with a lower likelihood of developing Alzheimer's disease (90,97,110,115). A few examples, such as the Washington Heights–Inwood Columbia Aging Project involving 2,364 nondemented individuals in New York, have shown adherence to the Mediterranean Diet to be associated with a borderline reduction in risk for developing MCI and a reduction in risk for progression from MCI to Alzheimer's disease. Even in individuals with increased genetic risk for development of Alzheimer's disease due to the apolipoprotein E (*APOE*) $\epsilon 4$ allele, long-term adherence to the DASH Diet for more than 16,000 women over 70 years of age in the Nurses' Health Study was associated with better than average cognitive functioning (118). High adherers had cognitive scores that measured them as an average of one year younger than their actual ages.

The positive impact the Mediterranean Diet has on cognitive function has not only been shown in cohort and case-control studies, but also in the large PREDIMED intervention trial with participants ($N = 522$) at high risk for vascular disease (119). In the intervention trial, those following the Mediterranean Diet had higher mean Mini-Mental State Examination (MMSE) and other cognitive test scores compared with those following a low-fat diet (119).

Although the findings from many studies support the benefits of these balanced dietary patterns, there are three large cohort studies that failed to show that adherence to healthy patterns helped to prevent cognitive decline. For example, in the Women's Health Study with more than 6,000 U.S. women over 65 years of age adherence to the Mediterranean Diet did not impact cognition measures, but intake of whole grain was one factor that appeared to lower risk for cognitive decrement (79). In addition, adherence to the DASH Diet, Mediterranean Diet, or any other of four healthy dietary plans for 9 years among more than 6,000 postmenopausal women over 65 years of age in the Women's Health Memory Initiative proj-

ect was not associated with risk for cognitive impairment (120). (The latter study was criticized because diets may not remain stable over time, and diet measures were only recorded at baseline (121).)

Concerns about maintaining optimal cognitive functioning resulted in the creation of a hybrid of the Mediterranean and DASH Diets—the MIND Diet (122). The MIND Diet focuses on foods and nutrients that scientific research has shown to be associated with prevention of dementia (123–125). This diet emphasizes inclusion of green leafy vegetables, nuts, berries, beans, whole grains (at least 3 servings/day), oily fish, poultry, olive oil, and wine and recommends limiting inclusion of red meat, butter/stick margarine, cheese, pastries, and sweets, as well as fried or fast foods (126). In a prospective cohort study of 923 participants (ages 58–98 years) those with high adherence to the MIND Diet lowered their risk for Alzheimer's disease by about 50% over those with poor adherence (127). Interestingly, even those who modestly adhered to the diet lowered their risk for developing Alzheimer's disease by about 35%.

Thus, the majority of studies show that balanced dietary patterns are most beneficial for maintaining or improving cognition, and they may reduce the risk for or delay the onset of MCI and Alzheimer's disease. It is also true that unbalanced patterns that include high intakes of red meat, saturated fat, and CHO, as well as bread and grain-based desserts, and inadequate intakes of fish, fruits, vegetables, and dietary fiber promote oxidation, insulin resistance, and other metabolic reactions that do not favor optimal cognitive functioning and may increase the risk for developing MCI and Alzheimer's disease.

EVIDENCE FOR THE PROTECTIVE ROLE OF BALANCED DIETARY PATTERNS IN PARKINSON'S DISEASE

Balanced dietary patterns may be useful in reducing the risk for Parkinson's disease, but only a limited number of studies have been published. Higher adherence to a Mediterranean-type diet, as assessed in a case-control study ($n = 257$ Parkinson's disease patients and 198 controls), was associated with reduced risk for Parkinson's disease (128), whereas lower adherence was associated with earlier onset. Similarly, a "prudent" diet with high intakes of fruits, vegetables, and fish was inversely associated with Parkinson's disease risk in the Health Professionals

Follow-Up Study and the Nurses' Health Study ($n = 49,692$ men and 81,676 women), whereas a Western dietary pattern was not (129). Adherence to the Japanese healthy dietary pattern (characterized by high intakes of vegetables, seaweed, pulses, mushrooms, fruits, and fish) was inversely related in a case-control study to risk for Parkinson's disease (130). Although other identified patterns did not increase the risk for Parkinson's disease, patterns with a high glycemic load (GL) were inversely associated with risk for Parkinson's disease. The latter may mean that when rice is included in the right amount as part of a health-promoting pattern that it contributes to GL but does not increase risk. This suggests the right balance of grains, both whole and refined, and a balanced dietary pattern are required to reduce risk. More research is needed to determine how balanced patterns impact Parkinson's disease.

CONCLUSIONS

Grain-based foods are important contributors not only of macronutrients and vitamins (1,2,9), but also of minerals and phytonutrients that impact brain health and cognitive function. Maintaining an optimal balance of minerals, nutrients, and phytonutrients is critical for minimizing creation of free-radical products from oxidation and inflammation. In addition, phytochemicals from whole grains, such as phytate or ferulate, may act as anti-inflammatory, antioxidant, and chelating agents, which are all activities that help protect brain functioning (58). In addition, betaine may work with certain B vitamins to inhibit tHcy, a known risk factor for MCI and Alzheimer's disease. Inadequate intakes of grain-based foods may lead to mineral imbalance or insufficient antioxidant protection, which is associated with higher risks for MCI, Alzheimer's disease, and Parkinson's disease.

Although whole grains fed to high-risk individuals, even when part of an otherwise unbalanced diet, reduced inflammation (131), it appears that the beneficial components in grain-based foods are more useful when they are consumed as part of a health-promoting dietary pattern. Higher risks for MCI, Alzheimer's disease, and Parkinson's disease have been linked to habitual consumption of "Western" diets that are high in red meat and refined carbohydrates and grains and low in fruits, vegetables, and whole grains. Lower risks are associated with habitual

consumption of balanced dietary patterns such as the DASH or Mediterranean Diet. Because of much confounding, it is not possible to attribute the cause of common dementias to excessive intakes of refined CHO-rich staple foods such as bread, rice, and cereal- or grain-based desserts and snacks or animal products that are high in saturated fat; to low intakes of recommended fats, fish, fruits and vegetables, whole grains, nuts, seeds, low-fat dairy products, or dietary fiber; or to a combination of nutrient inadequacy in the face of excess calories or overall dietary imbalance.

What is clear is that there are many components found in both whole and enriched refined grains that contribute to cognitive health and reduced risk for developing MCI, Alzheimer's disease, and, perhaps, Parkinson's disease. Dietary fiber, vitamin E, and magnesium are all provided by grain-based foods and are nutrients of concern because many people fail to ingest adequate amounts. Further, it is important that enriched and refined grain-based staples not be placed in the same category as grain-based indulgent foods such as snacks and desserts in dietary recommendations.

The prevention of dementias is a growing public health concern because there is no effective cure and rising global prevalence (86). Because MCI seems to be part of the continuum from normal aging to development of Alzheimer's disease and other dementias, identifying dietary patterns that can help delay this progression is important (114,132). Dietary approaches that include grains and whole grains and their beneficial components as part of a balanced pattern appear to be associated with reduced risk (not with increased risk as has been alleged by some) and delayed onset of MCI, Alzheimer's disease, and Parkinson's disease.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Role of Carbohydrates and Grains in Nutrition and Neurological Disorders: Headache, Attention Deficit Hyperactivity Disorder, and Depression^{1,2}

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ABSTRACT

Claims made in the popular press allege that grain-based foods, and the carbohydrates (CHOs) they contain, cause or worsen various neurological disorders, including headache, attention deficit hyperactivity disorder (ADHD), and depression. This article reviews the scientific literature to assess the role of these foods in nutrition and their impact on headache, ADHD, and depression. The bulk of the scientific literature shows that nearly all grain-based products are listed as nonoffending foods and are not thought to increase the risk of most types of headaches. When grain-based foods, and their CHOs, are consumed as part of balanced dietary patterns that emphasize an optimal mix of whole and refined grains, such as DASH (Dietary Approaches to Stop Hypertension) or Mediterranean Diets, they are associated with reduced headache risk. Although there are a number of food triggers for headache, grain-based foods are not listed as likely triggers. Evidence linking specific grain-based foods to headache is either lacking or extremely weak. However, excess weight, poor blood sugar control, and grain allergies or intolerances may increase risk. ADHD is a brain disorder that has many etiologies. Diet and food additives are suggested causes of ADHD, and elimination diets have been proposed as one strategy to decrease risk. However, study results are inconsistent, and controlled studies with gluten have failed to show that its elimination impacts ADHD. If anything, ingestion of grain-based foods as part of a healthy dietary pattern appears to reduce risk and improve symptoms. Abnormal glucose control may increase behavioral issues, and some small studies have shown that low-glycemic cereals or diets may be helpful in controlling behavior. However, low intakes of dietary fiber and n-3 fatty acids, unbalanced diets with frequent ingestion of indulgent foods, and disordered eating patterns are all associated with ADHD. Balanced dietary patterns are associated with reduced risk of depression. However, intake of CHOs or grain-based foods as part of high-fat, high-sugar food patterns are associated with the onset of symptoms of depression. Study results relating glycemic index or load and depression are mixed, but higher dietary fiber intake is consistently associated with reduced risk. Balanced dietary patterns incorporating a mix of grains and adequate dietary fiber have the most data supporting a positive relationship with all of these conditions. Brain health greatly depends on mitigation of oxidative stress and inflammation. The vitamins, minerals, and phytochemicals in grains provide many antioxidants and dietary fiber, in the diet. Scientific literature reporting findings that grains, grain-based foods, and their CHO components either cause or exacerbate any of these conditions is lacking.

Grain-based foods, and the gluten and carbohydrates (CHOs) they contain, have been blamed in the media and popular press for causing adverse health effects, including neurological disorders. Popular press books such as *Grain Brain* (1) and *Wheat Belly* (2) suggest that grain-based foods are related to headache, attention deficit hyperactivity disorder (ADHD),

and depression. Although scientific studies do show that under certain conditions grain-based foods may impact blood glucose and markers of inflammation (3–6), many studies show their importance in reducing or alleviating these conditions.

This article joins those in the CIMMYT series of articles on CHOs, grains and health (7–16). Search terms linking headache, ADHD, and depression with “carbohydrate,” “glycemic index and glycemic load,” “dietary or cereal and grain fiber,” and “grain, whole grain, and refined or enriched grain”; specific grain-based foods such as “bread,” “cereal,” “pasta,” and “rice”; and dietary patterns such as the “Mediterranean Diet” or “Western diet” were used to create this review.

OVERVIEW OF HEADACHE

Fifty to seventy-five percent of adults report having a headache at least once a

year, and thirty percent of these adults report having a migraine. Headache disorders, characterized by recurrent headache, are one of the most common neurological problems, with women having a higher rate than men (17–19). Frequent and debilitating headaches negatively impact the quality of life for those who are plagued by them (1,20). The major types of headaches (20) include

- Primary Headaches
 - o Migraine
 - o Tension-type
 - o Cluster
 - o Other primary headaches
- Secondary Headaches
 - o Headaches related to another disorder or condition

CHOs, Grains, and Diet

There is a connection between diet, nutritional status, and headache. Although a

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number of foods are headache triggers, no food or food group is a trigger for all headache types or sufferers. Fermented foods, such as aged cheeses, wines, whiskies, and some Asian sauces, are associated with the onset of headaches and migraines. Because these products contain tyramine and other vasoactive amines, these may be the trigger compounds for some individuals. The levels of these amines in nearly all breads and cereal products (except for sourdough) are low. Withdrawal from caffeine or the ingestion of certain food additives, such as nitrates, may also be triggers. Common dietary triggers of headache (12,20) include

- Fermented Foods
 - Cheeses, especially cheeses aged for long periods
 - Alcoholic drinks, especially aged red wine, champagne, whiskies, and beer
- Specific Food and Dietary Components
 - Chocolate
 - Citrus fruits
 - Hot dogs
 - Fatty foods
 - Ice cream
 - Caffeine withdrawal
- Additives and Amines
 - Monosodium glutamate
 - Aspartame
 - Nitrites
 - Sulfites
 - Tyramine
 - Phenylethylamine
 - Histamine

More than 30 years ago Egger et al. (21) reported that 93% of children ($N = 88$) who suffered from migraine improved when placed on a very restrictive (oligo-antigenic) diet and that reintroduction of foods one at a time could be used to identify the offending food(s). However, a recent two-part narrative review (11,22) found that the evidence was fairly weak for most foods.

Lack of food in general or inadequate glucose for the brain also may trigger headaches (20,23,24). When blood glucose levels are too low (hypoglycemia) or during periods of fasting, headaches, including migraines, may occur. Consuming CHO every 4–5 hr is a strategy some headache sufferers use to stabilize blood glucose levels and reduce the risk of headache. Headache prevalence and frequency is related to BMI (body mass index) in many studies (25). Foods that deliver slowly avail-

able CHOs may be most useful for maintaining steady blood glucose levels. In the large Canadian Trial of Carbohydrates in Diabetes (CCD), a low-glycemic index (GI) diet (52% of energy from CHO; GI = 55) was associated with lower headache frequency than either a high-GI diet (47% of energy from CHO; GI = 64) or a low-CHO diet (40% of energy from CHO; GI = 59) (3).

Counterintuitively, a ketogenic diet in which CHO intake was extremely restricted has been shown in a few case reports and small studies (26,27) to reduce cluster headaches or migraines (28). For example, for 45 chronic migraine sufferers, those who followed a ketogenic diet for 1 month significantly reduced migraine frequency. Further, there was continuous improvement during the 6 month duration of the study (28). However, an Atkins-type, low-CHO diet was not found to be beneficial for adolescent headache sufferers, and compliance was a problem (29). Nonetheless, preliminary results indicate that diet modification might warrant further trials, especially for those with intractable headaches. B vitamins, especially riboflavin, and vitamin E found in grain-based foods in rodent models have been shown to possibly provide antioxidant protection to various parts of the brain and might be helpful in the prevention of migraines. As sources of these vitamins, grains may help prevent migraines in humans (30).

A March 2017 search on “headache and grain,” “headache and wheat,” “headache and cereal,” and “headache and rice” yielded no citations, with two exceptions: 1) grain with some form of contamination, such as the presence of mycotoxins; and 2) for those with celiac disease or non-celiac gluten sensitivity (NCGS) or allergies to wheat or another grain (31–35).

Allergies and Celiac Disease

Headache may be one of many symptoms of celiac disease and NCGS in both adult and pediatric populations, and migraines may be more prevalent in these patients than in general populations (31–35). Following a strict gluten-free diet has been found to significantly reduce headache symptoms and frequency in celiac patients (33,34). Headache may indicate inadvertent gluten exposure in patients with celiac disease who are following a gluten-free diet (36). However, migraine sufferers do not show a greater prevalence of celiac disease (37).

Thus, aside from those with allergies and gluten-related diseases, there is little

data showing that specific grains or grain-based foods are related to headache.

Dietary Patterns

Although there has been little information published concerning specific grain-based foods and their relationship to headaches, these foods consumed as part of balanced dietary patterns may be involved in their reduction and treatment. Diets such as Dietary Approaches to Stop Hypertension (DASH) (described in an earlier article in this series [9]) that are balanced nutritionally and provide adequate intakes of fruits, vegetables, and whole grains, and potassium and other minerals may positively impact blood pressure. Patients with hypertension tend to have a higher frequency of headache, so diets designed to address elevated blood pressure are thought to be helpful (38). Studies show that patients experienced reduced headache frequency when following a low-sodium DASH Diet (19). However, the data on sodium do not provide a clear picture of its effects. In an NHANES analysis, men in the highest quintile of sodium intake had fewer headaches irrespective of BMI, but for women this was only true for those with lower BMIs (39).

Total diet quality appears to impact headache. Analysis of NHANES data shows that normal weight women who do not suffer from severe or migraine headaches were more likely to consume diets that were more closely aligned with the U.S. Department of Agriculture (USDA) *Dietary Guidelines for Americans* than patients who experience migraines. Similarly, headaches are more likely in normal weight women with lower scores on the Healthy Eating Index (20). However, diet quality scores did not differ for women who suffered headaches who were either under- or overweight.

Summary

Grain-based foods are not included in lists of headache triggers and are usually found on lists of foods to include in the diet. Diets that supply steady levels of CHOs for the brain are associated with reduced headaches. A few small studies suggest that a ketogenic diet may be a useful treatment strategy for those with severe migraines or intractable headaches, but much more testing is needed before widespread adoption of such treatments can be recommended. In general, a diet that promotes health, together with a regular pattern of eating, is one that is generally beneficial for headache sufferers.

OVERVIEW OF ADHD

ADHD is a brain disorder that is characterized by difficulty staying focused and completing tasks, controlling behavior and impulsivity, and, in many cases, hyperactivity. The severity of symptoms varies among patients and throughout the life of a patient (40). It is more often seen in children and may impair development, but can occur at any age (1,41). Estimates of incidence in U.S. children range from 3 to 11% due to nonuniform definitions, reporting, and diagnostic criteria. U.S. estimates are much higher than those globally, which in 2010 was 2.2% for males and 0.7% for females (42).

The etiology of ADHD is not well understood but appears to encompass a combination of genetic, lifestyle, and environmental components (43–45). Some gestational factors (46–48) may be involved in ADHD and include

- Cigarette smoke
- Alcohol
- Lead
- Gestational diabetes
- Maternal obesity

Diet quality and dietary components, especially food additives, have been postulated as being associated with ADHD, but the findings are mixed (40,49,50). Poor diets are also suggested as a causal factor—diets low in copper, iron, zinc, and magnesium are associated with ADHD (49,51).

Grains, CHOs, and Dietary Patterns

Total calories, time of food ingestion, and diet quality may all be associated with ADHD. For example, calorie intake was lower in ADHD patients in a case-control study in Spain. However, the distribution of calorie intake throughout the day differed with ADHD patients. ADHD patients ingested fewer calories during the day and more in the evening. Healthy children compared with those with ADHD had overall better diet quality and ingested more cereals, CHO, dietary fiber, protein, and fat (52). Similarly, Korean school-aged children whose diets were high in CHO, mainly rice, and low in fat were less likely to have ADHD (51).

For a sample of about 2,000 children who were followed through adolescence, an unbalanced “Western” dietary pattern that was high in saturated fats and refined sugars was associated with development of ADHD (53). In contrast, diets low in sat-

urated fat and refined sugars and high in dietary fiber and folate were not associated with ADHD diagnosis (53). In a small cohort of Iranian schoolchildren ($N = 375$), neither “Western” nor “traditional” patterns were associated with ADHD (54). In contrast, those children in the highest quintiles for adhering to either a sweet dietary pattern or a fast-food pattern had a threefold to fourfold higher risk for ADHD compared with those in the lowest quintiles. Data from a U.K. cohort (measured for both 4–6 and 6–8 year olds) showed that diets high in foods labeled as “junk” (e.g., burgers, coated poultry, and snack foods high in fat and/or sugar, such as crisps and chocolate) and low in overall nutritional quality on initial analysis were associated with ADHD, but significant associations were attenuated when other confounding factors were considered in the model (55,56). The authors concluded that “there is no association between a ‘junk’ pattern score or sugar intake, and hyperactivity in children or other behavioural problems” (55). They did note that these patterns had lower intakes of recommended foods, such as fruits and vegetables, compared with the “health-conscious pattern” (i.e., vegetarian-style foods, rice, pasta, salad, and fruits) and the “traditional diet” (i.e., meat, potatoes, and vegetables) (56).

Despite these findings, the role of CHOs, especially sugars and those from refined grains and grain-based desserts and snacks, in ADHD remains a source of controversy. Many studies fail to support the hypothesis that refined CHOs per se are responsible for ADHD symptoms, but rather show that inadequate intakes of necessary dietary components appear to be a factor in ADHD (40). For instance, for Korean fifth graders, both the ADHD and control groups ingested more sugary snacks than recommended, but there was a difference of only 8 g of sugar between the ADHD group and the controls and no difference in intake of grain-based snacks, but there was a significantly lower intake of fruits and vitamin C and twice the amount of protein ingested by those with ADHD (57). The role played by sugar remains controversial, however, because many studies assessing the impact of sugar on ADHD have few subjects, as well as other methodological issues (58).

Nevertheless, both high and low blood glucose levels can be problematic for proper brain functioning and the ability to focus and control impulsive behavior (49,59,60). For all students in a study by

Ciok and Dolna (60) both no CHOs and no breakfast in the morning were associated with decreased attention and ability to learn. British children eating low-GI cereals with breakfast, compared to high-GI cereals, were less restless and able to complete tasks more readily (61). Further, a study conducted in Poland found low-glycemic diets reduced symptoms in some ADHD children (58). Thus, research suggests that diets high in CHO, especially those with adequate fiber intakes, when not high in saturated fat may be beneficial in managing ADHD symptoms.

Mineral and vitamin status may also play a role in ADHD. In a Spanish case-control study, ADHD patients had lower calcium, iron, magnesium, zinc, selenium and phosphorous, thiamine, niacin, vitamin B₆, and folate intakes than control subjects (52). Similarly, low levels of copper, iron, zinc, and iodine were associated with ADHD in a Korean study (49,51), and certain ADHD symptoms were linked to low levels of magnesium and zinc in Australian adolescents (62). Low zinc was also identified as being associated with ADHD in a case-control study of Chinese children (63).

Because these minerals are cofactors for many enzymes that affect metabolism of neurotransmitters such as dopamine, their deficiency is postulated to worsen behavior (49). Although small intervention studies show that supplementation decreases behavioral symptoms associated with ADHD (64,65), the benefits of supplementation have only been documented in populations with marginal intakes or overt deficiencies. In a systematic review, Hariri and Azadbakht (66) note that evidence on the effects of mineral supplementation for children with ADHD is inconclusive, and data showing a positive impact of iron, zinc, or magnesium supplementation in non-nutrient deficient populations is lacking (67).

Other Dietary Components

Food additives and artificial food colorants used in foods, including grain-based foods, have been suggested as a cause of ADHD, but associations have been disputed and are inconsistent when studied using well-controlled protocols (40,68–74). When using an uncontrolled diet methodology, ADHD symptoms have been shown to improve when following a diet without artificial colors. However, randomized controlled trials did not find significant effects of diets without artificial colors on ADHD symptoms (68–74). A recent meta-analysis reinforced findings that suggest

“research is required for AFC (artificial food color) elimination before advising this intervention as ADHD treatment” for children (75).

Diet and Treatment of ADHD

ADHD is often treated with amphetamines to influence dopaminergic and noradrenergic systems (43). Dietary regimens for children with ADHD are often coupled with prescription medications or are used when drugs do not sufficiently reduce symptoms. Dietary regimens for ADHD have two foci: 1) removal of elements or specific components or large groups of food from the diet (e.g., sugar, artificial food coloring, food groups, gluten); and 2) addition of specific elements to the diet (e.g., zinc, fish oil) (49). Although these dietary interventions for managing ADHD have been proposed by practitioners of both Western and traditional Chinese medicine, limited research exists on the efficacy and safety of dietary intervention as an adjunct to conventional medications (40,49,76–79). To date, findings suggest elimination diets and fish oil supplementation may hold promise in certain cases (40,75,76) and may offer treatment opportunities for subgroups of children with ADHD who do not respond to or are too young for medication (75).

A few-foods diet, or oligoantigenic diet, is an elimination diet that is used to determine food sensitivities and has been associated with relief of ADHD symptoms in some children (80). The diet starts with the elimination of most foods, usually allowing two types of meat, two sources of CHOs (originally rice and potato), two vegetables, two fruits, oil, and water. A number of poorly controlled reports show that within 1–5 weeks of following such a diet some children exhibited fewer ADHD symptoms (40,80–87). However, the lack of methodologies that can eliminate bias makes the results questionable. Therefore, well-constructed studies need to be completed before any final conclusions can be drawn about their efficacy (88).

Another type of elimination diet is one that specifically eliminates dairy and gluten. Gluten in the diet has been proposed as contributing to both the cause and severity of symptoms of ADHD (89). However, a gluten-free diet has not been shown to significantly improve ADHD symptoms in children who have not been diagnosed with celiac disease, an autoimmune disorder that is triggered by ingestion of gluten (90).

Summary

The cause and treatment of ADHD has long been debated. Dietary factors have been suggested as both causative factors and treatment components (12,40,43), with CHOs and grains playing a role. Balanced dietary patterns that include optimal amounts of grain-based CHOs show promise for improving ADHD symptoms. A Korean diet with a “traditional-healthy” pattern (i.e., high in CHOs [especially rice], as well as low in fat, but with high intakes of important fatty acids and minerals) was associated with significantly reduced risk of ADHD. Because the “traditional” pattern and the “egg seaweed pattern” did not change risk, the diet’s healthy components might be important. There might be some increase in risk with the “snack” pattern (51). Similarly, adherence to a Mediterranean Diet by Spanish children and adolescents was associated with a sevenfold lower risk of ADHD. Lower frequency of consuming fish, fruit, vegetables, pasta, and rice and higher frequency of skipping breakfast and eating at fast-food restaurants were associated with ADHD diagnosis. High consumption of sugar, sugar-sweetened beverages, and candy (and low consumption of fatty fish) were also associated with a higher prevalence of ADHD diagnosis. A study of dietary patterns in Iranian children also showed that diets higher in sweets or fast foods were associated with a greater than threefold increase in risk of ADHD. However, no increase in risk was associated with either the “healthy” or “Western diet” patterns. Thus, grain-based foods such as rice and pasta were associated with decreased risk (91).

Carbohydrate source, quality, and glycemic status should all be considered when addressing their impact on ADHD symptoms (51,53,56,58). Diets high in sugar and snack foods and low in n-3 fats, fruits, vegetables, and grains or lacking in fiber, vitamins, and minerals are associated with increased risk of ADHD. The ingestion of grain-based staple foods as part of a healthy dietary pattern appears to reduce risk and improve ADHD treatment. Because whole grains contribute zinc, magnesium, and iron and enriched and fortified grains contribute iron, these foods may play a role in maintaining a diet replete with these minerals and, thereby, may impact ADHD incidence and management.

OVERVIEW OF DEPRESSION

Depression is a common mood disorder that manifests itself in a variety of forms and circumstances. Accurate statistics regarding the incidence of depression worldwide are lacking, but it has been found in every country and culture and is estimated to impact from 3 to 17% of the global population (92,93). There is greater prevalence in high-income versus low- and middle-income countries. Depression is a frequent comorbidity factor with many other diseases, including diabetes and Alzheimer’s disease. There is a higher incidence of depression in the elderly, especially those who are institutionalized.

Symptoms of this serious mood disorder may include a combination of feelings of inadequacy, despondency, and pessimism; decreased physical activity; an inability to experience pleasure; and sadness. Depression may severely impact a person’s thoughts, feelings, and ability to handle daily activities and disrupt their daily life. Depression is caused by a combination of factors, including genetic, psychological, biological, and environmental. This discussion will focus on diet and grain-based foods.

Grains, CHOs, Glycemic Index, and Glycemic Load

Nutrition can influence various neurotransmitters that regulate brain chemistry, which, in turn, can impact depression. These neurotransmitters include dopamine, norepinephrine, γ -aminobutyric acid, and serotonin (94). Low serotonin levels are implicated in the etiology of depression, and increased levels of serotonin are related to improved mood (95). Serotonin synthesis requires adequate dietary sources of tryptophan and vitamin B₆, a coenzyme for the reactions (94–98). It has been theorized that serotonin synthesis occurs when an insulin-raising CHO is consumed, because insulin is needed to trigger tryptophan uptake by the brain; however, if even a small amount of protein is present, tryptophan uptake is blunted. Further, impaired glucose tolerance may affect serotonin transporters in the bloodstream and may be associated with depression (99,100).

In terms of the impact of dietary CHOs on depression, the data show mixed results. In a small sample of obese women, nondepressed elderly women consumed more CHOs than those who were depressed (101,102). Depressed individuals in a small Turkish study consumed 55% of

their calories as CHOs, and nondepressed individuals consumed 50% of their calories as CHOs; however, there was no significant difference ($P = 0.055$) between the two groups (103). In a much larger study of nearly 1,000 homebound elderly individuals who were or were not depressed, there was no difference in total CHO intake (104). However, dietary fiber intake was significantly lower for depressed patients (104). Similarly, the percentage of energy from CHO was not associated with scores on the Center for Epidemiologic Studies Depression Scale (CES-D) for type 2 diabetics ($N = 4,218$) in the Fu-kuoka Diabetes Registry (105).

Findings with respect to glycemic index (GI), glycemic load (GL), and depression are also mixed. Because insulin release is related to serotonin synthesis and transport, some researchers suggest there might be an association, but results appear to depend on many different factors, including the study population and foods selected (3). Several studies have found that depression was related to high GI. In a sample of nearly 1,000 homebound elderly individuals in the United States (104), the diets of depressed patients were slightly higher in GI and GL. In the Women's Health Initiative Observational Study (WHIO) ($n = 69,954$ at three year follow-up), higher depression scores were related to higher dietary GI but were unrelated to GL (106). Similarly, among more than 3,000 university staff members in Tehran, those with intakes in the top tertile of GI had greater risk of depression (107). However, as with the WHIO results, higher GL was associated with lower risk. The authors (107) note that some high-GI foods have low nutrient contents.

In contrast, some studies found that higher GI was related to a lower risk of depression. In a small study of obese women ($n = 30$), those with a greater intake of high-GI foods reported a lower level of depression than those with lower intakes of high-GI foods. However, the difference in GI between the groups, while significant, was 0.7, which is a very small difference for a rather imprecise measure (101). In a larger cross-sectional study of 140 institutionalized elderly Spanish individuals, high dietary GL and GI were associated with a lower risk of depression. In a large sample of institutionalized elderly individuals, higher GL diets were associated with decreased risk of depression. In the Blue Mountain Eye Study conducted in Australia ($N = 2,334$ participants over 55 years of age), participants in the highest

and lowest tertiles of GI intake had increased risk of symptoms of depression (108).

A randomized clinical trial with poorly controlled diabetics following a low-GI diet compared with the standard American Diabetes Association-recommended diet did not find differences in symptoms of depression (109). In another study, neither the GI nor GL of the diet impacted the risk of postpartum depression in Japanese women ($N = 865$) (110). The definitive role of GI or GL for depressed patients remains to be determined.

Dietary Fiber Intake

Dietary fiber intake is associated with a reduction in depression. In a prospective cohort study examining postmenopausal women ($N = 87,618$), greater consumption of fiber was associated with lower prevalence of depression, while consumption of refined grains was associated with an increased risk of depression (106). In 849 Korean adolescent girls, depression was negatively correlated with folate, vitamin B₆, and dietary fiber intake (111).

Findings are inconsistent concerning the impact of different types of fiber. In the Blue Mountain Eye Study those with the highest total fiber intake, vegetable fiber intake, and bread and cereal fiber intakes were associated with a lower risk of symptoms of depression (108). However, in Japanese adults fiber derived from cereal was not associated with symptoms of depression, while fiber derived from fruits and vegetables was associated with a reduced likelihood of symptoms of depression (112). The lack of effect of cereal fiber intake in the Japanese study might be due to the fact that rice and brown rice, which are low in cereal fiber, would be the major grain sources, and participant diets included many vegetables.

The relationship between nutrient intake and depression was examined in schoolchildren in Spain. Slightly higher, although not statistically significant ($P = 0.107$), intake of fiber was observed in children with depression compared with children without symptoms of depression (113). However, in this same study, children who consumed higher amounts of overall CHOs were less likely to be depressed.

In the WHIO study non-whole or refined grain consumption was associated with increased odds of depression, with the risk increasing as consumption increased (106). However, higher consumption of whole grains was associated with lower risk for depression. In addition,

refined rice is a high-GI food and a staple in Asia, but the incidence of depression in Asia is low. The low rates of depression found in Asia may be due to cultural, genetic, and/or dietary factors.

Refined-grain foods include not only staple foods but sweetened grain-based desserts. Diets high in sweets, refined foods, and pastries may increase risk of symptoms of depression (106,114). Depression may decrease motivation to follow a healthy diet, promote unhealthy food choices, or result in emotion-driven eating (106,114–116). In several studies, depressed patients have shown a significant preference or craving for sweet, high-CHO, and high-fat foods, such as pastries and cakes (106,116,117). However, ingestion of these types of foods can be associated with reduced feelings of unhappiness (101,116).

Savory foods have also been associated with depression. A positive association was found between depression and fast-food consumption in women (114) and greater symptoms of depression in elderly French men who ate ≥ 3 servings of pasta/week versus those who ate fewer servings (118).

Diabetes

Depression has been shown to increase the risk of type 2 diabetes for midlife and elderly patients (119). When feeling depressed, people have a tendency to overconsume high-glycemic CHOs (120). Both hypo- and hyperglycemia were related to depression in studies of patients with type 2 diabetes in Mexico, Peru, China, and Japan (121–123). Better glycemic control was associated with less depression, and depression was associated with poorer control.

Mediterranean Diet

The Mediterranean Diet pattern contains a balanced mix of vegetables, fruits, legumes, grains and whole grains, nuts, fish, wine, dairy, and meat and is documented to have multiple positive physical and neurological outcomes, including an association with reduced risk of depression (124–127). A group of young females randomized to follow the Mediterranean Diet showed improvement in symptoms of depression over those following the standard diet (124). Similarly, the DASH Diet showed an inverse relationship with depression in the SUN population study (125). Those with high adherence to the DASH and Mediterranean Diets and the Healthy Eating Index had a significantly

lower risk of developing depression over the 8.5 years of a follow-up study by Perez-Cornago et al. (128). In addition, a balanced Japanese dietary pattern (high intakes of vegetables, fruits, mushrooms, and soy products) and adequate serum folate intake were associated with less depression (129).

Summary

Carbohydrates, grains, and whole grains are dietary components that affect depression. As a result, their roles in the cause and treatment of depression have been of great interest. In some studies food patterns rich in high-fat, high-sugar, CHO-based foods were also associated with onset of symptoms of depression. However, in other cases, studies found no association between dietary pattern, including CHO intake, and risk of depression (130). Dietary modifications have been found to relieve symptoms of depression in some individuals (94). Age, gender, and geographic region all have an impact on the role of CHO- and grain-based foods in the diet and symptoms of depression (106,116,125). Optimization of glucose control may help reduce depression, especially for those with diabetes. As a consequence, balanced intakes and adequate amounts of dietary fiber and slowly digestible whole grains and other CHOs may be a beneficial dietary strategy to combat depression. Balanced dietary patterns, such as the Mediterranean or DASH Diet, are one way an optimal balance of CHOs, fiber, protective antioxidants, and grains can be delivered by the diet.

CONCLUSIONS

Existing evidence suggests that both whole and enriched grains, especially staple grain-based foods, and the CHOs they deliver in the diet, when part of a balanced pattern, contribute important dietary fiber, vitamins, and antioxidants that can help mitigate or reduce the risk of headache and depression. For ADHD, adoption of a balanced dietary pattern is one of several strategies that might be used to help address some aspects of the disorder. No one group of foods or dietary pattern seems to be a causal factor, but for all of these disorders unbalanced patterns increase the risk or symptoms. With the exception of celiac patients, there is little evidence that grain-based foods cause headaches or change their severity. For many, diets incorporating a balance of food groups and enriched and whole

grains may help reduce headaches. The avoidance of grains as part of a ketogenic diet to reduce certain types of severe headaches has only been researched in a few studies. Findings suggest it might be a useful strategy; however, much more research is needed before such a protocol receives widespread acceptance.

Balanced diets such as DASH and Mediterranean Diets and the inclusion of adequate dietary fiber intakes may be beneficial for those who suffer from depression. Although some studies suggest that low-GI foods or diets may help reduce depression, others suggest the opposite. Few published studies exist that associate specific grain-based foods with headache, ADHD, or depression. Large cohort data from many countries show that adherence to a balanced dietary pattern that contains an optimal mix of foods and grains and whole grains is inversely associated with either the onset, severity, or behaviors attendant with headache, ADHD, and depression. These diets incorporate antioxidant- and polyphenol-rich foods and dietary fiber that may protect against oxidative damage in nervous tissue.

Dietary patterns associated with overall health that incorporate food groups in an optimal balance, including grains and whole grains, appear to also be associated with proper functioning of the nervous system and may be useful in reducing headache frequency and symptoms of ADHD and depression. More research is needed on all of these disorders and the impact of diet.

What is known is that in many Western countries, a large percentage of the population fails to follow recommended calorie targets, eat recommended amounts of foods from a variety of food groups, including inadequate intakes of dietary fiber and whole grains, and consume too many nutrient-poor foods. Adoption of recommended dietary patterns such as the DASH, Mediterranean, or USDA MyPlate Diets might help manage these disorders, as well improve overall health.

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CIMMYT Series on Carbohydrates, Wheat, Grains, and Health

Wheat-Based Foods: Their Global and Regional Importance in the Food Supply, Nutrition, and Health^{1,2}

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ABSTRACT

Meeting the growing demand for food over the next 20–30 years will be challenging, mainly because the fastest population growth is occurring in already highly populated developing countries and because producing cereal crops (the main source of nutrients in these countries) requires that serious production constraints, due mainly to the effects of climate change, be overcome. Wheat supplies the most calories and proteins to the global population in the form of diverse wheat-based foods. Wheat-based foods are staples that are major sources of micronutrients that are fundamental for normal development, as well as metabolic and cognitive functioning, from childhood to adulthood. Furthermore, whole grain, wheat-based foods have potential additional health benefits because they contribute fiber and bioactive compounds that can help reduce the risk of chronic conditions, such as cardiovascular disease, type 2 diabetes, and other chronic conditions. In this article, we describe common wheat-based foods consumed globally and regionally, as well as consumption trends for the most important wheat-based foods. Changes in consumption patterns are strongly associated with population shifts from rural to urban areas, which cause changes in both lifestyle and dietary habits. It is recognized that wheat production and wheat-based foods will continue to be important for the well-being of millions of people, especially for low-income farmers and consumers. Finally, we briefly discuss trends in wheat production and supply impacted by potential climate change and outline some important research and development strategies needed to improve grain productivity, grain processing quality, and the nutritional value of wheat-based foods.

Agricultural foods, particularly cereal grains, continue to play a central role in satisfying the food demands of a growing global population, especially in developing countries, where populations derive a significant proportion of their nutrient requirements from cereal-based foods (1,2).

In this respect, wheat (*Triticum* spp.) is particularly important for several reasons. 1) Wheat is cultivated in nearly all regions of the world, from the equator to temperate lands (as high as latitudes 60°N and 44°S) and at altitudes as high as 3,000 m above sea level—totaling ~230–250 million ha (3). Thus, it represents the main

source of income for millions of small-scale farmers living in developing countries around the globe (4). 2) Wheat, like other cereal crops, can be stored for long periods of time, and throughout history, this has been fundamental to build up of food reserves to prepare for bad crop years (due to climatic conditions and/or disease/pest infestations). Reserves also help to prevent extreme price increases that could make wheat-based foods unaffordable for most of the middle- and low-income sectors of the population. 3) Wheat is the most versatile grain among the cereals for the preparation of diverse foods, providing more calories and proteins to the global population than any other agricultural food (5,6). 4) All of the qualities described above have made wheat the most traded cereal crop in the international agricultural food market, impacting the economy of farmers and other food-chain sectors in countries around the world (2). Wheat-based foods are, therefore, highly important for food security, contributing an affordable source of nutrition to a large portion of the global population, particularly millions of people with low to middle incomes.

The main objective of this review article is to describe the diversity of wheat-based foods, their consumption, and their importance and contribution to nutrition and health globally. We will begin by briefly reviewing the recent literature on trends in population growth and food demands. This will be followed by descriptions of the main classes of wheat and the grain attributes required to attain desirable end-use quality for the main wheat-based foods in various regions of the world. The differences in use and consumption in various regions across the globe will be characterized, along with documented relationships between consumption of wheat-based foods and nutrition and health. Finally, current challenges in the production of wheat and innovation in processing technologies will be briefly addressed.

POPULATION GROWTH AND WHEAT CONSUMPTION

Population Growth

It has been estimated that the world population will continue to grow until the end of the century, after which it will likely

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stabilize (7). By 2050, the population could reach between 9.3 and 10 billion people, concentrated mainly in the developing countries of Asia and Africa (8–10) (Fig. 1). Shifts in populations to urban areas, especially in developing countries, are occurring such that the Food and Agricultural Organization of the United Nations estimates that by 2050 70% of the global population will be living in cities, which is 20% higher than today (Fig. 2) (8).

Wheat Consumption as Food

Cereal grains satisfy a large proportion of the global food demand, but to meet the needs of the projected population growth by 2050, cereal production needs

to grow by at least 1.1%/year. Such increases would result in a 60% higher yield in 2050 than in 2007 (1,8). Similar increases in annual wheat production have been estimated (2,4).

The per capita consumption of wheat varies markedly around the world. As shown in Figure 3, the highest per capita consumption of wheat for 2005–2009 was in Central Asia at 171 kg/year. This was followed closely by North Africa, West Asia, and the Eastern Europe/Russia region. Among high-income countries, the highest consumption occurred in Western Europe at 86.8 kg/year. This was followed closely by the United States, Canada, and Australia. The consumption of wheat in

East and South Asia and South America ranged from 42.6 to 66 kg/year (2).

The average per capita consumption of cereals is growing, and there are demographic and income shifts in emerging countries that all increase the demand for processed convenient and low-cost sources of calories and proteins (1,2,8,11–13). For example, the per capita demand for wheat in Sub-Saharan Africa has increased by 2–3%/year during the last five decades. Similar trends in per capita demand for wheat have been seen in the non-wheat-producing countries of the southeastern region of Asia (1,2,8,14).

WHEAT QUALITY CHARACTERISTICS

Modern wheat has evolved from its primitive parents (emmer and spelt wheat), in part through natural events and in part through traditional and modern breeding technologies, to become the modern varieties that feed most of the global population (15). The most important cultivated wheat species are hexaploid common wheat (*Triticum aestivum* L. var. *aestivum* L.) and tetraploid durum wheat (*Triticum turgidum* L. subsp. *durum* (Desf.) Husn.), which differ from each other in genomic makeup, grain composition, processing quality, and main food uses (5).

In general, small-scale wheat farmers consume wheat-based foods prepared at home or purchased in local, small artisan bakeries, where locally produced wheat is used. Simple adjustments in processing formulas and methods may be required to achieve desirable dough-making properties because each year's crop may have different qualities. However, when wheat-based foods are industrially manufactured, there are specific quality requirements that a wheat crop must fulfill, or blends of wheat varieties can be used to create a product that is acceptable for industrial processing.

Wheat Classes

There are quality differences in physical and compositional characteristics between and within the more than 10,000 wheat varieties and wheat species that exist worldwide. Although the main quality traits are under genetic control, these may vary significantly due to soil fertility, grain yield (which is also genetically influenced and is negatively correlated with protein content), and environmental stressors (e.g., heat, drought, and high rainfall during grain development), as well as other

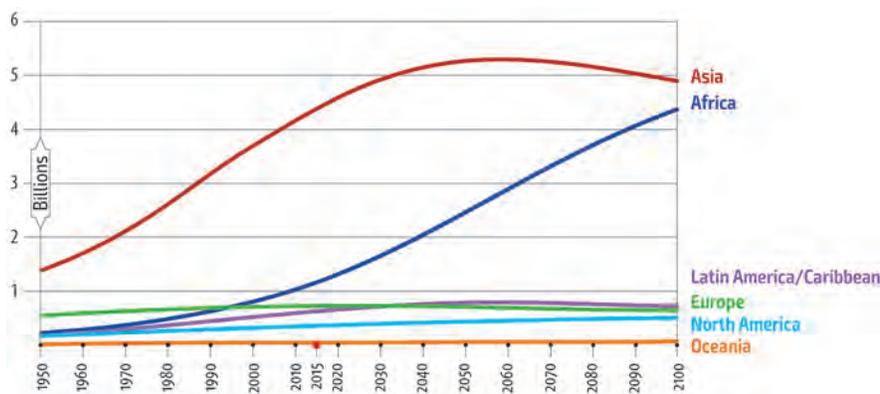


Fig. 1. Anticipated population growth from 1950 to 2100. Image source: FAO (8).

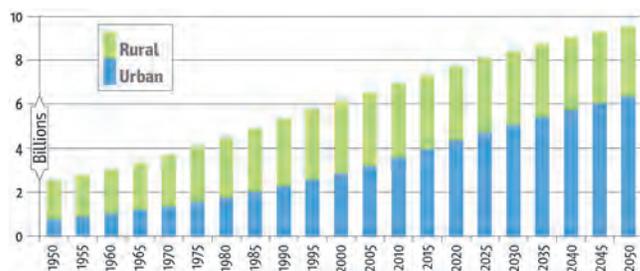


Fig. 2. Anticipated growth in global urban and rural populations from 1950 to 2050. Image source: FAO (8).

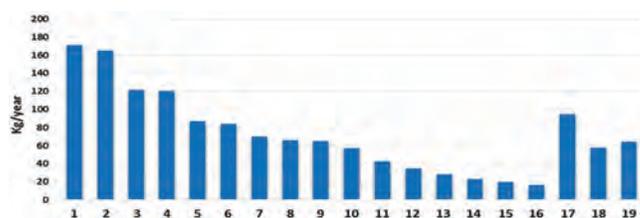


Fig. 3. Wheat demand per capita (kg/year) during 2005–2009. 1) Central Asia; 2) North Africa; 3) West Asia; 4) Eastern Europe and Russia; 5) Western Europe and other high-income countries; 6) North America (United States and Canada); 7) Australia; 8) East Asia; 9) Southern Cone, South America; 10) South Asia; 11) Andean region, South America; 12) Mexico and Central America and the Caribbean; 13) eastern and southern Africa, including the Republic of South Africa; 14) eastern and southern Africa, not including the Republic of South Africa; 15) Southeast Asia and Pacific; 16) western and central Africa; 17) developed countries; 18) developing countries; 19) world. Image modified from source: FAO (8).

external factors (16–21). Therefore, many breeding programs determine the release of a commercial variety based not only on yield but also on grain quality attributes and stability under variations in crop management and environmental conditions.

Usually, a wheat crop is graded based on grain quality characteristics to establish the trading price and determine its appropriate use in the manufacture of major wheat-based foods (e.g., breads, noodles, biscuits, and pastas). Wheat quality is first judged based on grain color and milling quality (flour extraction rate), which is mainly determined by grain size, plumpness, density (kg/hL), and hardness of the endosperm (22). Other primary quality traits for common wheat are protein content, gluten strength and extensibility, and starch composition. The main quality traits of durum wheat are grain color and vitreousness, gluten strength, and yellow pigment content. Together, these traits define the water absorption capacity of the dough, its performance during processing, and the textural and shelf-life properties of the end product (23). The physical and compositional characteristics of wheat can be used to categorize it into three major end-use classes:

- **Bread:** Common, hard or medium-hard wheat, with white or red grain color.
- **Biscuit** (e.g., cookies, crackers, and pastries): Common, soft wheat, with white or red grain color.
- **Pasta:** Durum wheat, which is genomically different from common wheat, which has a very hard endosperm (harder than common wheat), bright amber grain color, and bright yellow endosperm.

Main Wheat Quality Traits

Grain Color. Grain color is under genetic control for both red and white classes of wheat. Milled flour color is important and dependent on the wheat flour being prepared. When producing flat, unleavened breads or noodles, white or creamy whole meal flour or refined flour from white wheat is preferred over the darker flour produced from red wheat (24). Durum wheat is generally bright amber, with the brightness originating from the very hard endosperm (25). This color is desirable in the production of pastas and couscous.

Grain Hardness. Differences in the texture of the endosperm (or grain hardness) permits the classification of common wheat

into soft, hard, and medium-hard. In hard wheat, there is a tight linkage between the protein matrix and the surface of the starch granule; the opposite occurs in soft wheat. Grain hardness is under genetic control (differences in the allelic composition of the puroindoline genes located in chromosome 5D) and depends on the integrity of the starch membrane and the adherence of the protein matrix to the surface of the starch granules (26,27). The ease of milling and the proportion of damaged starch in the flour are determined by grain hardness. The amount of damaged starch, in turn, strongly influences the water absorption capacity of bread and cookie doughs and flour noodles (28). In cookie dough, a very low water absorption capacity is desirable.

Durum wheat, which does not possess D genome chromosomes, has a very hard endosperm. Recently, soft endosperm durum wheat varieties have been developed, which could extend the use of durum wheat in the food industry to products beyond their traditional applications (29,30).

Proteins. The functionality of the gluten-protein complex in wheat contributes to its being the most widely traded food commodity because it imparts a versatility that permits the manufacture of a great diversity of wheat-based foods. The storage proteins found in wheat (15), which form an extended protein matrix on the surface of the starchy endosperm cells (31), contribute the unique viscoelastic properties of the gluten network. When wheat proteins (glutenin and gliadin plus albumins and globulins) are mixed with water and then kneaded or mechanically mixed, a viscoelastic gluten network is formed. The resulting network structure determines the viscoelasticity of the dough, which, in turn, allows the dough to be shaped into diverse forms. The gluten-protein matrix forms films that can trap air and CO₂ from leavening to provide cell structure and allow for the development of breads with diverse forms, volumes, and textures.

Soft wheats, with their lower protein content in the endosperm, are used to produce viscous sugar-fat-flour doughs. These doughs are used to produce a great diversity of biscuits, cakes, desserts, and pastries. For some of these products, such as cookies, gluten viscoelasticity is undesirable because viscous, but not elastic, flow of the dough is desirable during baking. Even a small degree of elasticity in the cookie dough interferes with the free viscous flow of the cookie during baking,

altering the shape, spread, and thickness of the final product. On the other hand, cakes require modest gluten development and viscoelasticity for their structure.

In durum wheat, the gluten proteins have limited extensibility (less than in common wheat). This characteristic is very important for pasta, for which a firm, al dente texture is desired that does not exhibit surface disintegration and stickiness when the pasta is slightly overcooked (25).

Starch. The starch in wheat is present in large and small granules and comprises more than 70% of refined wheat flour. Wheat starch is composed of 22–35% amylose and 65–75% amylopectin (32). The amylose content of wheat starch is controlled by the action of waxy genes, which express granule-bound starch synthase or the waxy (Wx) proteins. The lack of Wx proteins, as defined by the absence or modification of one, two, or three alleles, determines the level of reduction in amylose content (33–36). Variations in the amylose/amylopectin ratio determine the pasting and gelling properties of starch and influence the functional properties of doughs and the texture and shelf life of wheat-based foods. Low-amylose wheat flour has a low gelatinization temperature and a high paste consistency due to the expansion of amylopectin, conferring desirable volume and softness to Japanese udon noodles. Additionally, low-amylose flours tend to produce breads with soft crumbs and an enhanced shelf life due to greater retention of moisture, as well as an increased freezing tolerance. Flours with high-amylose starch (resistant starch) can be used to produce foods with a low glycemic index (33).

Endosperm Carotenoids. Durum wheat endosperm possesses carotenoid pigments (predominantly lutein), which confer a bright yellow color to semolina and to the wheat-based foods prepared with it. The yellow color of durum wheat-based foods is highly preferred by consumers. In durum wheat, the accumulation of yellow pigment is controlled by the phytoene synthase (*PSY-1*) gene located in chromosome 7B (37). The yellow pigment content of semolina and its pasta may be decreased when high levels of lipoxygenase (LOX-2 and LOX-3 isozymes) activity result in oxidative degradation of the yellow pigment in the semolina during pasta making (25). It is important to note that a few common wheat genotypes may possess small amounts of yellow pigment that result in slightly yellow wheat-

based foods, which are generally undesirable to consumers.

Quality Attributes Required to Manufacture Specific Wheat-Based Foods. In general, hard or medium-hard common wheat varieties are suitable for making viscoelastic doughs used to manufacture breads and noodles, but they are unsuitable for the manufacture of biscuits and pastries. In contrast, common wheats that have a soft texture and low protein (and limited viscoelasticity) are suitable for producing biscuits, pastries, and certain noodles but are highly unsuitable for the preparation of most breads. Durum wheat is suitable for producing Italian-style pastas, couscous, regional breads, and bulgur but are highly unsuitable for the manufacture of biscuits and most breads.

The processing of major wheat-based foods (e.g., leavened, flat and steamed breads; biscuits, Asian noodles; and pastas) requires specific grain quality attributes that depend on the level of technology used in their preparation (i.e., a household or semi- or fully mechanized industrial bakery). General grain quality attributes required to make common wheat-based foods are summarized in Table 1.

MAIN FOOD USES OF WHEAT

Main Bread Classes

It was around the fourth to third century B.C. when the Egyptians observed that a dough made with flour and water would ferment, resulting in a leavened dough that upon baking produced a soft-crumbed bread. Thus began the demand for bread, which spread to many different cultures around the world. For many populations, bread became the “staff of life,” and its dominant role in the diet influenced economic, political, social, and religious aspects of society in many cultures from ancient to modern times (5,38).

Bread is prepared from cohesive, viscoelastic flour-water doughs (and other diverse ingredients). Depending on the type of bread, the process can vary from simple household operations to highly automated industrial processes. There are hundreds of versions of breads of different densities, sizes, shapes, and textural characteristics that can be grouped into classes. Faridi (39) suggested a classification system based on specific volume (bread density): high (e.g., pan bread); medium (e.g., baguette); and low (e.g., Indian chapatti). In this article we grouped bread into three classes, each of which is predominant in major regions around the world: leavened breads, which are mainly consumed in Europe, the Americas, and Oceania; flat breads, yeast fermented and unleavened, which are mainly consumed in North and Sub-Saharan Africa and West and Central Asia; and steamed breads, usually yeast leavened, which are mainly consumed in East and Southeast Asia.

Leavened Breads. Leavened breads, mostly yeast fermented, are the most popular breads around the world. During mixing and after yeast fermentation, the flour-water dough expands due mainly to the production of CO₂ but also to the incorporation of air trapped in gas cells in the dough. Density and uniformity of the crumb; color and hardness of the crust; and aroma and flavor of the bread are all influenced by the formulation, fermentation time, amount and type of dough manipulation, time given to the dough before baking, and baking conditions (5,24,40). The size and shape of the bread are determined by the baker or by the molding and pans used to bake the bread.

The making of leavened breads by hand or semi-mechanized baking processes (e.g., baguette or any yeast-fermented, hearth-baked breads) requires flour with medium-strong gluten to facilitate its mixing or

kneading and handling. In this case, the amounts of flour, water, or other ingredients used in the bread formula, as well as mixing, handling, and fermentation conditions, can be adjusted during the bread-making operation. For the mechanized production of bread (e.g., pan-type leavened breads and hamburger and hot dog buns), flour with strong gluten is required to tolerate high-speed mixing and mechanical handling of the dough. This process is continuous and automated and allows for minimal adjustments.

Flat Breads. Flat breads are very important components in meals consumed in North Africa, the Middle East, and Central and South Asia because they are commonly used, rather than cutlery, as scoops or carriers of the main components (vegetables and meat) of the meal (24,41–43). Flat breads are made from viscoelastic doughs prepared with whole meal or high-extraction flours (mostly from white wheat, not red), water, salt, and, in some cases, added fat. Some are unleavened, while others are leavened either by dough fermentation or chemical-leavening agents (24,42). Flat breads, because of their large surface area, stale very rapidly and are best when consumed within a day of preparation. Most flat breads are baked for 1–2 min on hot clay or metal plates.

Flat breads are generally round or oval and may be thin and crispy (e.g., Iranian lavash, 2–3 mm thick) or soft and flexible (e.g., Indian naan and chapatti) (39,41,42, 44). Double-layered flat breads (e.g., Arabian or Greek pita and Egyptian *baladi*) are created by cooking the dough at a very high temperature to quickly turn the water to steam, which creates the “pocket.” Single-layered flat breads include the Indian chapatti, the Mexican flour tortilla, and the Norwegian lense.

Flat breads were traditionally made daily at home or in local bakeries. Recently,

Table 1. Summary of key quality characteristics sought by breeders for development of common types of wheat-based products

Product Category	Type	Grain Color	Flour Protein Content	Grain Hardness	Flour Pigment	Dough Strength	Dough Extensibility
Industrial bread	Pan-type buns	Red or white	High	Hard	Low	Strong to medium	High
Bakery bread	Hearth, French	Red or white	Intermediate	Hard to medium	Low	Medium	High
Flat bread	Arabian, chapatti, tortilla	White	Intermediate	Hard to medium	Low	Medium to strong	Intermediate
Cracker		Red or white	Intermediate	Medium to soft	Low	Medium to weak	Intermediate
Steamed bread	Northern	Red or white	Intermediate	Hard	Low	Medium	Intermediate
	Southern	Red or white	Intermediate	Soft	Low	Medium to weak	Intermediate
Noodle	White, salted	White	Intermediate	Medium and soft	Low	Medium	Intermediate
	Yellow, alkaline	Red or white	Intermediate	Medium	Not defined	Medium to strong	Intermediate
Biscuit	Cookies	Red or white	Low	Soft	Low	Weak	High
	Pastries	Red or white	Low	Very soft	Low	Weak	High
Pasta	Durum wheat-based	Amber	Intermediate to high	Vitreous	High	Strong	Low

some flat breads, such as the Mexican flour tortilla, the Indian naan, the Egyptian *baladi*, and the Arabian pita, have become very popular because they fit the needs of the fast and/or convenience foods industry. Currently, mechanized, large-scale production of these breads is satisfying the demands of urban consumers in many parts of the world (39,45).

Steamed Breads. Steamed breads may be prepared with soft or hard wheat flour possessing medium to slightly weak gluten. Steamed breads require less dough strength than do baked breads because steam is the principle leavener (40,46,47). They are often prepared with refined flour (preferable from white wheat flour) and water using methods similar to other bread baking processes, in that a viscoelastic dough is formed and allowed to ferment. However, the dough is steamed rather than baked, so no crispy brown crust is formed. Steamed breads in Western cultures may also be leavened with the aid of eggs and chemicals.

Steamed breads, which are especially popular in Asia, are often formed into individual buns, dumplings, and other shapes that may be plain or filled with sweet bean paste, meat, fish, and/or vegetables (46). The styles vary by region. For example, in China, there are three main

types of steamed breads: northern-style Chinese, southern-style Chinese, and Southeast Asian and/or Cantonese steamed breads. The northern-style Chinese steamed bread is spongy and chewy, while southern- and Cantonese-style breads are soft and dense and have limited cohesiveness (48,49). Southern-style Chinese and Cantonese and/or Southeast Asian steamed breads are made with soft wheat flour that has low protein and weak gluten (46).

Breads in Major Regions of the World

Europe, the Americas, and Oceania. Europe produces the greatest variety of yeast-leavened breads (Fig. 4). Some of the most popular traditional breads include the French baguette, the Italian focaccia, the German pumpernickel (made with a mix of rye and wheat flours), and the English sandwich bread (pan bread), cottage loaf, and muffin. In Northern and Eastern Europe, rye, wheat, and rye-wheat dense breads are quite popular and characterized as having a prolonged shelf life (50–52) and numerous health benefits (53).

Breads in the Americas are essentially the same as those consumed in Western Europe and were brought to the Americas during colonial times and later (nine-

teenth to twentieth centuries), during massive migrations that occurred mainly in the United States and Canada. The major influences on adopted bread types were from England, France, and Germany into the United States and Canada; from Spain and France into Mexico; and from Spain, Portugal, France, Italy, and Germany into South America. Among the most common breads are baguette-type sweet breads made from sweet yeast-leavened doughs, pan breads, molded (hamburger and hot dog) breads, and flour tortillas, the Mexican flat bread, which has become highly popular in North America (40,54–56).

Breads were introduced into Oceania (Australia and New Zealand) by Europeans during colonization of the region. In addition, a more diverse variety of breads exist due to the dynamic migration of people from all over the world. Leavened, flat, and steam breads are well known in this region (57).

Africa and West, Central, and South Asia. Throughout North Africa, Central Asia, and West Asia, leavened and unleavened breads are a long-standing, integral part of the culture and civilization. In many of these countries, bread is consumed at least twice a day and, in many cases, more often. These regions feature a

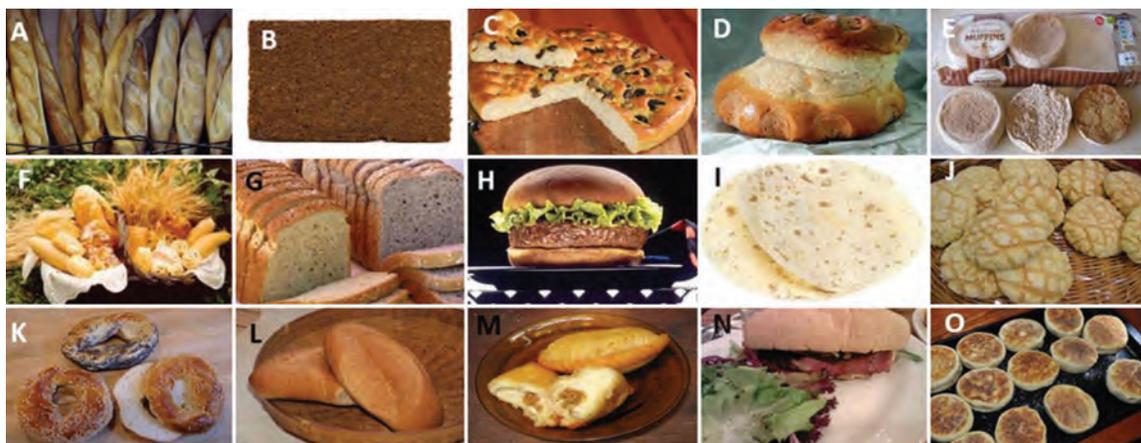


Fig. 4. Breads consumed in Europe, the Americas, and Oceania: **A**, French baguettes; **B**, German pumpernickel; **C**, Italian focaccia; **D**, English cottage loaf; **E**, English muffins; **F**, European variety of leavened breads; **G**, pan bread; **H**, hamburger bun; **I**, flour tortillas; **J**, sweet yeast bread; **K**, bagels; **L**, Latin America leavened bread; **M**, South America filled bread (empanada); **N**, ciabatta (chapata); and **O**, Latin America muffin.

(Image source: **A**, Amarant, from commons.wikimedia.org/wiki/File:NI-baguettes2.jpg, CC BY-SA 3.0; **B**, Rainer Zenz, from en.wikipedia.org/wiki/Pumpernickel#/media/File:Pumpernickel.jpg; CC BY-SA 3.0; **C**, J. P. Lon, from es.wikipedia.org/wiki/Focaccia#/media/File:Focaccia-erbe-olive.jpg, CC BY-SA 3.0; **D**, SilkTork, from en.wikipedia.org/wiki/Cottage_loaf#/media/File:Cottage_loaf_2.jpg, CC BY-SA 3.0; **E**, Maproom, from en.wikipedia.org/wiki/English_muffin#/media/File:Tesco_muffins.jpg, CC0 1.0; **F**, R. J. Peña; **G**, kspoddar, from www.flickr.com/photos/feastguru_kirti/2232778800/sizes/o/, CC BY-SA 2.0; **H**, Len Rizzi (photographer), from es.wikipedia.org/wiki/Hamburguesa#/media/File:NCl_Visuals_Food_Hamburger.jpg, released by the National Cancer Institute, an agency of NIH, ID 2518, and in the public domain; **I**, Renee Comet (photographer), from es.wikipedia.org/wiki/Tortilla_de_harina_de_trigo#/media/File:NCl_flour_tortillas.jpg, released by the National Cancer Institute, an agency of NIH, ID AV-9400-4222, and in the public domain; **J**, Sakurai Midori, from es.wikipedia.org/wiki/Concha_(pan)#/media/File:Melonpan.jpg, CC BY-SA 2.1; **K**, Garyperl-man, from en.wikipedia.org/wiki/Bagel#/media/File:Bagels-Montreal-REAL.jpg, released into the public domain; **L**, Glane23, from es.wikipedia.org/wiki/Bolillo_(pan)#/media/File:Bolillos_rolls.jpg, CC BY-SA 3.0; **M**, Gunawan Kartapranata, from en.wikipedia.org/wiki/Empanada#/media/File:Panada.jpg, CC BY-SA 3.0; **N**, Chensiyuan, from es.wikipedia.org/wiki/Ciabatta#/media/File:Ciabatta_beef_pastrami.jpg, CC BY-SA 3.0; **O**, jeffreyyw, from whats4dinnersolutions.com/2011/01/27/english-muffins/, CC BY 2.0)

wide variety of breads differing in size, shape, dimension, and texture (Fig. 5). Some representative examples include Moroccan dense bread, Egyptian *baladi*, Arabian double-layered pita bread, Iranian ancient flat breads (e.g., *barbari*, *lavash*, *sangak*, and *taftoon*), and other regional *tanoor* (*tandyr*) breads, which are more common in West and Central Asia than in North Africa (39,42). Western-type breads (especially industrialized versions) were introduced by Europeans during colonial times. Cultures in Sub-Saharan Africa consume breads introduced by Europeans, particularly British, French, Belgian, and Portuguese types, and some flat breads are popular in urban areas (2,58,59).

Flat breads are a staple in Central and South Asia. *Tandyr* bread is the main flat bread consumed in Central Asia. European-type breads (especially industrialized versions) were introduced into Central Asia from the Soviet Union. In South Asia, breads are made mainly with whole meal flour called “*atta*.” Chapatti, a griddle-based bread, is the main bread type, fol-

lowed by naan and *tandoor* breads, which get their name from the hot ceramic oven used to bake them. Other types of regional breads are consumed mainly during celebrations or religious events (23,41,43).

East Asia. As mentioned previously, steamed bread, in various versions, is the most popular type of bread consumed in East Asia (Fig. 6). Many breads from the Western Hemisphere are known by urban consumers in East Asia, mainly due to colonization, globalization, and the recent introduction of Western-type convenience fast foods, such as sandwiches and hamburgers.

Biscuits

The term “biscuit” has several meanings. In countries once part of the British Empire, “biscuit” refers to small, flat, usually crisp, baked items with either a savory/salty or sweet flavor. In the United States, a “biscuit” is a quick bread, similar to a scone, and especially popular in southern states. The term “cracker” is applied to products with a savory/salty flavor, and

the term “cookie” is applied to those with a sweet flavor.

Crackers, cookies, and pastries are consumed globally, although per capita consumption of these products varies widely. Consumption depends mainly on the economic condition and place of residence, with urban populations having better access to these products than rural populations. Consumption of these products is expected to continue to increase globally, particularly in urban areas of emerging and developing economies, where these products are in high demand and offer indulgent and health-promoting properties (60).

Crackers. A cracker is a flat, dense, low-moisture baked product typically made from soft wheat flour. The basic ingredients include flour, water, leavening agents, and fat, which are combined to form a slightly elastic dough. The dough is fermented or chemically leavened and then sheeted and laminated several times and rolled into a thin dough. It is cut into the desired shape and docked with thin pins to produce small holes that prevent the formation of large bubbles upon baking. There are three main classes of crackers: saltine (or soda) crackers; chemically leavened snack crackers that are slightly sweet, such as graham crackers, which originally were made only with whole wheat (graham flour); and flavored or savory crackers. Flavorings, salt, herbs, seeds, and/or cheese are added to the dough or sprinkled on top before baking, depending on the cracker type. Crackers are eaten on their own or with other foods, such as cheese and meat slices; dips; and soft spreads, such as jam, butter, or peanut butter (40).

Cookies. There are hundreds of types of cookies (Fig. 7), varying in shape, texture, size, and flavor. These products are popularly prepared at home or may be manufactured by a highly specialized industry using strictly controlled formulations and processes. Cookies, cakes, and pastries are generally prepared with soft wheat flour to ensure very low water absorption of the flour components, leaving most of the added water free and available to dissolve the sugar. When making products with soft wheat flour, gluten hydration and development of elasticity is prevented by having roughly $1/2$ to $2/3$ sugar and fat and $1/3$ to $1/2$ wheat flour in the formula, so the product does not have an optimal level of gluten development, and manipulation of the dough is minimal. Depending on the cookie formulation and

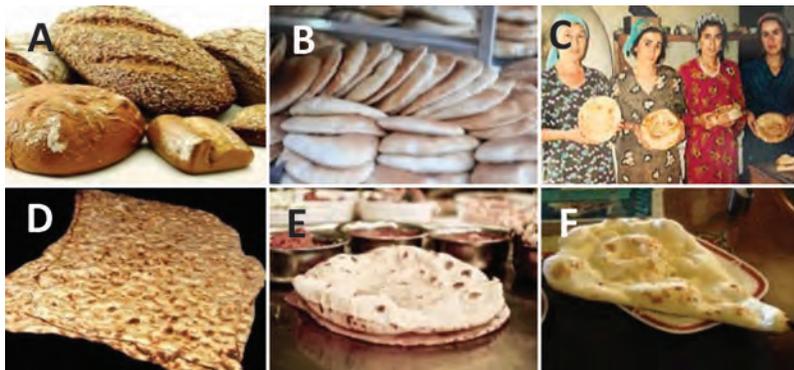


Fig. 5. Breads consumed in Africa and West, Central, and South Asia: **A**, variety of leavened breads of North Africa; **B**, Arabian pita; **C**, *tandoor* bread; **D**, Iranian *sangak*; **E**, Indian chapatti; and **F**, South Asian naan.

(Image source: **A**, Klaus Höpfner, from es.wikipedia.org/wiki/Pan#/media/File:FD_1.jpg, CC BY-SA 3.0; **B**, Guillaume Paumier (guillaume-paumier.com), from en.wikipedia.org/wiki/File:Nablus_souq_pita_118_-_Aug_2011.jpg, CC BY 3.0; **C**, R. J. Peña; **D**, Ensie & Matthias from San Diego, CA, from commons.wikimedia.org/wiki/File:Naan_Sangak.jpg, CC BY-SA 2.0; **E**, KittyKaht from Hong Kong, from www.flickr.com/photos/kittykaht/6439270727/, CC BY-SA 2.0; **F**, OpenCage, from opencage.info/pics/large_3799.asp, CC BY-SA 2.5)



Fig. 6. Breads consumed in East Asia: **A**, northern-style steamed; **B**, southern-style steamed; **C**, salty, filled steamed (dumplings); and **D**, steamed sandwich bread.

(Image source: **A** and **B**, R. J. Peña; **C**, Mizu basyo, from en.wikipedia.org/wiki/Dumpling#/media/File:Uyghur_manta.jpg, CC BY-SA 3.0; **D**, LeoAlmighty, www.flickr.com/photos/hjc218/6957350758/, CC BY 2.0)

flour/liquid ratio, the dough can be an inelastic, rollable dough or a soft, drop batter. Expansion or spreading of these food systems during baking is largely determined by the viscosity of the food system, the amount of free water converted into water vapor, heat, and the chemical reactions of chemical-leavening agents present in the formula (61). In some cookies, the only leavening is the incorporated air and steam formed during heating or the air trapped with the eggs.

There are three main processes used for producing cookies. 1) Rotary molded cookies are made from a stiff, cohesive dough that is pressed into engraved molds on a rotating roll. The molded dough then falls onto the moving baking band. The formed cookies are uniform in density, size, and shape and have limited spread during baking. 2) Wire-cut cookies are made with a soft dough that is extruded through an orifice and cut by a reciprocating wire and falls onto a baking band. The cookie dough spreads to uniform dimensions during baking. 3) Extruded cookies or bars are made from a soft dough that is either extruded or coextruded with a filling, such as fruit jam, and deposited on a conveyor as strips that are cut to the desired length, either before or after baking (40).

Cakes and Pastries. Cakes and pastries are very common breakfast items, sweet snacks, and desserts and may be consumed as part of holiday and other celebrations. There are several types of cakes and pastries, both plain and filled, but cakes, doughnuts, and pies are the most common products.

Cakes are usually made with a low-protein, finely ground flour. The batter may be thick, similar to a soft, cakelike cookie, or may be more fluid. Cakes have a 2:1 flour/liquid ratio but require some gluten development, which is achieved by beating the batter. Beating is required because of the high levels of sugar and fat used, which impede gluten hydration and development. Some gluten development is required so the starch matrix can attach to the gluten and form the cake cell structure around the starch. Creaming the shortening (fat) allows the incorporation of small air bubbles, which act as sites where the gas produced from chemical leavening is deposited.

Pies are a pastry that usually have a crust on the bottom and some type of filling. The crust is either a thin, layered, steam-leavened flaky pastry or is made from a mixture of crumbs and butter. The pastry

may or may not be sweetened. The filling can be either a thickened, sweetened fruit, custard or pudding, or cream cheese- or nut-based mixture (40). Fruit pies may also have a second crust (double crust), which covers the top.

Savory pies are popular in many parts of the world, such as quiches in France and meat pies in Britain. Pastries for such pies may include cheese or herbs in the nonsweetened crust.

Noodles

Wheat Flour Noodles. Wheat flour noodles are widely consumed in East and Southeast Asia (Fig. 8) and are a staple in northern China (62,63). The popularity of noodles, particularly that of instant noodles, has spread globally. There are two general types of wheat flour noodles: Chinese white salted noodles and yellow alkaline noodles, known as udon and ramen noodles, respectively, in Japan. Chinese white salted noodles are made with low-extraction flour (<70%, resulting in a flour ash content <0.5%), and udon noodles are made with flour streams that

produce very white flour with a very low ash content (roughly 40% extraction rate). Low-extraction flour helps to reduce possible contamination with polyphenol oxidase, which negatively affects (darkens or decolorizes) the whiteness of noodles (64,65).

To make noodles, flour, salt, and water are used. In the case of yellow alkaline noodles, roughly 1% alkaline salts, known as *kansui*, is added to develop a yellow color through the reaction of alkali and flour proteins. When making noodles, the ingredients are mixed at low speed until a stiff, crumbly dough is formed. After a rest period, the dough is passed a few times through sheeting rolls and is rotated 90° before each pass until the dough is slightly elastic and smooth. The smooth dough is cut or extruded to produce the desirable noodle shape and size (65,66). Noodles are sold either fresh or dry. One popular way of producing fresh noodles is by pulling very soft, extensible dough to produce noodle strands, which are immediately boiled in water (62,67). An additional way of con-



Fig. 7. Crackers, cakes, and pastries: **A**, saltine crackers; **B**, graham crackers; **C**, water biscuits; **D**, matzo; **E**, cake; **F**, muffins; **G**, doughnuts; and **H**, pastries.

(Image source: **A** and **B**, Evan-Amos, from commons.wikimedia.org/w/index.php?curid=11475109 and commons.wikimedia.org/wiki/File:Graham-Cracker-Stack.jpg, respectively, taken as part of Vanamo Media and in the public domain; **C**, J. P. Lon, from en.wikipedia.org/wiki/Water_biscuit#/media/File:WaterBiscuit-Trio.jpg, CC BY-SA 3.0; **D**, Yoninah, from en.wikipedia.org/wiki/Matzo#/media/File:Machine-made_Shamura_Matzo.jpg, CC BY 2.5; **E**, Kurt James, from en.wikipedia.org/wiki/Cake#/media/File:Download_(53).jpg, CC BY-SA 4.0; **F**, en.wikipedia.org/wiki/Muffin#/media/File:NCI_Visuals_Food_Muffins.jpg; **G**, Towne Post Network, from www.flickr.com/photos/atgeist/8367852364/, CC BY 2.0; **H**, jtytl, from en.wikipedia.org/wiki/Pastry#/media/File:Palmeras_de_hojaldre_1.jpg, CC BY 2.0)



Fig. 8. Wheat flour noodles: **A**, white salted; **B**, yellow alkaline; **C**, hand-pulled; **D**, dry white; and **E**, instant.

(Image source: **A**, prattflora, from es.wikipedia.org/wiki/Fideo#/media/File:Oyster-Vermicelli.jpg, CC BY-SA 3.0; **B**, NMajik, from en.wikipedia.org/wiki/Noodle#/media/File:Egg_noodles.JPG, CC BY-SA 3.0; **C**, © Cephoto, Uwe Aranas, from commons.wikimedia.org/wiki/File:Dalian_Liaoning_China_Noodlemaker-01.jpg, CC BY-SA 3.0; **D**, R. J. Peña; **E**, Takeaway, from commons.wikimedia.org/wiki/File:Mama_instant_noodle_block.jpg, CC BY-SA 3.0)

suming noodles is by deep-frying fresh noodles or first boiling and then stir frying the noodles before they are consumed in soups or with other foods. White salted noodles should be creamy white (darkening due to high polyphenol oxidase activity is highly undesirable) and soft with enough elasticity to permit a clean bite. Yellow alkaline noodles are yellow and smooth and firmer and more elastic than white salted noodles due to their higher protein content, which includes slightly more elastic gluten (62,65–67).

Instant Noodles. Instant noodles packaged in a cup or bowl were developed in the 1970s to satisfy the demand of Japanese consumers for convenience (67). There are Chinese and Japanese versions of packaged instant noodles. Both white salted noodles and yellow alkaline noodles can be processed to produce instant noodles. According to Nagao (67), 0.2% (flour basis) *kansui* is added to the noodle formula. To achieve rapid hydration, the instant noodles are thinly cut. The noodles are folded and steamed for 1–3 min at 95–100°C. During the production of nonfried noodles, steaming time should allow for starch gelatinization. Drying is performed by frying for 2–3 min at 135–140°C (67). Ready-to-eat packaged instant noodles are sold with flavorings, seasonings, and dehydrated vegetables and/or meat. In this case, consumption of the instant noodles only requires the addition of hot water. Instant noodles are also sold packaged as blocks to be cooked in boiling water at home and served with homemade broths or as an accompaniment to other dishes. Ramen noodle soup is a common descriptor of the Japanese version of instant noodles, and this name has been adopted in countries outside East Asia.

Durum Wheat-Based Foods

Durum wheat is the main raw material used in the manufacture of diverse foods, including regional dishes in the West Asia/North Africa region, the Mediterranean Basin, and the Indian subcontinent (19,25).

The most common durum wheat-based foods are pasta, bread, couscous (small circles of pasta dough made in two sizes), and bulgur (dried cracked durum kernels, cooked in water, often with flavorings and other items, and eaten either hot or cold in salads such as tabbouleh) (25,41,68,69) (Fig. 9).

Durum wheat's very hard endosperm allows for high extraction rates in making semolina (coarse flour particles), which is the main raw material in pasta formulations. The high yellow pigment content in semolina confers the intense bright yellow color that characterizes pasta products, which is highly desirable.

Pasta. Nearly 95% of durum wheat produced globally is used in pasta, which is made from a mixture of semolina and water and, in some cases, egg or other ingredients. Pasta is a global food, with high consumption in southern Europe and North Africa, as well as in non-Mediterranean regions, such as North America and the former Soviet Union. There are more than 350 different types of pasta, and many pastas may have different names in different parts of the world. They can be grouped within two main classes: long and short. Among the first, the best known pastas are spaghetti and lasagna and, among the latter, macaroni and rigatoni, as well as others with names reflecting their shape.

The basic ingredients in pasta manufacturing are semolina (coarse durum wheat flour) and/or flour and water. In some pasta products, whole eggs or egg whites are included. Ingredients are kneaded to form a stiff, crumbly dough (with water absorption around 30–32%), which is extruded under vacuum through dies with diverse shapes, yielding long pasta strands or short pasta pieces. Filled pastas, such as tortellini or ravioli, are made with fresh pasta sheets cut to desired shapes and filled with vegetables, meat, or cheese. Any of these pastas may be eaten or sold fresh or frozen or held under a modified atmosphere and sold in refrigerator cases. Some are canned with a sauce (70). How-

ever, most pasta is sold dried. Drying the cut pasta is done under well-controlled temperature and relative humidity conditions to avoid cracking, particularly in long pasta products, to reach ~12–12.5% moisture. Drying periods vary from 3 hr for short pastas to 7–8 hr for long pastas (70). The end product is uniform, bright yellow, hard, and translucent.

Dry pasta is typically cooked in boiling water for 5–12 min, depending on the shape, density, and characteristics of the product. Fresh pasta cooks in much less time. Cooked pasta should be firm, non-sticky, and slightly elastic, offering some resistance to the bite (*al dente* texture). Sauces or mixtures of other ingredients, including cheese, vegetables, meat, fish, and nuts, are often added to cooked pasta. Short or small pastas may be used in pilafs, soups, and salads.

In some parts of Asia and Latin America, where durum wheat is not as readily available or is expensive, wheat flour is used instead of durum wheat to make pasta. Fresh egg may be included in the formula to add color and a firmer texture through the addition of protein (54). Overcooking such pastas must be avoided since these products are prone to stickiness.

Durum Wheat Breads. Durum wheat leavened and flat breads are consumed mainly in Mediterranean countries and West Asia (25,68,70,71). The preparation of doughs for leavened and flat breads from durum wheat is similar to that used with common wheat flour. However, water absorption is generally higher in durum wheat than in common wheat doughs due to the inherent elastic properties of the gluten proteins and, especially, to the larger amount of damaged starch produced during the milling of durum wheat flour (68,72–74). Water absorption, mixing, and fermentation conditions can also vary, depending on the type of flour used (semolina, semolina–flour blends, flour, or whole meal flour). The combination of bread formula, dough viscoelastic properties, length of fermentation, and oven conditions determine the size, volume, crust thickness, and crumb structure of the bread. Hearth breads baked on the oven floor generally have a semihard to hard crust and unevenly distributed crumb structure (25, 68,74). Durum yeast-leavened breads usually have a medium density (75) and are yellow and have a durum wheat aroma that is highly desirable (68,69).

Flat breads, such as chapatti, tortilla, *baladi*, *tanoori*, and pita, can be made



Fig. 9. Durum wheat-based products: **A**, long pasta; **B**, short pasta; **C**, filled pasta; **D**, couscous; and **E**, bulgur.

(Image source: **A**, **B**, and **D**, R. J. Peña; **C**, Jon Sullivan, from commons.wikimedia.org/wiki/File:Ravioli.jpg, released into the public domain; **E**, Noumenon, from commons.wikimedia.org/wiki/File:Kisir.jpg, CC BY-SA 3.0)

with durum wheat. Traditionally, the making of flat breads was most often performed at home or in small local bakeries. However, the current demand for these products at both their place of origin and in many countries around the world has resulted in industrial production in many regions (25,39,41,76,77). Durum wheat flat breads retain their freshness longer than those made with common wheat, which is advantageous to the consumer.

Couscous and Bulgur. Couscous is a durum wheat-based food. It is often consumed two to three times per week in parts of North Africa, the Middle East, and West Asia (42). It is prepared by moistening semolina, rubbing and kneading, mainly by hand, to agglomerate wet semolina particles and form granules that are steamed and then traditionally dried under the sun. After sifting the dry dough granules, small granules are treated again to achieve a uniform granule size. Couscous is generally accompanied by vegetables and/or meat, although sweet couscous is also prepared (25,42). In large, industrial-scale production of couscous, semolina is mixed with water to achieve 30–40% moisture. The semolina aggregates are steamed, dried, sifted, and reduced with a roller mill to a uniform particle size. Good-quality couscous should be yellow and porous to absorb the juices of the added ingredients and acquire the desired flavor, texture, and smoothness. Packaged couscous is in high demand in urban populations of North Africa and France and is becoming increasingly popular in North America (42).

Bulgur is more common in West and South Asia than in North Africa, with Turkey having the highest consumption (42). Although bulgur can be prepared with both common wheat and durum wheat, the latter is preferred, because it is harder in texture and has an amber color (42,78). Bulgur is produced by boiling the clean wheat kernel in excess water, followed by drying to 10–12% moisture, which was traditionally done in the sun. The dried grains are then cracked in a stone mortar. Because of the possibility of infestation and degradation, commercial bulgur is dried using controlled drying methods and milled with a vertical emery stone or disc mill (hammer mills make the poorest quality bulgur) (79). The reduced bulgur particles are sifted to remove the separated outer bran layers. High-quality bulgur has an amber-yellow color, a hard texture, and characteristic durum wheat flavor. Bulgur is typically served with vegetables and/or meat. Bulgur's popularity is increasing

around the world because of the consumer interest in diets that are plant based, contain whole grains, and have proven health benefits, like that of the Mediterranean Diet. Bulgur is also used by the World Food Program of the United Nations as a commodity for food aid (42).

Wheat-Based Breakfast Cereals

Wheat and grains are used in the production of many breakfast cereal products (Fig. 10) and are considered a good source of nutrition. For children and teenagers, these foods are a particularly good source of energy and nutrients, especially when consumed with milk and foods such as fruits and nuts (80). Wheat-based breakfast cereals are widely consumed, particularly in the Western Hemisphere and parts of East and South Asia and Australia and in urban areas in many countries. There are four main breakfast cereal types, and wheat is used in all of them. 1) Hot cereals are made by cooking the raw grits or rolled cereal in water or milk. They are consumed hot, often with milk or yogurt. 2) Instant hot cereals are made from cooked hot cereals that are dried so they can be prepared and ready to eat by simply adding hot water or milk. 3) Ready-to-eat cereals are made from grains that are cooked, extruded, rolled, flaked, shredded, or puffed and are usually consumed with milk. 4) Ready-to-eat-cereal mixtures are mixtures in which pieces of various raw

or cooked cereal grains and dry fruits, oil-seeds, nuts, etc. are combined. Granola and muesli are good examples of this type of cereal (40).

Whole Wheat Products

Whole grain (including wheat) products are increasingly popular mainly due to their enhanced nutritional quality and the health benefits associated with their high fiber content and the presence of bioactive compounds (81,82). Most wheat-based foods prepared with refined flour can also be prepared with whole wheat flour (Fig. 11). However, adjustments to baking formulas must be made to account for differences in the functional properties of the doughs and batters. These differences are mainly related to the decreased amounts of gluten protein and starch and increased water absorption capacity of whole wheat doughs. All of these factors impact the flow of dough through extruders, baking performance, and other aspects of home, bakery, and industrial production of whole wheat foods. The bitterness and other characteristics of whole wheat flour may require additional formula changes.

In many countries, dietary guidance suggests that at least half of grains consumed be whole grains; therefore, manufacturers are working to incorporate whole wheat in its many forms, including bulgur, into wheat-based food. Despite the push



Fig. 10. Wheat-based breakfast cereals: **A**, puffed; **B**, shredded; **C**, bran with raisins; **D**, shredded with frosting; and **E**, granola.

(Image source: **A**, BMK, from commons.wikimedia.org/wiki/File:Puffed_wheat_BMK.jpg, CC BY-SA 2.0; **B**, Pete unseth, from commons.wikimedia.org/wiki/File:Bite-sized_shredded_wheat.jpg, CC BY-SA 3.0; **C**, Evan-Amos, from commons.wikimedia.org/wiki/File:Raisin-Bran-Bowl.jpg, taken as part of Vanamo Media and in the public domain; **D**, Seanutbutter, from commons.wikimedia.org/wiki/File:Frosted_Mini_Wheats.png, CC BY-SA 3.0; **E**, © David Corby, from commons.wikimedia.org/wiki/File:Granola03242006.jpg, CC BY-SA 3.0)

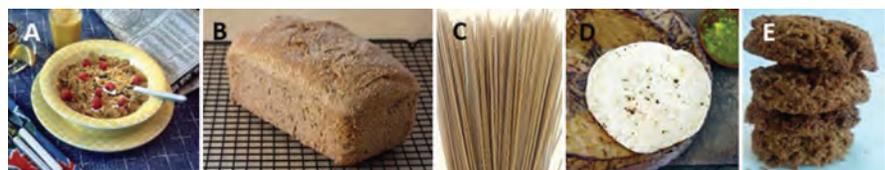


Fig. 11. Whole wheat products: **A**, breakfast cereal; **B**, bread; **C**, long pasta; **D**, flat bread; and **E**, cookies.

(Image source: **A**, Unknown, from en.wikipedia.org/wiki/File:NCI_Visuals_Food_Meal_Breakfast.jpg, released by the National Cancer Institute, an agency of NIH, ID 2460, and in the public domain; **B**, Veganbaking.net, from www.flickr.com/photos/31104779@N02/5056609572, CC BY-SA 2.0; **C**, **D**, and **E**, R. J. Peña)

for an increase in whole grain intake, data for 2001–2010 show that the 10 year consumption trend was relatively flat, with only a very slight upward trend. Thus, for example, whole grain intake goals are met by only 1% of the population in the United States (83).

TRENDS IN WHEAT-BASED FOOD CONSUMPTION

The demand for industrially processed traditional and new wheat-based foods continues to increase. *The Economist* (84) reported on increasing per capita wheat consumption in several countries of South, East, and Southeast Asia. This trend is mainly driven by changes in lifestyles linked to urbanization, more women in the workforce, and the establishment of formal food stores, supermarkets, and fast-food outlets (12,14,85,86). Among the wheat-based foods that are increasingly in demand are products offering convenience (e.g., ready-to-use, ready-to-eat, frozen, microwaveable, and instant products), such as pan breads, sandwich breads, instant noodles, and biscuits (e.g., cookies, crackers, and snack bars), which are purchased mainly in supermarkets and food stores (14,87), and products used as components of fast-food items, such as hamburgers, hot dogs, and pizza, which are dominant in urban areas and food courts in shopping malls/plazas (2, 12,14,84,85). The demand for whole grain and for options such as bulgur is part of the move by some consumers toward healthier diets. The growing trends in consumption of some wheat-based foods are discussed below.

Pan (e.g., English Sandwich) and Molded Breads. In the United Kingdom in 2014, sandwich (pan) bread accounted for 50% of the nearly 12 million loaves sold daily, with large bakeries producing wrapped and sliced breads, corresponding to 80% of U.K. bread production (88). Sandwiches made at home, or purchased, are eaten for lunch at school or work. Some 10 billion sandwiches were consumed in the United Kingdom in 2014, for a per capita consumption of ~200 sandwiches/year (88). Currently, the consumption of sandwich bread is growing at ~5%/year. According to Sandwich International, the growing consumption of pan bread and sandwiches is also happening in urban areas around the world because it is a convenient way to carry and consume a healthy, balanced meal (14,89). In Latin America and Europe, sandwiches made

with traditional hearth-baked breads are much more popular (54,90–92).

Hamburger Buns. Hamburger buns, a modification of the classic sandwich (pan) bread, are a component of a popular fast foods (14,93). In the United States, ~50 billion hamburgers are consumed per year, with ~50,000 burger restaurants and outlets located across the country. Hamburger restaurants chains are satisfying consumer demands globally. According to *BurgerBusiness*, in 2014, the top three American hamburger restaurants chains generated a revenue of more than US\$50 billion outside the United States in ~55,000 food outlets located in many countries around the globe (94).

Pizza. Pizza is also a popular wheat-based food globally. The wheat flour crust, traditionally covered with tomato sauce and cheese, can be prepared in diverse sizes, thicknesses, and textures and can carry diverse toppings, such as vegetables, meats, and seafood in many different combinations. Pizza fits well in many cultures, allowing for variations of toppings according to food habits, and is available as ready-to-eat, take-away, and prebaked pizza crust in supermarkets. In the United States, the largest pizza-consuming country (by volume) in the world, there are 70,000 pizzerias and a pizza industry with revenues worth about US\$32 billion (95). The United States is second only to Norway in per capita consumption of pizza (96). The top 11 pizza-consuming countries include, from lowest to highest, Turkey in West Asia; China and Japan in East Asia; Australia in Oceania; France, Russia, Italy, Germany, the United Kingdom, and Norway (first place per capita) in Europe; and the United States in the Americas (96). Developing and emerging countries, particularly in Asia, consume far less pizza, but the trend is increasing for this product.

Cookies and Crackers. Globally, sales of cookies and crackers are growing, particularly where the industry offers indulgent products containing more fiber, less saturated fat, and more polyunsaturated fatty acids, such as omega-3 fatty acids. The offering of whole grain, savory biscuits or natural crackers is also attracting middle- to high-income consumers, but concerns about excess sugar and calories may stall growth in these categories for some consumers. In regions or population segments where there is economic uncertainty, lower-cost plain biscuits and crackers dominate the biscuit market (54,60,97). According to *Euromonitor International* (60), the demand for cookies and crackers

is expected to continue to increase in Asia-Pacific and Latin America, particularly in urban areas, where the bulk of biscuit sales occur. Brazil and China are good examples of this trend (54,60,98). In contrast, the trend in consumption, particularly of sweet biscuits, is expected to fall in North America and Western Europe, mainly due to the demand for more health-oriented snacks, which may favor an increase in consumption of health-promoting bars.

Instant Noodles and Pasta. Instant noodles are East Asia's largest contribution to the global fast-food industry. Although instant noodles are very popular in East and Southeast Asia, their consumption has spread to other parts of the world as well. After China, with consumption of more than 45 billion units/year, Indonesia is the largest market, consuming 14.5 billion units/year, followed by Japan and Vietnam, with consumption rates above 5.5 and 5.0 billion units/year, respectively (99). Outside these regions, the largest consumption of instant noodles is in the United States, with 4 billion units/year. Demand is increasing in countries as diverse as India, Russia, and Brazil (99). Consumers are expecting continued enhancements in the quality of these products, particularly from a nutritional point of view, including the use of flour fortified with micronutrients and vitamins and innovations in flavors and ingredients with positive impacts on nutrition and health (98,100).

Pasta offers convenience, mainly as dry pasta and refrigerated or frozen fresh pasta, and can be a component of an economical, balanced meal at home when combined with vegetables, meats, and fish. It is also a popular dish in restaurants (101). Pasta shows a modest growth trend, particularly in Europe and the Americas (102).

CONTRIBUTION OF WHEAT-BASED FOODS TO FOOD SECURITY, NUTRITION, AND HEALTH

Food Security

Approximately 800 million people, most living in rural areas of Asia and Sub-Saharan Africa (Fig. 12), suffer from hunger because they do not have enough food to eat, leading to an undernourished condition. Stunting and decreased cognition are the main effects of undernourishment, making those affected more vulnerable to diseases and health problems (8).

The contribution of wheat-based foods to food security and nutrition is highly relevant, since they provide about one-fifth

of the daily calories and protein consumed globally, and even higher levels in North Africa and West, Central, and South Asia (Fig. 13).

Wheat, in many cases, is the only crop option for millions of low-income, small-scale farmers, who frequently lack access to improved, high-yield wheat varieties, efficient crop management practices, and the inputs required to achieve profitable production levels. These constraints contribute to frequent failures to harvest enough wheat to feed their families and obtain the profits required to meet their basic needs (1,2,4). Wheat productivity and production are expected to reduce undernourishment among those who depend on this crop. For this to happen, attention needs to be given to continuous scientific research to develop improved production packages, including resilient wheat varieties, improved crop management practices, and required crop inputs (4).

Micronutrient Malnutrition

More than 2 billion people worldwide suffer from micronutrient (minerals and vitamins) malnutrition. Micronutrient malnutrition, also known as “hidden hunger,” occurs when the diet supplies inadequate levels of the minerals and vitamins required to maintain general health (8,103). Micronutrient malnutrition includes deficiencies in several vitamins and minerals; however, vitamin A, folic acid, iron, and zinc are among the major micronutrients causing very serious health problems and death, mainly of preschool children and women, especially in developing countries. Severe vitamin A deficiency is associated with a weakening of the immune system, incidence and severity of infectious diseases, and blindness in young children (104). Folate acid plays an important role in the production of new cells and, therefore, is critical during the fetal development period for healthy development of multiple tissues, including the brain. Folate deficiency frequently results in neural tube defects (e.g., spina bifida). Sufficient folate intake by the mother prior to conception significantly reduces the potential for neural tube defects (104). Folate fortification of flour and wheat-based foods in numerous countries has reduced the incidence of neural tube defects by more than 50% (105).

Iron deficiency anemia is associated with maternal and perinatal mortality, as well as with impaired motor and cognitive development in childhood and the physical activity skills and productivity of those

affected (104). Zinc deficiency negatively affects the immune system, reduces resistance to infection, and impairs growth and development of the nervous system. Zinc deficiency significantly increases the risk of diarrhea, pneumonia, and malaria and, therefore, is a key factor in the high incidence of morbidity and mortality of those affected (104). Micronutrient malnutrition results in impaired child development, reduced adult productivity, loss of lives, and a very high-cost socioeconomic and healthcare burden, drastically affecting economies, especially in developing countries.

Enrichment and fortification (i.e., addition of nutrients) of wheat and processed foods with essential minerals and vitamins have contributed significantly to reducing micronutrient malnutrition in children, adults, and the elderly (104,106–108). Wheat-based foods, derived from either

whole grain or fortified refined flours, such as ready-to-eat breakfast cereals, breads, pastas, noodles, and biscuits, have been shown to contribute to increased intake of necessary vitamins and minerals (104,106, 107,109,110). According to the Micronutrient Initiative, the proportion of wheat flour fortified in the world increased globally from 18% in 2004 to 34% in 2016 (104,111). Currently, fortification of wheat flour with at least iron and folic acid is mandatory in 86 countries in different regions of the world (Fig. 14). Fortunately, in many cases, wheat flour fortification also includes iron, zinc, B vitamins, and folic acid. In addition, eight countries (i.e., Afghanistan, Democratic Republic of Congo, Gambia, Lesotho, Namibia, Qatar, Swaziland, and the United Arab Emirates) voluntarily fortify more than half of their industrially milled wheat flour (111).

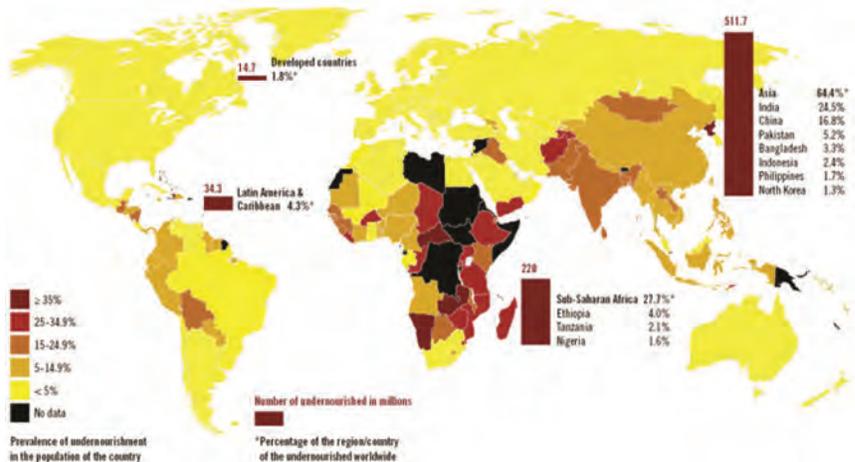


Fig. 12. World map of undernourishment for 2014–2016. Image source: www.globalagriculture.org/report-topics/hunger-in-times-of-plenty.html.

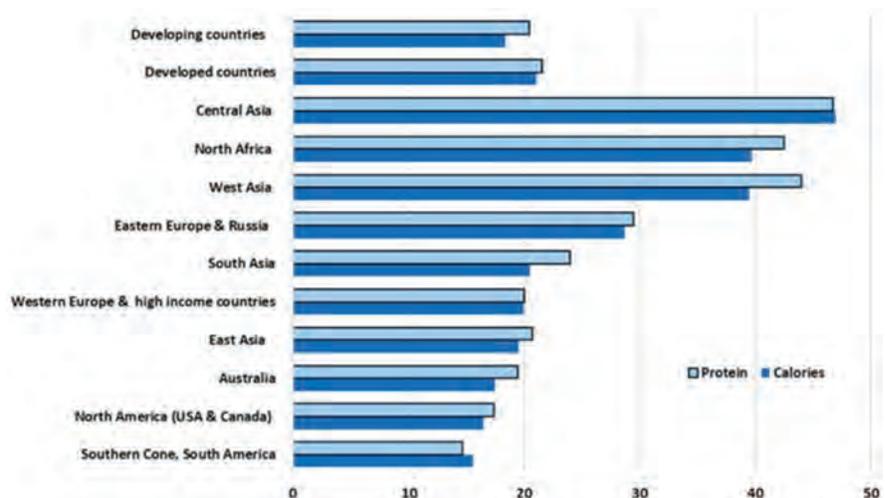


Fig. 13. Percentages of calories and protein from wheat in total dietary intake (%), 2005–2009. Source of data: Shiferaw et al. (2).

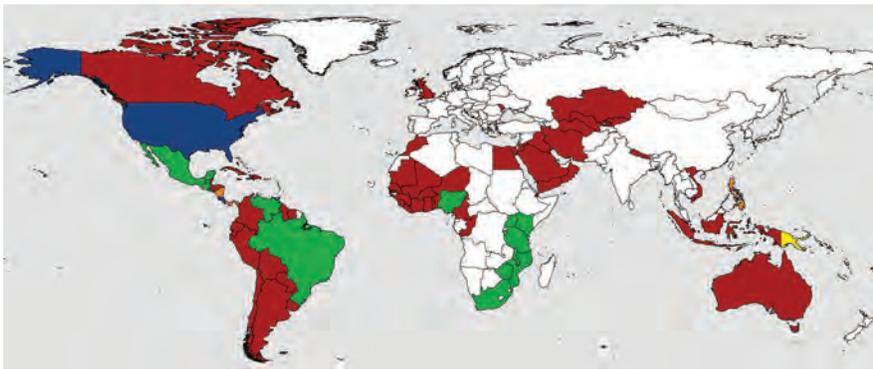


Fig. 14. Mandatory cereal grain legislation globally as of March 2017. Red = wheat flour (67 countries); green = wheat and maize flours (14 countries); orange = wheat flour and rice (3 countries); blue = wheat and maize flours and rice (2 countries); and yellow = rice (1 country). Image source: ffinetwork.org/global_progress/index.php.

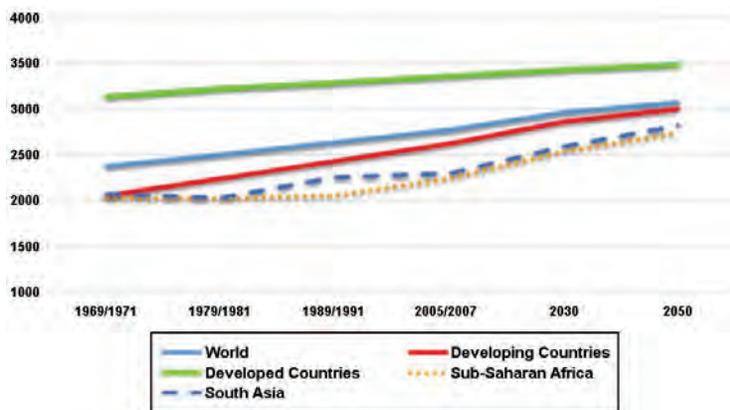


Fig. 15. Food consumption trends (kcal/person/day). Source of data: Alexandratos and Bruinsma (1).

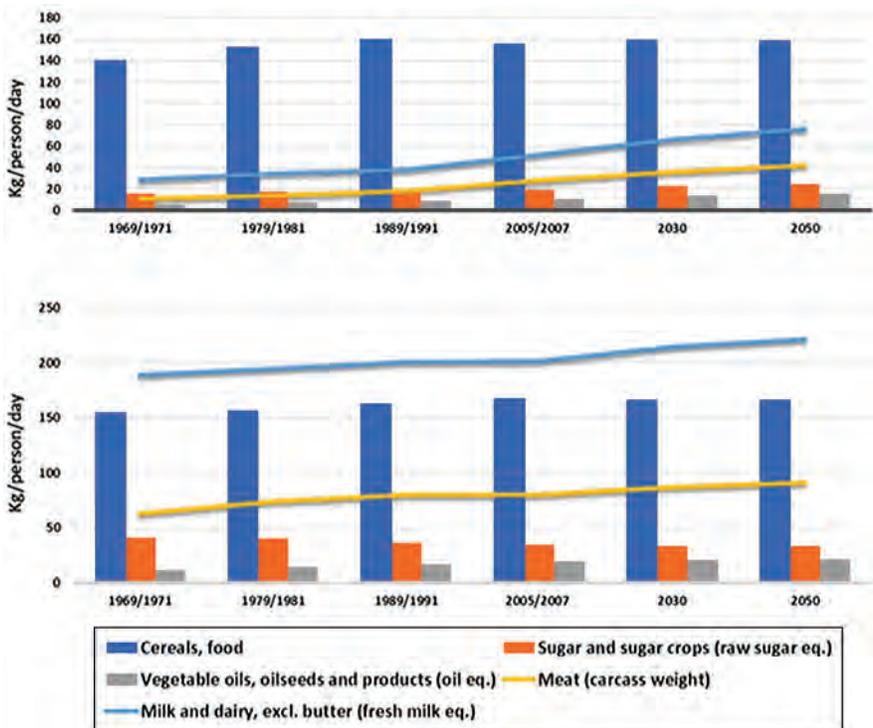


Fig. 16. Changes in commodity composition of food in developing (top) and developed (bottom) countries. Source of data: Alexandratos and Bruinsma (1).

Calorie Intake

During the last three decades, developing countries have shown an upward trend in food consumption. If this trend continues, calorie intake is predicted to be about 3,000 kcal/person/day in 2050. Although this reflects a significant increase, it is lower than intake levels predicted for developed countries. Sub-Saharan Africa and South Asia are predicted to continue to have calorie intakes below 3,000 kcal/person/day (Fig. 15). The main factor impacting the observed food consumption trend in developing countries is population growth, while a combination of population growth and diet change promoted by economic improvements are the main factors in developed countries (1,8,112).

Regarding the contribution of food groups to the increasing trend in calorie intake, it is important to note that this is related more to increases in the consumption of meats, oils, and dairy products than that of cereal-based foods (Fig. 16). As indicated earlier, the consumption of cereals is expected to remain stable or to decline slightly (1,10,11).

Areas with a large population showing an increase in calorie intake mainly from consumption of foods other than cereals are India (113), China (114), Brazil, Europe, and the United States.

Wheat-Based Foods, Overweight/Obesity, and Health

Changes in dietary and lifestyle patterns, including reduced physical activity, have led to a dramatic increase in the number of people suffering from overweight or obesity, particularly in rapidly urbanizing developing countries (10). Globally the number grew from 28 million in 1990 to 43 million in 2011 (10). Alarming, overweight and obesity are the main cause of a number of noncommunicable diseases, such as cardiovascular diseases, high cholesterol, and type 2 diabetes. Overall, adult overweight, obesity, and elevated blood glucose increased in every region of the world between 2010 and 2014, and heart disease is the leading cause of mortality worldwide, with three-quarters of related deaths occurring in low- and middle-income countries (10).

Dietary patterns that lack a balanced intake from the various food groups and in which portion control is poor, coupled with low physical activity, are central to the issue. No one food or food group is inherently unhealthy. Barnard (115) indicated that it is not cereal-based foods

(e.g., bread, rice, and grains in general) that cause high blood sugar levels. Dietary transition from traditional foods and excess consumption of all food groups, leading to overweight and obesity, are the real culprits in these noncommunicable diseases. The metabolism of fat accumulated in muscle and liver cells disrupts insulin signaling, causing insulin resistance (115). Weight reduction, calorie intake control, and replacement of excessive fat intake with legumes, grains (especially whole grains), vegetables, and fruits in the diet can all help reduce the risk for developing these diseases.

Because glucose is the preferred fuel for the brain, it is essential to include the right amount of this carbohydrate in the diet. Maintaining a balance between energy consumed and energy spent through physical activity is critical.

With regard to the impact of dietary patterns on overweight/obesity and related noncommunicable diseases, wheat-based foods play an important role in both positive and negative health effects, depending on the quantity and quality of the wheat-based foods included in the diet (116,117). Recent review articles concluded that, in general, consuming cereal foods, including wheat-based foods, can have beneficial effects in preventing obesity and associated noncommunicable diseases (118–121). Consumption of up to 50% of wheat-based foods as products made with refined flour (with low levels of added fat, sugar, and sodium) is not associated with increased disease risk (121). Adams (122) recently reviewed studies on the relationship between consumption of wheat-based foods (both refined and whole grain foods) and health conditions. The review indicated that refined grains are not detrimental when consumed as part of a balanced diet; on the contrary, these foods have beneficial health effects, and therefore, their consumption in recommended amounts is included in dietary guidance around the world (117,123,124). Such guidance promotes balanced, healthy dietary patterns, such as the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) Diets. These diets recommend that 45–65% of calorie intake come from carbohydrates; wheat and cereals may provide a significant portion of the carbohydrates in the diet (116,117,124). It has been suggested that for those who require 2,000 kcal/day and follow a balanced dietary pattern it is important that they consume approximately six 30 g portions of cereal-based foods

per day, with half as whole grains. Such a dietary pattern can be followed as part of a weight control regimen and is associated with improved health outcomes and a reduced risk of noncommunicable diseases (116,125,126).

Studies have shown an association between specific cereal foods and improved health outcomes. A systematic review showed that regular consumption of breakfast cereal, although resulting in a higher energy intake, was associated with a lower prevalence and risk of overweight in children and adolescents compared with those with infrequent consumption of breakfast cereals (127). Such findings suggest that those consuming breakfast cereal are more likely to be physically active as well, which would account for the higher energy intakes but lower body weights. The consumption of wheat-based foods (both whole and refined grains), such as breads, pastas, breakfast cereals, cookies, and crackers, contributes to body weight maintenance as well as to diet quality, providing a more balanced intake of nutrients (128–131).

Compared with refined wheat-based foods, whole grain, wheat-based foods have higher levels of dietary fiber, minerals, vitamins, and bioactive compounds. Wheat-based foods that are fortified or enriched also deliver important minerals and vitamins; some nutrients are fortified at higher levels or are more available than those present naturally in whole grain, wheat-based foods. Wheat-based foods prepared with refined flour should be consumed with other fiber-rich foods, such as legumes, vegetables, and fruits. If white (refined flour) bread is eaten alone as a meal, the glycemic index of the meal may be high, but if it is eaten with butter, olive oil, vinegar, cheese, meat, or vegetables, the glycemic index of the meal is reduced. The most important thing is to consume wheat-based foods as part of a balanced diet (116).

CHALLENGES IN SUSTAINABLE WHEAT PRODUCTION AND CONSUMPTION OF WHEAT-BASED FOODS

Wheat Production

Importance of Wheat in Food Security.

As discussed earlier, the supply of wheat is extremely important for the global population and even more important for the diets of the ~2.5 billion people living in poverty (2). Some 570 million farmers are responsible for the global food supply, pro-

viding a livelihood for about 40% of the world's population (132,133). Many of these farmers rely on wheat production as their main source of food and income required to ensure food security and to improve the livelihood of their family members. In poor, agriculture-dependent regions, production potential is low due to limited agricultural resources and poor access to innovative technologies and farming infrastructure. In addition, many small-scale farmers continually face constraints related to climate change (1).

The position of wheat in the international food market is another factor that makes wheat production and supply especially important. Several countries with limited or no production of wheat depend on the wheat supplied by the international market. Wheat is first among agricultural commodities trading and is the largest imported food in some developing countries (2). It is important to note that, even in modern times, a sharp increase in wheat prices, like that in 2008, can result in urban protests (e.g., the Arab Spring). Thus, a shortage of wheat and high wheat prices could be the cause of social and political instability, particularly in developing countries that rely on wheat as one of their main food sources.

Biotic and Abiotic Threat to Wheat Production. Globally, crop losses due to diseases and pests are estimated to be ~20%. Achieving current wheat yields requires the application of integrated pest management strategies that involve many components, including the judicious use of chemical protectants, especially in developing countries. Two of the major wheat pathogens include rusts and *Fusarium* species, the latter producing grain mycotoxins that are toxic to both humans and animals (3,134).

Climate change is already affecting the yield of cereal crops. Some studies predict that yield potential may fall as much as 25–30% in South Asia and other important wheat-producing areas. Diverse climate changes, mainly drought, heat, or a combination of both, have already affected mid-latitude, temperate wheat-producing areas, such as Mexico, Argentina, and northeastern Australia (135,136). Dawson et al. (137) created models to determine the effects of no climate change and climate change. In the model, various factors, such as population growth and land use, were considered to estimate the impact on food availability by 2050. With no climate change, ~30% of the global population is at risk of undernourishment.

With climate change, ~52% will be at risk if no adaptive or innovative actions are taken.

Ongoing efforts are required to improve the adaptation of wheat crops to diverse and contrasting climatic constraints and biological changes caused by global climate change (2). The frequency of extreme weather conditions, mainly heat and drought, in major wheat-producing areas and the advent of new biotypes that present new diseases, such as rusts and *Fusarium* species, are already challenging gains in wheat productivity in many wheat-producing areas around the world (2,138). Thus, continual support of agriculture research is needed to develop technologies and innovations to achieve sustainable grain yields. Further policies, education, and credit to enable small-scale farmers to acquire infrastructure are necessary to enhance productivity as well (1).

Innovations to Enhance Nutritional and Health Benefits of Wheat-Based Foods

Wheat Biofortification. In the Harvest-Plus biofortification program, the concentration of vitamins and minerals found in a crop is enhanced through plant breeding, transgenic techniques, and agronomic practices (139). Consuming biofortified staple crops can help increase the daily adequacy of micronutrient intakes (103). The aim is to make biofortified staple crops available (at low cost) to poor populations that usually do not have access to micronutrient-fortified foods. In the case of biofortified wheat, it has been shown that the bioavailability (absorption) of zinc in whole wheat meal and high-extraction (80%) flour is better than in traditional, nonbiofortified wheat (140,141). Bioavailability of enhanced iron and zinc in bread can be increased by extending fermentation time during breadmaking, due mainly to the reduction of phytate; the longer the fermentation time, the higher the retention of free iron and zinc present in the 80, 75, and 70% extraction flours used in the study (142,143). High-yield, high-zinc biofortified wheat varieties have already been released in India and Pakistan, and wide dissemination of biofortified wheat among farmers is occurring (144). Diverse genetic resources are being used for the development of biofortified wheats (145). In an optimistic scenario, 10 years after the first release of a biofortified wheat variety in South Asia, a high-zinc wheat could be consumed by 120 million resource-poor people (21).

Technological Innovations. Consumers are eager to choose wheat-based foods that offer convenience and acceptable sensory attributes, as well as enhanced nutritional and health benefits. Therefore, the wheat-processing industry is constantly looking for wheat varieties that possess specific grain quality attributes to produce traditional and new wheat-based foods. The value of a wheat crop in the market is frequently determined by grain attributes associated with its processing quality.

Wheat millers fortify or enrich flour and are trying to enhance the use of white wheats using high extraction rates to increase the amount of bran in the flour. Alternatively, the pearling and grinding of wheat and bran to obtain very fine particle sizes are also being used to enhance the fiber and bioactive compound contents of flour while avoiding negatively impacting the acceptability of wheat-based foods made from the flour (126, 146–149).

The food industry is interested in improving the fiber content of their products and, ultimately, the fiber intake of consumers. Therefore, manufacturers are assessing the influence of adding fiber from different sources (e.g., bran, bran fractions, complex carbohydrates such as β -glucan, inulin, and resistant starch) on the quality of wheat-based foods and monitoring research on the effects of enzymes on processing performance, shelf life, and textural properties of wheat-based foods. The goal is to enhance the nutritional and health benefits of wheat-based foods while still offering products that meet consumer expectations (126,142,146–148, 150–162). Attention is also being paid to the ingredients added to wheat-based food formulas, such as sugar, sodium, and fat, that may contribute negatively to the nutritional and health benefits of a wheat-based food.

Policy and Social Action. In reaffirming the relevance of wheat-based foods (and other cereals) in food security, nutrition, and health, it is important that governments do two things. First, they need to develop legislation that makes the fortification of wheat-based foods (and other cereal staples) mandatory and specific to the needs of a region. Second, they need to ensure affordable access to wheat-based foods, especially for poor populations living in cities and rural areas, particularly in Asia and Africa, the regions with the highest proportion of people affected (10, 104,163–165).

To address the rise in overweight, obesity, and associated noncommunicable diseases, consumer education programs in schools, healthcare facilities, and communities are needed. These should promote 1) the adoption of balanced dietary patterns, such as the DASH or Mediterranean Diets, that include all the food groups as well as balanced calories and intake from among the food groups and limit the intake of saturated fat and sugars; 2) awareness of calorie intake, especially for those who are sedentary; and 3) promote and communicate the benefits of physical activity to help individuals achieve healthy life styles (10,116,117,126,166).

CONCLUSIONS

The demands of a growing global population may outpace cereal food production if trends continue at their current rates. Wheat-based foods will continue to play an important role in addressing food security globally, particularly for the millions of farmers who make their livelihood from wheat production and use wheat as a staple to feed their families. In addition, wheat, in the form of biofortified crops, can help reduce the micronutrient malnourishment of those residing in Asia and Sub-Saharan Africa who do not have access to fortified wheat flour and food products.

Economic growth, urbanization, shifts in consumption, and other factors in developing and emerging countries are increasing the need for convenient, processed foods with high nutrient quality. As a result, processed wheat-based foods will continue to gain in popularity as convenient foods and low-cost sources of nutrients. However, shifts in dietary patterns, from traditional foods to greater consumption of meats, fats, and dairy products, and poor choices in or overconsumption of readily available foods can contribute to high calorie intake leading to overweight and obesity and related chronic diseases, which is occurring in most regions of the world (1,8,9,12,112,167).

When wheat-based foods, especially the right amount of whole and enriched grain staples, are consumed as part of a balanced diet (both quantity and quality), they promote health and can help prevent overweight and obesity and other related diet-related health problems. Although some beneficial nutrients (e.g., fiber, antioxidants, minerals, and vitamins) present in the grain are drastically reduced in refined flours, wheat-based foods prepared

with enriched and/or fortified (with minerals and vitamins) refined flours have been shown to help reduce or prevent micronutrient malnutrition.

Large investments in research are required to develop improved wheat varieties. Increases in wheat productivity and production should come mainly from research and breeding innovations to develop more resilient and more productive wheat varieties that possess the required quality attributes. Similar efforts are needed to advance industrial innovation to offer consumer wheat-based foods that are convenient, acceptable, nutritious, and promote health. In addition, policy and educational programs promoting healthy diets and greater physical activity are necessary to prevent overweight, obesity, and related diseases.

Currently, there are several studies and actions that are being undertaken to address challenges in producing cereals and wheat-based food over the next decades that will help satisfy the demands of a growing population (1,2,8,9,12,167). However, much more needs to be done.

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