Health benefits of whole grain: effects on dietary carbohydrate quality, the gut microbiome, and consequences of processing

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Abstract
Grains are important sources of carbohydrates in global dietary patterns. The majority of these carbohydrates, especially in refined-grain products, are digestible. Most carbohydrate digestion takes place in the small intestine where monosaccharides (predominantly glucose) are absorbed, delivering energy to the body. However, a considerable part of the carbohydrates, especially in whole grains, is indigestible dietary fibers. These impact gut motility and transit and are useful substrates for the gut microbiota affecting its composition and quality. For the most part, the profile of digestible and indigestible carbohydrates and their complexity determine the nutritional quality of carbohydrates. Whole grains are more complex than refined grains and are promoted as part of a healthy and sustainable diet mainly because the contribution of indigestible carbohydrates, and their co-passenger nutrients, is significantly higher. Higher consumption of whole grain is recommended because it is associated with lower incidence of, and mortality from, CVD, type 2 diabetes, and some cancers. This may be due in part to effects on the gut microbiota. Although processing of cereals during milling and food manufacturing is necessary to make them edible, it also offers the opportunity to still further improve the nutritional quality of whole-grain flours and foods made from them. Changing the composition and availability of grain carbohydrates and phytochemicals during processing may positively affect the gut microbiota and improve health.

KEYWORDS
Whole grain, carbohydrate quality, gut microbiome, food processing, cereal foods

1 | INTRODUCTION
Cereals are considered important low-fat staple foods in most diet patterns, and for many populations they are the dominant sources of dietary carbohydrate and protein. They are also important providers of dietary fiber, minerals, and water- and fat-soluble vitamins (OECD-Food Agriculture Organization of the United Nations, 2020). Annual
cereal production now exceeds 2,700 million tons with supply and demand closely matched (Food & Agriculture Organisation of the United Nations, 2021). All cereals commonly consumed in the diet need to be processed in order to make them palatable and to improve their digestibility (Tosi et al., 2020). Processing has a major impact on the nutritional value of cereals, especially the choices made during flour production with regard to incorporation of milling fractions and, then during food manufacturing processes such as extrusion and cooking. The impact of these processes on the nutritional value of the carbohydrate component of the food and subsequently on the gut microbiome has been a focus for much research and influences food public health policies as well as new product development in food processing and manufacturing; our aim was to provide an up-to-date review of these topics.

### 1.1 Whole grains and health outcomes

Whole-grain flours and whole-grain foods made from them are actively promoted as part of a healthy, sustainable diet profile based on the need for higher intakes of plant-based dietary fiber-containing foods and lower consumption of higher fat meat and animal products (Global Burden of Disease 2017 Diet Collaborators, 2019; Willett et al., 2019). This is supported by strong evidence from both observational and intervention studies showing that higher consumption of whole grain is associated with lower incidence of, and mortality from, cardiovascular diseases (Aune et al., 2016; Bechthold et al., 2019; W. Wang et al., 2020), type 2 diabetes (T2D; Tosh & Bordenave, 2020; Y. Wang et al., 2019; Wu et al., 2020), and some cancers (X. He et al., 2019; Hullings et al., 2020; Mourouti et al., 2016; Tullio et al., 2020; Xiao et al., 2018; Yu et al., 2020; X. F. Zhang et al., 2020). Many systematic reviews and meta-analyses have been published summarizing these benefits; these have now also been collated in so-called “umbrella reviews” (Gaesser, 2007; Kwok et al., 2019; McRae, 2017; Neuenschwander et al., 2019; Tieri et al., 2020) confirming these observations. Reported benefits of consuming whole grains include reduced peripheral insulin resistance and improved glucose kinetics (Malin et al., 2018, 2019), and improved inflammatory status (Ampatzaglou et al., 2016; Hajighasemi & Haghghatdoost, 2019; Rahmani et al., 2020; Sang et al., 2020; Xu et al., 2018). Effects on body weight and body fatness remain equivocal but slightly favor benefits (Maki et al., 2019; Sadeghi et al., 2019; Schlesinger et al., 2019). However, consuming whole grains may not be the full explanation for the improved health outcomes observed because people who consume whole grains tend also to follow a healthier lifestyle in general, including smoking less, drinking alcohol less, and being more physically active (J. L. M. Andersen et al., 2020; Egeberg et al., 2009).

### 1.2 Nutrient composition of whole grains

Whole-grain flours are more nutrient-dense than refined (white) flours because they retain the bran and germ fractions of the grain that are separated from the starchy endosperm during the manufacture of refined flours. The bran and germ contribute a range of nutrients including vitamins, minerals, phytochemicals (mostly polyphenolics and often referred to as “antioxidants”) and dietary fiber, so any food made with whole grain as a principal ingredient in place of refined flour will be richer in these nutrients and phytochemicals (Zhu & Sang, 2017). Individuals who consume larger amounts of whole grain are more likely to achieve recommended intakes of micronutrients and especially dietary fiber to improve the overall quality of the diet (Mann et al., 2015, 2018; Seal, 2019). The improved dietary nutrient profile, together with the higher consumption of bioactive/phytochemical components, may be factors that cause the improved biomarkers of health reported for consumers of whole grains, although the exact mechanisms remain an area of considerable debate (Bach Knudsen et al., 2017). This review focuses on the role of whole grains in improving health outcomes by changing the quality of dietary carbohydrates consumed, the consequences of these changes on the gut microbiome, and how this may be affected by processing and food manufacturing.

### 2 EFFECTS OF WHOLE GRAINS ON DIETARY CARBOHYDRATE QUALITY

#### 2.1 Dietary carbohydrates

Carbohydrates are an essential part of the human diet, but there is some debate on the amount and type of dietary carbohydrate required for health (Dall’Asta et al., 2020; Reynolds et al., 2019; Shahdadian et al., 2019; Willett & Liu, 2019; Zafar et al., 2019), including whether whole-grain consumption should be favored above consumption of refined grains (Jones et al., 2020; Williams, 2012). Dietary carbohydrates found in cereals encompass the full range of different chemical compounds ranging from complex polysaccharides to smaller oligosaccharides, disaccharides, and monosaccharides each requiring different levels of metabolic processing/digestion and each causing different metabolic responses (Dall’Asta et al., 2020; Tappy, 2018). Polysaccharides with a degree of polymerization (DP) >9 units can either be digestible by
amylolytic enzymes produced in the mouth and the small intestine of the human gut, such as starches (of plant origin) and glycogen (of animal origin), or indigestible such as resistant starches (RSs; including chemically modified starches) and complex nonstarch polysaccharide plant cell wall structures including pectin (Bello-Perez, Flores-Silva, Agama-Acevedo, & Tovar, 2020; Bird & Regina, 2021; Sajilata et al., 2014; Tungland & Meyer, 2020), and are found naturally in cereal grains and some plant tubers but also include synthetic maltodextrins formed from starch hydrolysis. Some such dietary fibers, particularly inulin, are often added to processed foods as texture modifiers and so can be consumed in higher amounts than would be predicted from the amount of unprocessed foods consumed (Schafisma & Slavin, 2015; Shoabi et al., 2016). Dietary fibers that reach the lower bowel undigested can become substrates for microbial hydrolytic enzymes, releasing bound compounds and nutrients that can be utilized by the body (Tannock, 2020; Tungland & Meyer, 2002). The amount, chemical nature, and physical form of dietary fibers arriving in the lower gut are the principle drivers of the composition/diversity of the gut microbiome (Ho Do et al., 2020; Tamura & Brumer, 2021; Tuncil et al., 2020) that can affect pH and composition of digesta and has been linked to health outcomes (Swanson et al., 2020; Tamura & Brumer, 2021) as discussed later in this review.

### 2.2 Carbohydrate and nutrient content of cereals

Cereals are complex mixtures of all the different forms of carbohydrate that are distributed in different fractions of the grain, and are found in different amounts in different cereals as shown in Table 1.

In particular, the dietary fiber content and profile of the different cereals and cereal fractions are very different that affect their digestion and the physiological responses to consume different cereals (Brahma & Rose, 2018). Dietary fibers elicit different gastrointestinal responses largely due to their solubility and fermentability affecting transit time and stool weight. These effects vary between intact cereal fibers, and dietary fiber from fruits and vegetables (de Vries et al., 2016), and between cereal types (de Vries et al., 2015; Korczak & Slavin, 2020; Korczak et al., 2019). The impact of dietary fiber on health outcomes is indisputable and has been the subject of numerous reviews (see, e.g., Koç et al., 2020; Veronese et al., 2018) but the relative importance of cereal fiber compared with dietary fiber from fruits and vegetables is less certain (Cui et al., 2019), and while most food-based dietary guidelines stress the importance of whole grains as sources of dietary fiber, the emphasis

| per 100 g | FDC ID | Energy | CHO | Total sugars | Dietary fiber | Fat | Protein | Ca | Fe | Mg | P | Se | Na | Zn | Vit E |
|----------|--------|--------|-----|-------------|---------------|-----|---------|----|----|----|---|----|----|----|------|
|          |        | Kcal   | G   | G           | g             | G   | mg      | mg | mg | mg | mg | mg | mg | mg | mg   |
| WG wheat flour | 168893 | 340    | 71.9 | 0.4         | 10.7          | 2.5 | 13.2    | 34 | 3.6 | 137| 357| 61.8| 2  | 2.6 | 0.7  |
| Wheat bran | 785757 | 216    | 64.5 | 0.4         | 42.8          | 4.3 | 15.6    | 73 | 10.6 | 611| 1013| 77.6| 2  | 7.3 | 1.5  |
| RG wheat flour | 169761 | 364    | 76.3 | 0.3         | 2.7           | 1.0 | 10.3    | 15 | 1.2 | 22 | 108| 33.9| 2  | 0.7 | 0.1  |
| Wheat germ | 785750 | 382    | 49.6 | 7.8         | 15.1          | 10.7| 29.1    | 45 | 9.1 | 320| 1146| 65.0| 4  | 16.7| 16.0 |
| Oats       | 785758 | 379    | 67.7 | 1.0         | 10.1          | 6.5 | 13.2    | 52 | 4.3 | 138| 410| 28.9| 6  | 3.6 | 0.4  |
| Oat bran  | 785759 | 246    | 66.2 | 1.5         | 15.4          | 15.0| 7.0     | 58 | 5.4 | 235| 734| 45.2| 4  | 3.1 | 1.0  |
| Pearled barley | 170284 | 352    | 77.7 | 0.8         | 15.6          | 1.2 | 9.9     | 29 | 2.5 | 79 | 221| 37.7| 9  | 2.1 | 0.0  |
| Dark rye flour | 168885 | 325    | 68.6 | 2.3         | 23.8          | 2.2 | 15.9    | 37 | 5.0 | 160| 499| 18.0| 2  | 5.0 | 2.7  |
| Medium rye flour | 168886 | 349    | 75.4 | 1.1         | 11.8          | 1.5 | 10.9    | 24 | 2.5 | 63 | 225| 14.4| 2  | 2.2 | 1.4  |
| Light rye flour | 168887 | 357    | 76.7 | 0.9         | 8.0           | 1.3 | 9.8     | 13 | 0.9 | 32 | 130| 17.6| 2  | 1.3 | 0.8  |
| WG rice   | 169703 | 367    | 76.3 | 0.7         | 3.6           | 1.4 | 7.5     | 9  | 1.3 | 116| 311| 17.1| 5  | 2.1 | 0.6  |
| RG rice flour | 169714 | 366    | 80.1 | 0.1         | 2.4           | 1.4 | 5.9     | 10 | 0.4 | 35 | 98 | 15.1| 0  | 0.8 | 0.1  |
| Quinoa    | 168874 | 368    | 64.2 | NR          | 7.0           | 6.1 | 14.2    | 47 | 4.6 | 197| 457| 8.5 | 5  | 3.1 | 2.4  |
| Amaranth  | 170682 | 371    | 65.3 | 1.7         | 6.7           | 7.0 | 13.6    | 159| 7.6 | 248| 557| 18.7| 4  | 2.9 | 1.2  |
| Buckwheat | 170286 | 343    | 71.5 | NR          | 10.0          | 3.4 | 13.3    | 18 | 2.2 | 231| 347| 8.3 | 1  | 2.4 | NR   |

Abbreviations: FDC ID, Food Data Central identification code; NR, not reported; RG, refined grain; WG, whole grain.
in most guidelines remains on fruits and vegetables as primary sources of dietary fiber. Some observational studies, the majority on cardiovascular disease risk, have attempted to quantify the health effects of cereal fiber separately from whole grains. Barrett et al. (2019) recently reviewed these studies and showed that cereal fiber and whole grain were both associated with lower cardiometabolic disease risk, but that after adjustment for total fiber consumption the associations remained, suggesting that additional components within whole grain contributed to the cardioprotective effects. Current dietary advice is to consume a diet in which carbohydrates provide 55% to 60% of daily energy, predominantly in the form of starchy carbohydrates, about 25 to 30 g of dietary fiber per day and less than 5% of daily energy in the form of free or added sugar (Reynolds et al., 2019; Willett et al., 2019). Currently, there are no specific recommendations on the relative proportions of different dietary fiber types (based on variability in fermentability or degree of solubility) to consume. Rather, a variety of grains is recommended in dietary advice in order to provide a balance of both alongside consuming other high-fiber foods such as fruits, vegetables, and pulses (Buyken et al., 2018).

2.3 Whole grains and dietary carbohydrate quality

The term “dietary carbohydrate quality” has been conceived as a means of describing the nutritional value of high-carbohydrate foods based on the metabolic fate of the carbohydrate(s) rather than focusing on the total amount of carbohydrate in the food/diet, which does not always correlate with disease outcome (Lamothe et al., 2017). When describing dietary carbohydrate quality, it is important to consider the whole diet and the range and amount of different carbohydrates contained within it. One aspect of quality is linked to the magnitude and duration of postprandial glycemia following consumption of high-carbohydrate foods. A large and prolonged exposure to high blood glucose concentrations is a recognized risk factor for chronic diseases, especially for the development of T2D and metabolic syndrome (Richter et al., 2018). Thus, carbohydrates that are rapidly digested and give rise to high blood glucose concentrations are perceived as of lower quality compared with carbohydrates that are more slowly digested and result in lower blood glucose concentrations over time. Free sugars are to be avoided because they are associated with processed foods (such as sugar-sweetened beverages) linked to overweight and obesity, and because they have a high cariogenic potential (Blostein et al., 2020; Pitchika et al., 2020). The glycemic index (GI) and glycemic load (GL) metrics have been widely applied as indicators of this aspect of dietary carbohydrate quality but are often criticized for not representing responses to complex food mixtures. Nevertheless, these measures have been associated with risk of disease where hypoglycemia is a known risk factor. For example, results of a comprehensive recent meta-analysis show increased risk of T2D with consumption of high GI diets but there was considerable variability in the results with a wide range and variable relative risk values (Livesey et al., 2019).

A second aspect of quality is linked to the amount of dietary fiber delivered in the foodstuff, recognizing the benefits of dietary fiber described above, and it is this aspect of whole-grain composition that is perhaps the most relevant in this context. It is suggested by the American Heart Association that the optimum ratio of total carbohydrate to dietary fiber content of the diet is ≤10:1, reflecting the total carbohydrate:fiber ratio of whole wheat (Lloyd-Jones et al., 2010) and that consuming whole-grain cereals can help achieve this ratio in the diet. This suggestion is consistent with the recommendation to consume about 55% to 60% of daily energy as carbohydrates; for a 2000 kcal diet, the ≤10:1 ratio would deliver 30 g of dietary fiber based on 300 g of carbohydrates (60% of energy intake). Using this carbohydrate profile readily identifies healthy cereal-based foods with higher dietary fiber, lower free sugars, trans-fats, and sodium content, many of which are whole grain (Mozaffarian et al., 2013).

It is important to note that cereal-based foods encompass the full range of GI values, and also vary widely in their dietary fiber content, depending on the form of starch present in the grain and the amount of bran retained in the flour or intact grain after processing. This is well-illustrated for rice, where GI values span a twofold range for both refined and whole-grain rice products, including both high- and low-GI values (Kaur et al., 2016). Compared with whole-grain wheat, the dietary fiber content of brown rice is also much lower and only slightly higher than that of refined white rice (Table 1). Similarly, whole-grain wheat breads and refined-wheat breads both have higher GI values of around 75 that are further affected by storage and toasting (Burton & Lightowler, 2008), whereas whole-grain spaghetti and refined-grain spaghetti have very similar but lower GI values of around 48 (Atkinson et al., 2008; Ludwig et al., 2018). For both food categories switching from the refined-grain to the whole-grain option will deliver more dietary fiber and nutrients associated with the bran and germ and improve the quality of the diet by this measure, but it would not affect the GI of the diet and so this component of diet quality would be unaffected. Thus, whole-grain bread and spaghetti could be classed as having a better dietary carbohydrate quality on the basis of the delivery of additional dietary fiber compared with white refined-grain alternatives. On the other hand, whole-grain oat porridge would be identified as a higher carbohydrate

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*Note: The document contains references to other works, which are not included in this natural text representation.*
Quality food because it is both a low GI, high dietary fiber breakfast choice compared with a refined-grain cereal such as cornflakes. J. Liu, Rehm, et al. (2020) have suggested that the $\leq 10:1$ ratio has some limitations because it does not differentiate between starches and free sugars present in foods. As there is increased emphasis on reducing free sugars intake, J. Liu, Rehm, et al. (2020) calculated the apparent “quality” of 2208 high-carbohydrate foods from the US Food and Nutrient Database for Dietary Studies (US Department of Agriculture, Agricultural Research Service, 2020) after taking into account the free sugars content relative to the total carbohydrate and dietary fiber content of the foods. They considered whether the high-carbohydrate foods met the $\leq 10:1$ ratio and three additional measures ($10:1:1, \geq 1 \text{ g of dietary fiber and } < 1 \text{ g of free sugars}; 10:1:2, \geq 1 \text{ g of dietary fiber and } < 2 \text{ g of free sugars}; 10:1:3:2, \geq 1 \text{ g of dietary fiber and, per each } 1 \text{ g of dietary fiber, } < 2 \text{ g free sugars})$. The rationale for including a measure of the free sugar content was to identify foods that might contain whole-grain ingredients but also be high calorie and high sugar and therefore not as desirable in the diet. Approximately 20% of the foods met the 10:1 and 10:1:2 criteria and they were generally lower in total energy, fat, free sugars, and sodium and higher in protein, dietary fiber, potassium, magnesium, iron, vitamin B6, vitamin E, zinc, and iron. The results suggest that applying these criteria may provide a mechanism for identifying healthier nutrient-dense high-carbohydrate foods (Figure 1).

Table 2 shows the results from a number of studies that have compared the impact of different metrics for determining dietary carbohydrate quality in the same study analysis, taking into account the relative proportions of different carbohydrates in the diet on health outcomes and allowing for comparison between the different metrics. These include the quantities of different types of dietary fiber (cereal, vegetable, and fruit sources); and ratios of different forms of carbohydrate in the diet such as total carbohydrate to total dietary fiber ratios and carbohydrate to cereal fiber ratios; studies that examined only...
TABLE 2  Outcome of studies that include and compare more than one measure of carbohydrate quality as an indicator of disease risk

| Source | Population studied | Dietary carbohydrate (CHO) quality measures tested | Outcomes |
|--------|--------------------|-----------------------------------------------------|----------|
| AlEssa et al. (2015) | F, Nurses’ Health Study (NHS) 1.484 m person-years follow-up | Total CHO; starch; total fiber (TF); cereal fiber (CF); fruit fiber (FF); vegetable fiber (VF); CHO:TF ratio; CHO:CF ratio; starch:TF ratio; starch:CF ratio. | ↑ Risk of T2D for higher intake of starch and for lower intakes of TF, CF, and FF. ↑ Risk of T2D, and strongest association for increasing starch:CF ratio. No association between total CHO intake and T2D risk. |
| (Kim et al., 2018) | F, (n = 7347) and M (n = 4680) Korean National Health and Nutrition examination Survey. Cross-sectional survey | TF; dietary glycemic index (DGI); whole grains:total grains ratio; solid CHO:liquid CHO ratio; Total Index (CHO Quality Index, CQI, Σ of other indices). | Higher CQI negatively associated with risk of obesity and hypertension, but not associated with other factors linked to metabolic syndrome. |
| AlEssa et al. (2018) | F, NHS (1.905 m person-years follow-up) and M, Health Professionals Follow-Up Study (HPFS, 0.921 m person-years follow-up) | Total CHO; starch; CF; FF; VF; CHO:TF ratio; CHO:CF ratio; starch:TF ratio; starch:CF ratio. | No association for total CHO intake, TF intake, or CHO:TF ratio and CHD risk. ↓ Risk of CHD with higher intake of CF risk of CHD. ↑ Risk of CHD for increasing CHO:CF ratio and starch:CF ratio. |
| (Hruby et al., 2017) | F, NHS and NHS2 and M, HPFS 1.643 m person-years follow-up | CF content of diet; GI of diet. | ↓ Risk of T2D with higher magnesium intake is modified and stronger with reduced dietary GI and higher CF intake. |
| (Martínez-González et al., 2020) | F and M (n = 5373) PREvención con DIeta MEDiterránea-Plus (PREDIMED-Plus) 6- and 12-month follow-up | Total F; GI of diet; whole grains:total grains intake; solid CHO:(solid CHO + liquid CHO) ratio; CHO Quality Index, CQI, Σ of other indices. | At 6- and 12-month higher change (improvement) in CQI was associated with greater reduction in body weight, systolic and diastolic BP, reduced fasting glucose, HbA1c, and improved lipid profile. At 12-month additional benefits seen in HDL-cholesterol and total cholesterol:HDL cholesterol ratio. |

Abbreviations: F, females; M, males; T2D, type 2 diabetes.

the effects of GI and GL are not included in the table, as these have previously been reviewed extensively (e.g., Barclay et al., 2008; Brand-Miller & Buyken, 2020; Cheng et al., 2009; Cheng et al., 2017; Gangwisch et al., 2020; Livesey et al., 2019; Zafar et al., 2019). The results clearly illustrate and support the notion that it is the quality of the carbohydrates rather than the quantity that has the greater impact on health outcome. In most cases, summative measures such as a “carbohydrate quality index” (CQI) where several measures are combined (Zazpe et al., 2014) showed the strongest associations with health outcome, and cereal fiber was a better indicator of health than total fiber, fruit fiber or vegetable fiber separately. Recently there have been a number of systematic reviews and meta-analyses that have summarized evidence for the benefits of increasing carbohydrate quality and health outcome; the most comprehensive and recent by Sievenpiper (2020) and Reynolds et al. (2019). Other reviews have summarized the effect of carbohydrate quality on biomarkers of disease risk in an attempt to identify potential mechanisms of action. For example, Gaesser (2007) explored data from cohort studies on relationships between carbohydrate intake, dietary GI, GL, and intake of whole grains and showed that only intake of whole grains was consistently inversely associated with BMI in women and men. Buyken et al. (2014) collated evidence on the impact of GI, GL, dietary fiber, and whole grain on the inflammatory markers high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6). They showed considerable variability in study outcomes but suggested that overall inflammatory status was better and more consistently improved with a lower GI/GL diet than was seen for higher dietary fiber
or whole-grain diets. Interestingly for whole grains, there were significant negative associations between increasing whole-grain intake and lower hsCRP and IL-6 in observational studies but not in intervention studies. The failure of intervention studies to demonstrate the beneficial effects of whole grain compared with results from observational studies has been reported previously (Seal & Brownlee, 2010), and may be due to a number factors such as the smaller size of intervention studies, the use of mixed grain interventions and the shorter duration of the interventions. Some of these shortcomings are overcome in the PREDIMED-Plus study, a multicenter, randomized, primary-prevention trial with >6800 overweight/obese older adults (aged 55 to 75 years) in an intensive weight-loss lifestyle intervention. The intervention is based on an energy-reduced Mediterranean diet pattern with physical activity, including promoting consumption of fruits, vegetables, and whole grains (Martínez-González et al., 2019). A recent prospective analysis for 5373 of the participants analyzed relationships between 6- and 12-month changes in dietary carbohydrate quality index (CQI) and biomarkers of CVD risk (Martínez-González et al., 2020). CQI was based on quintiles of intakes of total dietary fiber, glycemic index (reverse quintiles), whole grain/total grain ratio, and solid carbohydrate/total carbohydrate ratio; CQI was improved by higher intakes of fruits, vegetables and whole grain and lower intake of refined grain. The results showed strong relationships between increasing CQI and improvements in body weight, glycemic indices and blood lipid profiles. A higher CQI has previously been associated with better micronutrient intake profiles (Sánchez-Tainta et al., 2016; Zazpe et al., 2014) confirming the observations reported earlier that healthy foods and diets with improved carbohydrate quality also have overall improved nutrient profiles.

3 | EFFECTS OF WHOLE GRAIN ON MICROBIOTA COMPOSITION AND ACTIVITY

3.1 | The gut microbiota

Indigestible carbohydrates (dietary fibers) that contribute to improving dietary carbohydrate quality are the major substrates for microbes in the GI tract, particularly the colon, together with proteins that are not digested and absorbed in the small intestine. Humans live in symbiosis with trillions of microbes in and on their body, of which most are found in the gastrointestinal (GI) tract, particularly the colon. Approximately $5 \times 10^{33}$ to $10^{14}$ bacteria inhabit the colon, which exceeds the number of cells in the human body by a factor of approximately 1.2 (Sender et al., 2016). Apart from bacteria, the human gut is also inhabited by fungi and yeasts (roughly a factor 10 to 100 lower in amounts than bacteria), and by viruses and bacteriophages (in numbers about a factor 10 to 100 higher than bacteria; Kapitan et al., 2019; Virgin, 2014). Together these are called the gut microbiota, although mostly when people refer to the gut microbiota, they mean the bacterial components. Over the past decades it has become clear that the gut microbiota is very important in health and diseases, and although most of the research is focused on the bacterial component, there now also is evidence that fungi and yeast and bacteriophages contribute to this role in health and disease, if alone by the fact that they influence the bacterial component of the gut microbiota by transkingdom cross talk (Pfeiffer & Virgin, 2016; Sartor & Wu, 2017; Virgin, 2014).

Estimates of the total number of different species that can inhabit the colon have surpassed 2500. Yet, each individual harbors only approximately 250 different species, which is influenced by a number of factors. These include our own genetics (explaining approximately 12% of the variance), diet (approximately 57%), use of drugs (e.g., antibiotics), and other (environmental) factors (C. H. Zhang et al., 2010; Zmora et al., 2019). Due to this, the microbiota composition shows a large individual variation, which is a contributing factor that leads to inconsistencies between studies (see below).

3.2 | Microbial fermentation

Two of the major substrates for colonic microbes are carbohydrates and protein. Although some of these stem from the host (Table 3), in this review, the focus is on dietary sources, in particular whole grain. As alluded to before, most carbohydrates that escape digestion in the upper small intestine and reach the colon are complex dietary fiber molecules, such as RS and nonstarch polysaccharides (Raninen et al., 2011). Although there is some spillover of mono- and disaccharides from the small intestine to the colon due to cases of fast transit, the amounts are minor, and mostly only oligosaccharides and polysaccharides reach the colon except in the case of lactose intolerance (T. He et al., 2008). Information on the composition and quantity of fermentable material reaching the large intestine is scarce and is mostly based on the original studies by Cummings and Englyst (1987), who collected and analyzed ileal effluent from subjects with a permanent ileostomy. This model has been used to quantify the digestion of starchy material both natural from different cereals and from synthetic starches after extraction and chemical modification (Birkett et al., 2000; Botham, 1996; Brouns et al., 2007; Clarke et al., 2007; Edwards et al., 2015; Iacovou et al., 2017; Langkilde et al., 2002; Livesey et al., 1995; Muir et al., 2016; Zmora et al., 2019).
et al., 1995; Zhou et al., 2010). Less commonly the techniques has been used to quantify digestion of other carbohydrates (Bach Knudsen & Hessov, 1995; Holub et al., 2010; Langkilde et al., 1994; Sandberg et al., 1994; Sundberg et al., 1996) and to quantify endogenous material such as mucin arriving at the terminal ileum (Lien et al., 1996). These studies, and calculations made using in vitro digestion and fermentation models, suggest that between 20 and 60 g of nondigestible carbohydrate, including RSs, plant cell wall polysaccharides, oligosaccharides, and sugar alcohols, escape the upper digestive enzymatic breakdown and reach the human colon each day (Table 3). This remains an area of uncertainty where improved knowledge of the composition and amount of material available for fermentation in the large intestine would be useful in being able to improve the healthfulness of the microbiome by changing dietary patterns.

Fermentation of carbohydrates leads to the production of so-called short-chain fatty acids (SCFAs; primarily acetate, propionate and butyrate), which are taken up by the epithelial cells and are used by the host as energy substrates, either locally (butyrate and colonocytes), or peripherally (acetate and propionate in liver, muscle, and even brain; den Besten et al., 2013). Particularly butyrate has attracted a lot of attention as it has been shown to have numerous benefits (Hamer et al., 2008). Besides providing 70% of the energy requirements of colonocytes, it influences gene-expression (as histone deacetylase inhibitor, or as ligand for G-protein coupled receptors), and modulates the immune system. Recently, acetate and propionate have also attracted attention. For instance, acetate infused in the colon distally, but not proximally, has been shown to lead to increased energy expenditure (van der Beek et al., 2016). The gut microbiota preferentially ferments carbohydrates, in order to incorporate any protein present in the colon into their own structural and enzyme machinery. Therefore, in the proximal colon carbohydrate fermentation prevails. However, as these microbes travel through the transverse colon to the distal colon, the fermentable carbohydrate becomes depleted, and the microbes switch to protein fermentation. Protein fermentation leads to the production of what are generally considered toxic metabolites, such as ammonia, hydrogen sulfide (H₂S), biogenic amines, and so on, although recently the tryptophan-derived metabolite indole-3-lactic acid, among other produced by *Bifidobacterium*, has been shown to be beneficial in the communication of the gut-brain axis and contribute to host homeostasis (Wong et al., 2020). Despite interindividual differences in microbiota composition, due to substantial overlap in functional capacity (Turnbaugh et al., 2009), production of microbial metabolites shows much more overlap between individuals than microbiota composition.

Although there is a tremendous amount of research that has focused on isolated dietary fibers (e.g., inulin, pectin, xylan, etc.) or derivatives thereof (e.g., fructooligosaccharides [FOS], pecticoligosaccharides, and xylooligosaccharides [XOS], etc.) and their capacity to change the composition and/or activity of the gut microbiota, this has so far not led to a much greater understanding of the structure-function relationship of these. In a recent recommendation, drafted by 16 presenters at an NIH/USDA organized workshop in 2017 on the role of diet in alterations of the gastrointestinal microbiome, the main recommendation was “to describe dietary ingredients and treatments in as much detail as possible to allow reproduction by other scientists” (Klurfeld et al., 2018). It is well-reported that the molecular structure of cereal fiber has a bearing on its health effects (Gemen et al., 2011). Similarly, in an as yet to be published extensive overview commissioned by ILSI-Europe on the structure–function relationship of prebiotics, the conclusion is that for the vast amount of the literature about the effect of dietary fibers (including prebiotics) on the gut microbiota, the characterization of the dietary fiber fraction is mostly lacking, even for purified components like prebiotics. It goes without saying that for complex substrates, like whole grains, which beside dietary fiber also contain mixtures of unsaturated fats and complex lipids, phenolics/phytochemicals, and protein (Brahma & Rose, 2018; Loo et al., 2020; Raninen et al., 2011), it is difficult to decipher the effect of the individual components present in whole grain on the gut microbiota. Moreover, some of the nonfiber components, sometimes referred to

| Substrate | Amount (g/day) | Origin |
|-----------|---------------|--------|
| Resistant starch | 1.5 to 40 | Diet |
| Total starch | 3 to 13.2 | Diet |
| Total nonstarch polysaccharides | 8 to 18 | Diet |
| Insoluble nonstarch polysaccharides | 6.5 to 7.0 | Diet |
| Cellulose | 3.2 | Host |
| Noncellulose | 3.4 to 3.8 | Diet |
| Soluble nonstarch polysaccharides | 5.3 to 8.7 | Diet |
| Unabsorbed sugars/sugar alcohols | 2 to 10 | Diet |
| Oligosaccharides | 11.8 to 16.4 | Diet |
| Lignin | 1 | Host |
| Dietary protein | 3 to 9 | Diet |
| Enzymes/secretions/mucus | 6 to 9* | Host |

*Plus an unknown quantity of sloughed-off epithelial cells.
as co-passengers, also may have biological activity (Fardet, 2010; X. Liu, Le Bourvellec, et al., 2020). For instance, in an elegant study, oat bran (including the co-passengers) has been shown to be effective in increasing *Bifidobacterium* populations in the gut, whereas the purified bioactive β-glucans did not show a bifidogenic effect (Kristek et al., 2019). Nevertheless, some interesting research has been performed on whole grains. To cover all of that is beyond the scope of this review, but selected examples are discussed below.

### 3.3 Microbial fermentation of complex carbohydrates

Fermentation of carbohydrates in the distal colon leads to several benefits. For instance, protein fermentation in the distal colon, with its associated production of putrefactive metabolites, will be reduced when dietary fiber makes it to the distal colon. Moreover, SCFA production in the distal colon may be beneficial (van der Beek et al., 2016). The more complex the substrate, the more distal it will be fermented in the colon. This complexity can be due to the DP, branching, esterification, or crosslinking of various cell-wall components by, for example, ferulic acid. An example of how DP is important has been published on inulin/FOS (van Nuenen et al., 2003). Three fractions of inulin/FOS (the difference being that at a DP > 10 it is called inulin, below that FOS), with an average DP of 3, 9, or 27 were tested in a TIM-2 in vitro model of the colon. The molecules with larger DP took more time to ferment than those with lower DP (van Nuenen et al., 2003). However, these were purified water-soluble linear fibers, containing a single monosaccharide and glycosidic linkage. In addition, even though the larger molecules were fermented slower, they were still fermented within the proximal colon. These results can give a good indication of what we can expect when dealing with cereal dietary fiber components like fructans. In rye and wheat, they are present up to 6% and 3%, respectively, with a DP ranging from 3 to over 10. It is expected that this will be similar for inulin/FOS from whole grain. Compared with fructans, pectin molecules contain multiple different monosaccharides, linked together with different glycosidic bonds, and they are heavily branched and also (partly) methylated or acetylated. The gut microbiota would need multiple enzymes to degrade these complex molecules, such as esterases, pectic lyases, and dedicated glycosyl-hydrolases to degrade the different glycosidic bonds. In an attempt to study how different structures in pectin molecules would lead to diverse changes in gut microbiota composition, nine structurally diverse pectins from citrus fruits and sugar beet, together with the pectic fragment rhamnogalacturonan-I were tested for their effect on gut microbiota modulation in the TIM-2 model (Larsen et al., 2019). Bacterial populations associated with human health, were either increased or decreased depending on the pectin used, suggesting that these bacteria can be controlled using the correct structurally different pectin. Some of the structural features that linked modulation of the microbiota to the different pectins included the degree of esterification, the composition of the monosaccharides (particularly neutral sugars), the degree of branching, and the presence of amide groups. These results point in the same direction as those observed by Van Craeyveld et al. (2008) for fermentation of isolated wheat bran arabinoxylans (AXs) with different DP and substitution in the GIT of rats. AX preparations with larger and more branched structures were fermented more distally in the gastrointestinal tract and suppressed protein fermentation more than short unbranched AXs. In another AX study, a combination of three different AX structures, small and large water-soluble AX and water-unextractable AX, led to the highest butyrate production (Damen et al., 2011). Moreover, the size of whole-grain fractions may lead to divergent outcomes, as studied for variously sized wheat bran fractions (Tuncil et al., 2018). Five size fractions from a single wheat bran source (ranging from 180 to 1700 μm) led to differences in SCFA production, as well as to the development of divergent microbial community structures upon in vitro fermentation with fecal inocula. Also, fine-structural differences in XOS and arabinoxyloligosaccharides (AXOS) dictated differential growth of a number of Bacteroides species commonly found in the colon (Mendis et al., 2018). Similarly, subtle variations in the chemical fine-structure of AXs from different classes of wheat (hard red spring, hard red winter, and spring red winter), with differences in backbone length and branching, led to the development of different community structure when incubated with fecal samples (Tuncil et al., 2020).

The examples above show how difficult it is to generalize effects of dietary fibers on changes in gut microbiota composition, and these are mostly examples with purified fibers. It is therefore not surprising that there are conflicting reports in the literature with respect to the effect of whole grains on the gut microbiota. Part of this is of course due to the fact that whole grains comprise a diverse group of staple cereal foods, including wheat, corn, rice, oats, barley and rye, and hence different effects on the gut microbiota are expected. Moreover, differences in study design, with respect to dose, duration, study populations, and so on, make it difficult to compare between studies and distil overarching similarities. Also, in earlier studies, the tools to measure microbiota composition (e.g., denaturing gradient gel-electrophoresis [DGGE] or fluorescent *in situ* hybridization [FISH]) led to much less detailed...
insights on microbiota modulation compared with the current high-throughput sequencing methods (focused on 16S rRNA sequencing). If anything, it can be concluded that (increased) ingesting of whole grains leads to an increase in production of SCFA, despite the fact that there are sometimes no or limited changes in gut microbiota composition (Cooper et al., 2015; de Angelis et al., 2015).

3.4 Whole grains and gut microbiota

The effect of whole grains on the gut microbiota has been the subject of a number of reviews in the past 5 years (Brahma & Rose, 2018; Cooper et al., 2015; Flint et al., 2015; Gong et al., 2018; Jefferson & Adolphus, 2019; Koecher et al., 2019). In one of these, a thorough review of the literature, 30 human studies on the effect of intact cereal grains (including wheat bran) on gut microbiota were discussed (Jefferson & Adolphus, 2019). Changes in microbiota composition were included (in 19 studies), but also changes in (only) microbial metabolism, in the form of production of bacterial metabolites, primarily SCFA and/or phenolics. The majority of the studies looking at changes in microbiota composition used 16S rRNA gene sequencing (n = 15). The others used variable methods that are considered to be outdated given the current state-of-the-art, ranging from classical plating to qPCR, DGGE, and FISH. One of the conclusions in the review is that many studies show large interindividual variation, most likely due to the interindividual microbiota composition. In some cases, this led to the observation that there is a split between responders and nonresponders, for example, Lappi et al. (2015). In other studies, no significant effects were observed at a group level (Kopf et al., 2018a; Roager et al., 2019; Vuholm et al., 2017).

Although intake of whole grains did not lead to (major) changes in gut microbiota composition in some cases, other benefits with respect to body weight and systemic low-grade inflammation (Roager et al., 2019), or fecal butyrate and gastrointestinal symptoms (Vuholm et al., 2017) were observed. However, most studies that looked at microbiota composition changes, observed significant changes, either compared with a control (in most cases refined flour), or with baseline. However, due to the multitude of different whole grains used (Table 4), as well as the different molecular tools used, results are not consistent and are difficult to compare. Some recent studies not published prior to the extensive review of Jefferson & Adolphus (2019) will be addressed here separately. All studies that investigated the effects of whole grains on the gut microbiota (composition and activity) that have been reviewed before by Jefferson & Adolphus (2019) and the additional studies are listed in Table 4.

The effects of foods made from whole-grain Himalaya 292, a novel hull-less barley variety lacking activity of a key starch synthesis enzyme resulting in less total starch, more amylose and higher total dietary fiber, with those made from whole-grain wheat and refined cereal foods on fecal microbial metabolites in adults was investigated by Bird et al. (2008) in a randomized cross-over design. Total dietary fiber intakes were 45, 32, and 21 g/day for the Himalaya 292, whole-grain wheat and refined cereal periods, respectively. Compared with the refined cereal foods, consumption of Himalaya 292 foods resulted in a lower fecal pH, a higher fecal concentration of butyrate and higher total SCFA excretion and a lower fecal p-cresol concentration. Fecal pH was also significantly lower, and both butyrate concentration and excretion were higher after consumption of Himalaya 292 barley products compared with whole-grain wheat consumption. Whole-grain wheat did not differ in any of these aspects compared with the refined cereal period (Bird et al., 2008). In a study with adolescents (average 12.7 years of age), the ingestion of 80 g/day of a variety of grain-based foods was shown to increase fecal lactic acid bacteria (measured by q-PCR) but not bifidobacteria. No microbial metabolites were measured (Langkamp-Henken et al., 2012). Sheflin et al. (2017) gave 30 g/day heat-stabilized rice bran to overweight/obese adults for 4 weeks and studied microbiota composition and activity. Taxa within the Bifidobacterium and Ruminococcus genera were increased after 2 and 4 weeks. The authors also observed changes in microbial metabolites, but rather than the saccharolytic, generally considered to be health-promoting SCFA, they reported an increase in the putrefactive metabolites branched-chain fatty acids, and an increase in colon cancer promoting secondary bile acids (Sheflin et al., 2017). Schutte et al. (2018) studied the effect of whole-grain wheat on gut microbiota and liver health in overweight adults (aged 45 to 70 years). They showed that whole-grain wheat, compared with refined wheat, maintained a higher gut microbiota diversity (thought to be a measure for a healthy microbiota), but that baseline microbiota did not predict health benefit with respect to liver health. Part of this was thought to be due to the high interindividual variation in gut microbiota composition, as there was no separation in clustering of the microbiota composition using principal coordinates analysis based on Bray–Curtis distance between the groups (Schutte et al., 2018), and samples before and after intervention of a particular individual seemed to cluster close together. In a randomized clinical trial, the effect of low-FODMAP (fermentable oligo-, di, and monosaccharides, and polyols) rye bread versus regular rye bread on the intestinal microbiota of irritable bowel syndrome patients was investigated (Laatikainen et al., 2019). Compared with baseline, consumption of the low-FODMAP rye bread
**TABLE 4** Overview of different whole grains used in human trials that studied gut microbiota changes \((n = 31; \text{for 19 of these the data are distilled from Jefferson & Adolphus, 2019})\)

| Whole grain | Population | Effect on gut microbiota composition/activity | References |
|-------------|------------|----------------------------------------------|------------|
| **Studies without changes in composition or activity** | | | |
| Rice | Adults | No changes in either composition or activity | (Nemoto et al., 2011) |
| Mixed whole grain | Overweight/obese adults | No changes in either composition or activity | (Cooper et al., 2017) |
| | Adults | Composition not significantly different/activity not measured | (Ampatzoglou et al., 2015) |
| | Adults at risk of developing metabolic syndrome | No changes in either composition or activity | (Roager et al., 2019) |
| | Adults with overweight or obesity | No changes in either composition or activity | (Kopf et al., 2018b) |
| Wheat | Adults | No changes in either composition or activity | (Bird et al., 2008)\(^a\) |
| **Studies with changes in activity (but not composition)** | | | |
| Rye | Adults | Activity (increased fecal butyrate) | (Vuholm et al., 2017) |
| Barley | Adults | Activity (increased fecal butyrate and total SCFA) | (Bird et al., 2008)\(^a\) |
| **Studies with changes in activity and/or composition** | | | |
| Wheat/wheat bran | Adults | Composition/activity (phenolics) | (Costabile et al., 2008) |
| | Overweight adults | Composition/activity (phenolics) | (Vitaglione et al., 2015) |
| | Overweight adults | Composition | (Schutte et al., 2018) |
| | Men with metabolic syndrome | Composition | (Eriksen et al., 2020)\(^b\) |
| | Adults with overweight or obesity | Composition | (van Trijp et al., 2020) |
| Barley | Adults | Composition/no change in SCFA | (Martinez et al., 2013) |
| | Adults | Composition/activity (SCFA) | (de Angelis et al., 2015) |
| Rye | Men with metabolic syndrome | Composition | (Eriksen et al., 2020)\(^b\) |
| | Adult IBS patients | Composition | (Laatikainen et al., 2019) |
| Rice | Adults | Composition/activity (butyrate) | (Sheflin et al., 2015) |
| | Adults | Composition/activity (SCFA) | (Sheflin et al., 2017) |
| Oat | Adults (mild hyperglycemia or hypercholesterolemia) | Composition/no change in SCFA | (Connolly et al., 2016) |
| Maize | Adults | Composition/no change in SCFA | (Carvalho-Wellset al., 2010) |
| Mixed whole grain (primarily wheat) | Obese males | Composition/activity not measured | (Walker et al., 2011) |
| | Males with metabolic syndrome | Composition/activity (SCFA) | (Salonen et al., 2014) |
| | Overweight/obese postmenopausal women | Composition/activity not measured | (E. Christensen et al., 2013) |
| | Adults | Composition/activity not measured | (Ross et al., 2011) |
| | Adults | Composition/activity not measured | (Tap et al., 2015) |
| | Adults | Composition/activity not measured | (Váñez et al., 2017) |
| | Overweight (but healthy) adults | Composition/activity (secondary bile acids; not SCFA) | (L. Christensen et al., 2019) |
| | Elderly | Composition/activity not measured | (Faits et al., 2020) |
| | Adolescents | Composition/activity not measured | (Langkamp-Henken et al., 2012) |
| **Reduction of fiber intake** | Adults with metabolic syndrome | Composition/activity not measured | (Lappi et al., 2013) |
| | Obese adults | Composition/activity (SCFA) | (Duncan et al., 2007) |
| | Overweight/obese adults | Composition/activity (SCFA) | (Brinkworth et al., 2009) |

\(^a\)Present in the table twice, as both whole-grain wheat and whole-grain barley were studied.

\(^b\)Present in the table twice, as both whole-grain wheat and whole-grain rye were studied.
decreased the abundance of Bacteroides, Flavonifractor, Holdemania, Parasutterella, and Klebsiella, whereas the regular rye bread decreased the abundance of Flavonifractor. When comparing between the two test breads, Klebsiella was decreased after low-FODMAP rye bread intake (Laatikainen et al., 2019).

Christensen et al. (2019) compared the effect of high versus low Prevotella abundance in the microbiota on weight loss of healthy, overweight adults consuming a whole-grain diet or refined diet. For this 46 (19 men, 27 women; aged 30 to 65 years) participants were stratified into low or high Prevotella abundance groups at baseline, and weight loss was followed on the two diets for 6 weeks. Those subjects with high Prevotella abundances lost more weight on the whole-grain diet than on the refined diet, whereas those with low Prevotella abundances were weight stable (L. Christensen et al., 2019). Another more recent publication (Eriksen et al., 2020) compared the effects of supplementation of whole-grain wheat with that of whole-grain rye (with or without additional lignans) on cardiometabolic risk factors in men with metabolic syndrome. There were only minor differences observed in gut microbiota composition between the interventions. Whole-grain rye resulted in a higher abundance of Bifidobacterium, but only when compared with baseline not when compared with whole-grain wheat. Moreover, whole-grain rye resulted in a lower abundance of the genus Clostridium compared with whole-grain wheat (Eriksen et al., 2020). In a randomized cross-over study, Faits et al. (2020) fed 11 subjects three diets for a period of 4.5 weeks with a 2-week washout between diets. The diets were labeled either simple, refined, and unrefined carbohydrate diets, differing in the dominant type of carbohydrate. The unrefined-grain carbohydrate diet contained a higher proportion of foods made from whole grains. Roseburia abundance was higher and the secondary bile acids lithocholic acid and deoxycholic acid were lower after consumption of the unrefined carbohydrate diet relative to the simple carbohydrate diet. There were no changes in SCFA with either diet (Faits et al., 2020). The most recent study investigated the intake of whole-grain wheat versus refined wheat in adults with overweight or obesity (van Trijp et al., 2020). Twelve weeks of intake of 98 g/day of whole-grain wheat or refined wheat induced small changes in the gut microbiota. Compared with refined wheat, whole-grain wheat specifically increased the relative abundance of Ruminococcaceae_UCG-014, Ruminiclostridium_9 and Ruminococcaceae_NK4A214_group, bacteria known to be involved in butyrate production. The relative abundance of Lachnospiraceae_UCG-008 was decreased. However, the observed changes were no longer significant after correcting for multiple comparisons. The difference in fiber intake between the whole-grain wheat and refined wheat intervention was 10 g/day. Despite this, only subtle differences between intervention groups over time with respect to microbiota composition were observed. No effect on stool consistency was observed, which may be caused by the relatively high intake of whole grains at baseline (55 to 60 g/day; van Trijp et al., 2020).

4 IMPACT OF PROCESSING ON WHOLE-GRAIN PRODUCTS

4.1 Processing of cereals to transform cereal kernels into nutritious end products

As mentioned before, processing is required for virtually all cereals that humans consume, transforming them into palatable, nutritious, convenient whole-grain food products that are higher in dietary fiber and associated nutrients and phytochemicals than refined-grain comparators.

The first transformation for the majority of cereals is milling, the process of separating the endosperm of a cereal kernel from the germ and bran. For small grains that have a crease, this implies the transformation of kernels to flour and separation of the bran from the flour during this process. Particle size reduction is required to separate the fraction of the bran that is folded into the crease from the endosperm. Given the morphology of rice kernels, the separation of the endosperm and the bran and germ does not require particle size reduction; the bran and germ are simply removed through abrasion, leaving the endosperm body largely intact. Prior to the milling process, cereals like rice, barley, and oats need to be dehulled, to remove the enveloping and inedible hull. In a second transformation step, flour, semolina, or intact endosperm bodies are subjected to processes that involve sequential unit operations such as soaking, mixing, kneading, sheeting, extrusion, resting, fermentation, heating, boiling, and cooling. The changes in cereal constituents during processing are driven by chemical reactions, physical transformation, enzyme action, and microbial conversions. These, in turn, depend on processing temperature, time, water content, and energy input (Table 5).

4.2 Processing to enhance the nutritional value or physiological impact of cereal products

Processing may have both positive and negative effects on the nutritional value of cereal products and the physiological response to consuming them. This may include but is not restricted to factors such as changing the digestibility or fermentability of the carbohydrate components,
TABLE 5 Overview of different unit operations used during cereal processing and their impact

| Unit operation     | Impact                                                                 |
|--------------------|------------------------------------------------------------------------|
| Milling            | Particle size reduction, tissue separation, shear                      |
| Soaking            | Hydration, enzyme action                                                |
| Mixing             | Hydration, shear, oxygen supply, enzyme action                          |
| Extrusion          | Hydration, high shear, high-pressure expansion, molecular degradation of starch leading ultimately to dextrinization |
| Resting/fermentation | Hydration of all components, enzyme action, yeast action              |
| Heating            | Gelatinization of starch, denaturation of proteins, degradation of components, Maillard reactions |
| Cooling            | Gelation and retrogradation of starch                                    |

releasing phytochemicals bound in the bran fraction, and changing flavor characteristics (Edwards et al., 2015; Holm & Bjorck, 1992; Holm et al., 1989; Vinoy et al., 2013). As discussed above, modification of the cereal to change the substrates available to the microbiota is a potential target for food processing. Full understanding of the impact of processing and manufacturing technologies allows nutritionists and food technologists to design them to further enhance the nutritional value or physiological impact of cereal products.

4.2.1 Changing the nutrient and dietary fiber profile: Whole-grain versus refined flour

The most evident step toward cereal-based products to improve carbohydrate quality with increased nutritional and physiological impact is the switch from refined-grain to whole-grain products. Although milling mostly leads to the separation of endosperm flour from germ and bran and discarding of the latter as animal feed ingredients, recombining these fractions in their original proportions to produce whole-grain flours (van der Kamp et al., 2014) is the single most impactful processing step toward more nutrient-dense and higher carbohydrate quality foods. The chemical composition of wheat bran in Table 1 illustrates the nutrient complementarity for different grain fractions and shows the higher nutrient density for whole-grain versions of flours.

The chemical composition of bran, coupled with its specific architecture including the presence of tissues with capillary properties leads to a high water holding capacity, in turn leading to an increased fecal bulk and normalization of gastrointestinal transit times upon consumption (de Vries et al., 2015, 2016). Bran particles also act as a niche for gut microbiota, as they represent a food source for bacteria and offer a physical platform to which they can attach (de Paepe et al., 2017, 2019; Duncan et al., 2016).

Split milling provides the opportunity to process the bran or germ material before recombination into a whole-grain flour. Moderate or extensive bran particle size reduction can be used to improve the organoleptic quality of foods in which bran is incorporated by decreasing the gritty texture resulting from it. Such a process that can lead to possible health benefits was shown for broilers; cecal colonization by Salmonella in chickens fed bran with reduced average particle size was strongly reduced (Eekhout et al., 2008; Vermeulen et al., 2017). The effect was attributed to increased production of fermentation metabolites (SCFA), similar to that observed upon administration of rapidly fermentable wheat bran-derived AXOS (Eekhout et al., 2008). In a human intervention trial, wheat bran with reduced particle size increased serum SCFAs and acetate concentrations in obese subjects, although health parameters were not improved (Deroover, 2018).

Particle size reduction can also lead to an increase in the concentration of water-extractable arabinoxylans (WE-AX) or β-glucan in the bran. Such soluble dietary fibers can lead to a strong increase in intestinal viscosity, slowing down nutrient uptake in the small intestine, reducing blood cholesterol concentrations (EFSAPanelonDieteticProductsNutrition&Allergies, 2011b, 2011c), and may well affect the microbiota composition and activity.

4.2.2 Modulating the speed of starch digestion and uptake

As discussed above, dietary carbohydrate quality is not only linked to the ratio of total carbohydrates to dietary fiber but also to measures such as GI and GL. In 2011, EFSA delivered an opinion on a health claim related to slowly digestible starch and the reduction of post-prandial glycemic responses (EFSA Panel on Dietetic Products Nutrition & Allergies, 2011a). The EFSA Panel had been asked to evaluate the claim that the consumption of 40% to 50% of slowly digestible starch in cereal products containing about 55% to 70% of available carbohydrates as starch and 30% to 45% as sugars induced significantly lower post-prandial glycemic responses than the consumption of all digestible starch as readily digestible starch. The submitted claim was the result of over a decade of research by industry and academia into (i) the impact of starch structure on starch hydrolysis behavior; (ii) ingredient, recipe, and process development geared toward the
preservation of the integrity of starch during processing; and (iii) the impact of such process and the resulting product, in casu a biscuit, on post-prandial glycemic responses in human intervention trials, compared with extruded cereal products with a low level of slowly digestible starch (Nazare et al., 2010; Vinoy et al., 2013). The biscuits, made using selected biscuit ingredients and a proprietary baking process, were shown to provide carbohydrates that were continuously and gradually released from the biscuit matrix. This resulted in a sustained release of energy and reduced post-prandial glycemic responses. The claim was approved (EFSA Panel on Dietetic Products Nutrition & Allergies, 2011a). The importance of processing during manufacture in affecting carbohydrate quality is also well-illustrated for oat porridge. Traditional rolled oat porridge made from minimally processed (rolled) oats has a GI of 55 units, whereas instant oat porridge made from more finely milled and processed oats has a GI of 79 units (Atkinson et al., 2008).

4.2.3 | Changing the fermentability and speed of fermentation of dietary fiber

The constituents of cereal dietary fiber take different structural forms. The large polymer networks consisting of covalently bound (e.g., AX) or noncovalently bound polymers (e.g., cellulose or β-glucan) are the most abundant and typically can hold much water and add to fecal bulking. High molecular weight polymers, such as WE-AX or β-glucan often impart viscosity in the gastrointestinal tract that has effects on rates of stomach emptying, gut transit time, and rates of nutrient absorption (EFSA Panel on Dietetic Products Nutrition & Allergies, 2011b). Oligomers with high solubilities, such as fructans, are typically easily fermented by gut microbiota (Verspreet et al., 2016) and thus have potential to change luminal pH, fermentation patterns and microbiota profiles as discussed above. The question has to be asked if the totality of these dietary fibers and their co-passengers, as they are found in cereals, whole-grain flour or end product, display their maximal nutritional and physiological potential. Could processing lead to a more optimal balance of fermentable, viscous, and water-holding dietary fibers (Delcour et al., 2012)? The case study presented here deals with AX and the use of endoxylanases during bread making to change the AX profile.

AX is the primary dietary fiber in whole-grain wheat and rye and the bran of oats and barley. It is present in cereals as large polymers with an average molecular weight of 300 to 1000 kDa. When the polymers are not covalently linked through ferulic acid bridges, they are for the largest part soluble in water, imparting viscosity to suspensions. When they are covalently linked into a network as part of a cell wall, they are unextractable with water but can hold much water in their matrix or within the pores and capillaries they form (Bach Knudsen & Lærke, 2010).

AX strongly impacts the technological performance of cereals due to their impact on viscosity and the emulsifying properties of the WE-AX and the high water-holding capacity of the water-unextractable arabinoylans (WU-AX; Courtin & Delcour, 2002). To tune the impact of these AX, endoxylanases are extensively used in cereal-based processes or products. Enzymatic hydrolysis leads to the conversion of WU-AX into WE-AX. In bread making, this enhances gluten hydration (Leys, 2019) and increased dough liquor viscosity (Janssen et al., 2020), enhancing dough stability and bread loaf volume, explaining the significant use of these enzymes in breadmaking for the past three decades.

With high enzyme dosages or long incubation times, hydrolysis leads to the production of smaller AX polymers and AXOS. Although these oligosaccharides have little technological functionality, a range of studies indicates that they are more rapidly and more extensively fermented by the gut microbiota in the colon than native AX as a result of prehydrolysis. In broilers, both the action of an endoxylanase, as well as AXOS inclusion at 0.5%, led to an improvement in the feed conversion rate by 5% (Courtin et al., 2008), attributed to the fermentation of these components. Observations on reduced Salmonella infection in broilers fed AXOS-enriched diets equally pointed toward the fermentation of AXOS and their impact on microbiota being the main reasons for the effects. Recent work by Bautil et al. (2020) revealed that dietary AXOS kick-start AX digestion in young broilers compared with broilers that did not receive these oligosaccharides. Such AX modification was also shown to lead to different gut fermentation profiles in rats and synergistic effects were observed when all three types of AX were present (Damen et al., 2011). All the studies point toward a prebiotic effect of AXOS.

These studies led to the development of technology to produce whole-grain bread in which part of the native AX population was hydrolyzed into AXOS during processing through the use of thermoactive endoxylanases. The latter has to be used to prevent significant AX degradation during bread fermentation, leading to excessive water release and unmanageable dough (McCleary, 1987). The AX modification in the whole-grain bread led to different gut fermentation outcomes in humans, with higher butyrate production, less protein fermentation, and higher fecal Bifidobacterium counts (Damen et al., 2012). These would predict better health outcomes if these changes could be sustained over prolonged periods, and so longer term human studies are needed to support this health benefit.
4.2.4 Changing fructan levels in leavened products using yeast technology

Cereal fructans are fructose-based oligomers that come in five different structural classes: inulin-, levan-, graminan-, neo-inulin, and neolevan-type fructans (Verspreeet et al., 2017). They contribute to daily intake of dietary fiber, and are most probably prebiotic in nature with the potential to induce favorable changes in microbiota profiles. They are, however, also FODMAPs. These components reportedly have negative impact on people with irritable bowel syndrome (IBS; 11% of EU (Hungin et al., 2003) upon consumption (Bellini et al., 2020). Approximately 70% of IBS patients are reported to be helped by a low FODMAP diet so developing whole-grain cereal-based foods that are low in fructans but have high levels of higher molecular weight dietary fibers would be advantageous for a significant number in the population. Indeed, FODMAP levels in bread are almost always above cutoff values for induction of symptoms in people with IBS (Hungin et al., 2003; Lovell & Ford, 2012; Varney et al., 2017), in spite of the fact that fructan is partially degraded by bread yeast (Saccharomyces cerevisiae) invertase activity during mixing and the first part of fermentation. To reduce fructan levels in leavened cereal products, fructan degradation by invertase during processing can be enhanced by increasing the yeast level, changing the yeast growing conditions or yeast strain selection. Using a different yeast species, Kluyveromyces marxianus instead of S. cerevisiae, recently proved efficient in reducing fructan levels to almost zero (Struyf et al., 2018). Specific strains of this yeast species produce inulinases, enzymes that are better capable of degrading the fructans than invertases. Screening of different K. marxianus strains for their capacity to ferment well in whole-grain dough and for their impact on fructan meant that low FODMAP, high dietary fiber whole-grain breads could be prepared. A recent double-blind study demonstrated that consumption of a high-dietary fiber low-FODMAP rye bread, produced by enzyme instead of yeast technology, had potential to support a healthy microbiota (Laatikainen et al., 2019).

4.2.5 Germination

Cereal kernels can be subjected to sprouting or germination before further processing or consumption as such. The natural process of germination is initiated by consecutive cycles of soaking and aeration of kernels and keeping them under controlled temperature and moisture conditions from a couple of hours to a few days. The germination is stopped and the kernels stabilized by drying or kilning before milling into useable flours. Although this process accounts for the transformation of 23 million ton of barley annually into malt for brewing, it is not frequently used for the production of other cereal-based products.

Several advantages are attributed to the consumption of germinated rather than un-germinated cereals. One possible benefit is the partial hydrolysis of cell wall components, leading to a shift in the ratio of water-extractable versus water-unextractable dietary fiber (de Backer et al., 2010) and, associated with this, the release of dietary fiber-linked antioxidant compounds. For example, fortification of bread with sprouted wheat was shown to increase the availability of ferulic acid (G. Andersen et al., 2011). In the same study, consumption of the fortified bread for 9 days resulted in a lowering of fasting glucose concentrations not seen when the bread was fortified with intact wheat kernels. The authors suggested that this was due to an improvement in peripheral insulin sensitivity due to the presence of phenolic compounds in general, and ferulic acid in particular released in the sprouted whole-grain wheat. They demonstrated that insulin and ferulic acid in combination significantly increased glucose uptake by adipocytes in vitro (G. Andersen et al., 2011). Confirmation that these compounds can be available in the gut and are absorbed in amounts that could potentially affect glucose metabolism has been shown for oat bran extracts (Schär et al., 2018) and whole-grain wheat (Bresciani et al., 2016). A recent review by Lemmens et al. (2019) concluded, however, that supportive data from clinical studies are scarce, and that at present it is impossible to draw any conclusion on health benefits of sprouted cereals. In addition, they stated that long sprouting times and high processing temperatures are needed to maximize the de novo synthesis or release of plant bioactive compounds (Lemmens et al., 2018). Such long sprouting times and the drastic increase in α-amylase they bring about in the grains in part limit the use of milled sprouted grains in applications in which starch network integrity is key. The high enzyme levels could equally lead to increased digestibility of starch in resulting food products.

4.2.6 Processing and the NOVA classification

The above examples show that specific choices made with regard to ingredients (whole-grain instead of refined-grain, yeast species, etc.), processing aids (enzymes) or processing technologies (germination, milling) can positively impact the nutritional quality of cereal-based foods to help increase dietary fiber and prebiotic intake, increase mineral bioavailability, and improve digestion characteristics such as decrease glycemic index. Categorization of
foods based on the extent of their processing and the environment in which they are processed (at home or industrially), rather than on their composition and nutrient and energy density, such as it is done in the NOVA classification (Monteiro et al., 2019) is, therefore, a questionable evolution. It risks diabolizing foods and food categories such as bread that are considered an inherent part of a sustainable diet (Willett et al., 2019). As argued by Gibney (2020), a distinction should be made between processing on the one hand and the ingredient bill and energy density of foods on the other hand. Although numerous examples can be given where the extent of processing and high energy density go hand in hand, sufficient high-profile, high-relevance examples, such as bread, can be given that should make nutritionists and food scientists wary of not tarring all foods with the same brush. This is done too often in studies relating (ultra)processing to chronic diseases. Although the fine print in such studies often details that associations are valid for specific food types within the categories of processed and ultra-processed food (Srour et al., 2019, 2020) the confusion and harmful association with processing per se often remain (Lawrence & Baker, 2019).

5 | PRESENT AND FUTURE RECOMMENDATIONS FOR INTAKE OF WHOLE GRAINS

Choosing whole-grain foods over refined-grain options is shown to be a good way to improve the carbohydrate quality of the diet, particularly the dietary fiber component (Mozaffarian et al., 2013). There is considerable scope to increase consumption of whole grains globally as there is no place where whole-grain intake meets current recommendations (Mann et al., 2017; Miller, 2020). A recent high profile review (Willett et al., 2019) has suggested that the daily target should be 232 g of cereals per day and that this should all be in the form of whole-grain foods, although this report has recently been challenged (Zagmutt et al., 2020). Achieving this level of whole-grain cereal-food consumption would require a dramatic change in dietary eating patterns across all populations globally (Blackstone & Conrad, 2020), and is unlikely to be achieved due to the myriad of barriers to increased consumption of whole grain identified for the population (Robinson & Chambers, 2018). To meet current whole-grain dietary recommendations as well as striving toward the aspirational target suggested by Willet et al. (2019), there needs to be a concerted effort to increase intake of whole grains for all populations (Toups, 2020). Building robust, evidence-based dietary guidelines should be a priority for health agencies globally, as well as clear guidance for population on how to select healthful whole-grain products. Part of the solution may be through standardization of agreed definitions for whole grain and whole-grain foods so that food manufacturers use consistent terminology and labelling on packaging, helping the consumer to make informed choices (Kissock et al., 2020; Mathews & Chu, 2020). This has been addressed by the Whole Grain Initiative (WGI, 2020), a nongovernmental organization of academic institutions and industry coordinated by the International Association for Cereal Science and Technology (ICC; Korczak et al., 2016). The WGI has global membership and has recently agreed a standard definition for whole grain as a food ingredient based on the earlier definitions proposed by the Healthgrain Forum (van der Kamp et al., 2014) and the AACC International (now Cereals & Grains Association, 2008). The agreed definition states “Whole grains shall consist of the intact, ground, cracked, flaked or otherwise processed kernel after the removal of inedible parts such as the hull and husk. All anatomical components, including the endosperm, germ, and bran must be present in the same relative proportions as in the intact kernel.” The definition acknowledges that the majority of whole-grain flours are made by recombination of fractions separated during roller milling (compared with traditional stone-grinding where the grain is crushed but not fractionated), and that this recombination does not impair health benefits. This processing step, together with mandatory fortification of some flours contributes to the “ultra-processing” NOVA categorization of most cereal-based foods (Monteiro, 2009; Monteiro et al., 2019). However, as discussed above, the NOVA categorization fails to recognize the health benefits of whole-grain over refined-grain and so fails to promote the consumption of whole-grain foods over refined-grain foods. The WGI has now also published a proposed definition for whole-grain foods updated from earlier definitions (Ferruzzi et al., 2014; Ross et al., 2017; Whole Grain Initiative, 2020). The agreed definition states “A whole-grain food shall contain at least 50% whole-grain ingredients based on dry weight.” Supporting documentation for both definitions is available on the WGI web site (Whole Grain Initiative, 2020). Adoption of these definitions by public health agencies and food manufacturers will be essential in developing public health policies that consumers can understand and use to inform positive changes to their dietary habits (Korczak & Slavin, 2020; Toups, 2020).

6 | SUMMARY

Although there has been an on-going debate for more than a decade on possible harmful effects of processing of foods on health, processing of grains is a prerequisite for
modifying their nutritional benefits; raw grains are hardly digestible for humans.

Stone milling, cooking, and baking were the first processing methods used to improve the nutritional characteristics of cereals. Nowadays, most cereals are consumed as refined grains that are preferred by consumers because of their palatability. However, eliminating bran has resulted in grain-based products that contribute to a lower-quality diet. This review focused on the role of whole grains, in maintaining a healthy and sustainable diet, with a special focus on the gut microbiota. There is considerable evidence that exchanging products based on refined grains with products based on whole grains reduces the risk of several noncommunicable diseases, by improving diet quality and changing the composition of the microbiota for the better. The exchange from refined to whole grain should be considered an easy step for consumers once the cereals have processed to form healthy energy-dense foods.

The review demonstrates that it is possible to further improve the nutritional quality of cereal foods beyond the exchange of refined to whole grain with additional processing techniques. For instance, carbohydrate quality can be improved by using specific enzyme technology to reduce the speed of digestion of the grain starch. In addition, other enzyme technologies can modify the less fermentable dietary fiber fraction to improve its fermentability by the microbiota. Using different enzymes, dietary fibers can contribute to fermentation throughout the length of the colon. Furthermore, phytases and germination improve the bioavailability of minerals in the grains and may alter the accessibility to, and metabolism of phytochemicals within the bran fraction. Without wasting the most nutritional part, such new technologies allow producers to use the complete grains and produce the palatable and enjoyable grain-based foods the consumers appreciate.

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AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The sponsor had no influence on the content of this paper that represents the views of the authors, who have no conflicts of interest to declare.

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