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Whole-grain foods and chronic disease: evidence from epidemiological and intervention studies

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Cereal-based foods are key components of the diet and they dominate most food-based dietary recommendations in order to achieve targets for intake of carbohydrate, protein and dietary fibre. Processing (milling) of grains to produce refined grain products removes key nutrients and phytochemicals from the flour and although in some countries nutrients may be replaced with mandatory fortification, overall this refinement reduces their potential nutritional quality. There is increasing evidence from both observational and intervention studies that increased intake of less-refined, whole-grain (WG) foods has positive health benefits. The highest WG consumers are consistently shown to have lower risk of developing CVD, type 2 diabetes and some cancers. WG consumers may also have better digestive health and are likely to have lower BMI and gain less weight over time. The bulk of the evidence for the benefits of WG comes from observational studies, but evidence of benefit in intervention studies and potential mechanisms of action is increasing. Overall this evidence supports the promotion of WG foods over refined grain foods in the diet, but this would require adoption of standard definitions of 'whole grain' and 'whole-grain foods' which will enable innovation by food manufacturers, provide clarity for the consumer and encourage the implementation of food-based dietary recommendations and public health strategies.

Whole grain: Evidence-based nutrition: Cardiovascular health: Cancer risk: Type 2 diabetes

The concept that whole-grain (WG) foods are associated with health is not new. Both Carl Linnaeus and Thomas Allinson previously extolled the virtue of wholemeal bread as part of a healthy lifestyle in the 18th and 19th century, respectively[1,2]. An early observational study also noted that Hunzukut males from a remote region of Northern Pakistan habitually consumed WG, other plant-based foods, goat's milk and cheese, grape wine and rice, with high levels of physical activity. These males were described as being particularly vigorous and suggested to frequently live well beyond the age of 100, although this has not been independently verified[3].

Recently, more quantitative population-based studies have highlighted the positive association between higher intake of WG foods and improved outcomes in relation to morbidity and mortality for major diseases such as CVD, type 2 diabetes and some cancers. Of key importance in this area are definitions of 'whole grain' and 'whole-grain foods' which can be applied to published data and, eventually, to allow for clear public health messages with recommendations for WG intake.

The present focus in WG food-related research and health has shifted towards the evaluation of the quality of the present evidence base in relation to health claims and dietary recommendations. A recent position statement was released by the Scientific Advisory Committee for Nutrition for further consultation in the UK[4]. The statement emphasises the importance of

Abbreviations: WG, whole grain.

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WG in the diet and, if implemented, will require a major change in emphasis by Public Health England and other agencies in promoting WG consumption in the UK.

Whole grain definitions

While the definition of a 'whole grain' or WG food appears to be simple, controversies as to exact definitions have been apparent since the first formal definition was proposed by the American Association for Cereal Chemists in 1999[5]. While the foundation of this definition, which acknowledges that a degree of processing of grains is acceptable as long as bran, germ and endosperm components remain in their natural ratios, has remained constant, further difficulties in defining what a grain is (for example should soya be included in this category) and the type and extent of processing which are acceptable in relation to changes in composition have arisen[6].

Most recently, WG have been defined by the European HEALTHGRAIN consortium as those from an inclusive list of commonly available grains, pseudograins and wild rice[7]. The definition of WG proposes that the grains may be processed in a variety of ways which ensures that the natural proportions of bran, germ and endosperm are retained. Crucially, and in contrast to the updated AACCI definition[8], this definition also allows for a minimal loss of these three components during the processing of these WG foods[9].

Similar issues in the standardisation of a definition for WG foods have also become apparent. A number of definitions agree that WG foods should contain over half their weight from WG sources. The disagreements come in relation to whether this should be expressed as the dry content of the product, or whether it should be based on ingredient declarations[8]. Such definitions may exclude products with a naturally high water content (e.g. breads) but would also be likely to exclude dried products (e.g. breakfast cereals and staples like brown rice and whole-wheat pasta) as served, due to the high moisture content caused by the addition of milk or water during preparation. While attaching a percentage-content value to a food product may appear a simple solution, it may also discount a range of other products that are frequently consumed in higher quantity in the diet but still provide the consumer with appreciable amounts of WG. A more recent and practicable definition was proposed based on the amount by weight that a portion of WG food might provide. The definition was proposed by an international cross-disciplinary group which suggested that the lowest amount a WG food product must contain was 8 g WG per 30 g product[8] in order to be labelled as a 'whole-grain food'. By making the recommendation in this way the panel aimed to provide WG food manufacturers with a target amount of WG within their products which was nutritionally meaningful. Further follow-up within the next few years will allow assessment of whether such practices have been adopted by manufacturers.

Health benefits of consuming whole grains: what is new?

A series of meta-analyses have previously reported that observational evidence consistently highlights an association between increasing intake of WG foods and reduced risk of CVD[9,10], type II diabetes[10,11], metabolic syndrome[10] and multiple-site cancers[12,13]. To the authors' knowledge, there are no previous published intervention studies linking WG consumption to cancer outcomes. The recent UK Scientific Advisory Committee on Nutrition draft report on Carbohydrates and Health[14] showed that consumption of carbohydrates from WG sources led to a significantly reduced relative risk for cardiovascular events. In contrast, the percentage dietary energy from carbohydrates, carbohydrates from legumes, refined grain consumption and intake of low glycaemic index carbohydrates were all not associated with subsequent CVD events. In the case of any CVD event reported in five previous meta-analyses, the pooled estimate of relative risk was 0·95 (95 % CI 0·92, 0·97) for each WG consumption event every 2 d[14]. While this effect is small, it must be noted that the frequency of consumption is low, perhaps as a result of low habitual intake of WG at the time of data collection in the original studies. Higher intake of WG by some populations would therefore be expected to have a more marked effect on reduction of the relative risk of all cardiovascular events. Although WG intake is presently low in many countries[15–17], it does appear to be increasing over time and this might be expected to lead to subsequent reductions in incidence of and mortality from cardiovascular events.

Intervention studies have been carried out in relation to the impact of WG consumption on markers of cardiovascular and metabolic health. The findings from these studies have been less consistent in reporting a positive impact of WG on health outcomes than those in population-based studies. Ferruzzi *et al.*[8] noted that part of the inconsistency may be a result of different study design and incorporation of different types of WG foods within the intervention diet regimen. In addition, methods for reporting and calculating WG intake vary considerably between studies making interpretation of results and comparison between studies even more difficult[18].

Whole grains and cardiovascular/metabolic health

Previous meta-analyses of intervention evidence show that existing evidence does not consistently support improved outcome measures as result of WG food-based intervention on body weight, indices of body fatness or blood pressure, although some improvements to the blood lipid profiles were evident[10,19].

Many of the previous population-based studies have suggested that a daily intake of WG, equivalent to about three slices of wholemeal bread, is associated with a reduced risk or prevalence of cardiovascular outcomes. As a result of these findings, specific target on daily WG intakes have been recommended in the USA and in Denmark. Many other countries have less specific recommendations such as 'eating more whole grain' or 'choose WG whenever possible[8]. It must be noted that WG vary greatly based on the chemical composition of different grain species[20]. Therefore, consideration of whether or not individual food items are independently associated with disease outcome is important, particularly as one source of grain may be the predominant staple within some populations (e.g. rye in Northern European countries). To date, only a few studies have focused on single WG staples. For example, Kazemzadeh *et al.*[21] and Sun *et al.*[22] demonstrated that brown rice was an independent marker of disease risk. Similarly Rebello *et al.*[23] recently suggested that wholemeal bread intake was negatively correlated with IHD risk in a Chinese cohort.

Whole grains and control of blood glucose

A recent meta-analysis of cohort studies suggested that increased intake of WG foods resulted in a reduced risk of type II diabetes[11]. Evidence from the Women's Health Initiative Observational Study also found an inverse dose–response relationship between WG food intake and decreased incidence of type II diabetes[24]. In both of these studies, there also appears to be an increased risk or incidence of type II diabetes with consumption of refined grain products. A previous study that focused on analysis of rice consumption patterns in the US population similarly noted that increasing regular brown rice consumption was associated with decreased risk of type II diabetes whereas habitual white rice consumption was associated with increased risk. Multivariate modelling within this pooled analysis also suggested that substitution of white rice for brown rice or other WG foods could reduce the risk of type II diabetes by 16 % per 50 g rice replaced with brown rice, but a greater reduction was predicted if the 50 g rice was with other WG foods[22].

Fewer intervention-based studies have suggested improvements in control of blood glucose as a result of WG intake. A series of recent studies has provided further information on how WG may affect glucose tolerance. Consideration of the types of foods used within the intervention, comparator diet and target group of choice may be key determinants on the outcomes noted. Previously published glycaemic index tables show that WG foods do not necessarily have a lower glycaemic index than comparable refined grain products[25,26], as milling and other processing parameters are likely to affect digestibility of such products. A two-group parallel design study compared the impact of inclusion of a range of WG products in comparison with well-matched refined grain control products in sixty-one men and women with metabolic syndrome over a 12-week period[27]. The WG intervention was found to improve postprandial insulinaemic response to a test meal (a reduction of 29 % compared with the control group) but did not improve glycaemic responses. Improvements in insulinaemic responses (but not glycaemic responses) were also noted in studies carried out with whole rye-included in the SYSDIMET Nordic dietary intervention lasting 24 weeks[28]. Similarly, after 6 months adherence to a New Nordic Diet (high in fruit, vegetables, WG and fish) Poulsen *et al.*[29] showed a significant reduction in fasting serum insulin and homeostatic model of insulin resistance compared with the Average Danish Diet with no difference between the groups in fasting plasma glucose concentrations. An effect on glucose concentrations was seen in a 12-week intervention study comparing dietary carbohydrate sources (white rice *v.* WG, barley and legumes) in Korean type II diabetics and individuals with impaired glycaemic control[30]. In this study, both fasting blood glucose and insulin concentrations were improved in the group receiving non-refined carbohydrates.

The afore-mentioned evidence appears to provide further support for the idea that WG-rich diets can reduce the risk of type II diabetes. It is interesting to note that the majority of these studies have highlighted an impact on the insulin response rather than affecting fasting or postprandial blood glucose concentrations, suggesting an increased sensitivity to insulin rather than a blunting of postprandial glycaemia. It is important to note that of all the studies listed earlier, however, only that of Giacco *et al.*[27] represents a well-controlled intervention of WG *v.* refined grains alone, whereas the other studies tend to compare refined grain diets with a healthier dietary template that includes increased WG intake.

Whole grains and body weight or body fatness

The recent meta-analysis of Pol *et al.*[19] noted a lack of effect of WG on the reduction of body weight. At the same time, a number of studies have highlighted changes to some (but not all) measures of body fatness as a result of WG-based interventions. For example, in the study of Katcher *et al.*[31] the reduction in percentage of visceral body fat was higher in the group receiving a reduced energy diet containing WG foods compared with the reduced energy diet alone. Small reductions in percentage of body fat were also noted in the study of Kristensen *et al.*[32]. In both these studies, a range of other body fatness parameters were also assessed, with no significant difference in these outcomes noted as a result of WG intervention[31,32]. The findings of these studies suggest small but measurable improvements in body fat distribution within an energy-restricted dietary pattern containing WG but these are not seen in the absence of energy restriction.

Whole grains and cancer risk or incidence

Due to a lack of well-defined biomarkers for assessment of risk of cancer, there is no evidence from intervention studies in relation to the impact of WG on cancer risk or outcome. While evidence from a variety of population-based studies from around the world have consistently highlighted a lower incidence rate of cancer with higher consumption of WG, it is surprising that

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these effects have not been the focus of previous WG health messages. The original WG health claim authorised in the USA[33] cited reduced cancer risk but this was subsequently removed from the health claim when it was revised[34].

A recent study noted that a dietary pattern rich in WG, fruit and vegetables was associated with a reduced incidence of breast cancer in a Greek case-controlled study[35]. A 'whole food' dietary pattern (i.e. one with higher consumption of fruit and vegetables, fish, poultry and WG) was also linked to reduced concentrations of pro-inflammatory cytokines in head and neck cancer patients[36] and also appears to reduce recurrence and mortality rates within this population group[37].

A number of previous studies have suggested that increased WG intake is associated with a reduced incidence of colorectal cancer[12], including some suggestion that WG intake is associated with a modest reduction in risk of colorectal cancer, whereas total dietary fibre intake does not reduce risk[38]. The recent study of Knudsen *et al.*[39] noted that inconsistencies in previous findings could be due to the use of FFQ as a (non-specific and self-reported) basis for dietary estimation. They found significant reduction in cancer risks when measured against plasma alkylresorcinol concentrations as a validated biomarker of whole wheat and whole rye intake[40,41] either alone or in combination with estimated WG intake by FFQ. While previous evidence would suggest a statistically significant correlation between alkylresorcinols and intake of WG, it must also be noted that the linearity of this association does not appear to be strong enough to effectively predict absolute amounts of intake of whole wheat and whole rye products but may be a useful adjunct to assess habitual/recent high and low dietary intakes of such foods.

Many previous studies on WG intake and colorectal cancer risk have utilised datasets collected in North America and parts of Europe where WG consumption is habitually low and the highest percentile of WG intake may also be modest[42,43]. The recent study of Egeberg *et al.*[44] focused on assessment of cancer risk in a Danish population where the median daily amount of WG foods consumed was high (130 g/d, which would approximate to about 65 g WG/d). The lowest intake noted within the study participants was still in excess of one serving of WG daily (which may represent the upper amount of intake in some previous observational studies). This study noted a modest reduction in colon cancer risk in males but not females[44].

Mechanistic studies on whole grains

Previously, a number of studies have compared the *in vitro* antioxidant content of WG foods to refined grain alternatives[45], although previous evidence would suggest that inclusion of high amounts of WG (60 %) in the diet of rats does not improve antioxidant status in comparison with refined grains[46]. However, there are surprisingly few studies assessing the impact of WG *v.* refined carbohydrate consumption on markers of health or disease occurrence in animal models. Some of the most recent data are discussed later.

While the rodent gastrointestinal anatomy and physiology differs significantly from that of human subjects[47] and rodent chow is not comparable with human diets in terms of form and composition[48], rat and mice models can at least provide further clues into the understanding of how WG might impact on acute physiology or longer-term disease progression.

Replacement of a high sucrose diet with traditional whole maize products resulted in improved metabolic profiles in rats[49]. While this study used foods prepared in the same way as they would be consumed by human subjects, a direct comparison is not possible between whole and refined grains (but rather WG and refined sugar). A series of recent studies assessed the effect of switching maize starch with 1–2 % by weight powdered millet extracts[50–52]. In these studies, these relatively small changes to the overall diet improved the metabolic profile and body weight of the millet-fed mice *v.* comparator groups with metabolic syndrome induced by either dietary or genetic manipulation. Substitution of white rice with WG (Job's Tears, buckwheat and glutinous/waxy barley) in rats fed an obesogenic diet resulted in lowered plasma triacylglycerols, total cholesterol and LDL-cholesterol concentrations and a significant reduction in aortic wall thickness suggesting that these grains had a cardioprotective effect[53,54]. Differential effects between grain types have been observed in mice fed WG wheat or WG rye[55]. In this experiment, WG rye reduced body weight and fatness, improved insulin sensitivity and lowered total cholesterol compared with the mice fed WG wheat. However, the experiment was not designed to compare WG with refined grain-containing diets limiting its value in this regard.

Studies in laboratory animals investigating possible effects of WG on cancer development are sparse. A recent study using a chemically-induced model of colorectal dysplasia involved feeding four parallel groups of rats diets containing refined and unrefined wheat from two different classes (soft white wheat and hard red wheat). The unrefined (WG) diets did not affect the number of aberrant crypt foci (an early mucosal change associated with the early stages of cancer development) occurring within the distal colon but the class of wheat did (with the red, hard wheat having reduced the incidence of aberrant crypt foci)[56]. These results are consistent with those of Maziya-Dixon *et al.*[57] also in an experiment with chemically-induced colon cancer in which the end point was tumour incidence, which was significantly lower in mice whole and refined red wheat diets compared with whole or refined white wheat diets. The reasons why the red wheat variety proved beneficial compared with the white wheat is unclear, but presumably is due to differences in phytochemical content between the two cereals.

The porcine digestive tract is anatomically similar to that of human subjects[47]. Nielsen *et al.*[58] compared that the metabolomic responses to test meals containing different types of bread were similar in pigs and human subjects and concluded that pigs were a suitable model for human metabolic studies in food research.

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However, only a few studies have used pigs to assess the impact of WG consumption on cardiovascular health so more work in this area is needed before firm conclusions about their value. For example, feeding 2–3 kg bread buns daily for up to 10 weeks containing either whole rye and rye bran improved lipid profiles and insulinaemic responses in hypercholesteraemic pigs compared with a control bread made with refined wheat flour and cellulose to match the total fibre content[59].

While animal models may not always be representative of the human system, their use may allow better insight into how grain-based foods could affect health outcomes. Parallel assessment of changes in bodily organs, such as the liver and brain, are unlikely to be possible in human subjects. Such studies also allow strict control of laboratory animal diets and manipulation of dietary intake or management of multiple comparative dietary treatments is much simpler compared with studies in free-living human subjects. As a result, such studies can provide clearer evidence of cause-and-effect in relation to an original hypothesis than human-based interventions can often provide.

The way forward

A number of countries across Europe, North America, Asia and Australia now include WG-based messages within their public health recommendations[60–63].The available evidence suggests that recommendations for increasing WG foods at a population level are justified in relation to attempting to reduce incidence of CVD. Evidence from intervention studies suggests that WG may have statistically and biologically significant impacts on some markers of cardiovascular health but they also show that not all WG and foods made from them are equal in their impact on cardiovascular health outcomes.

While many of the earlier studies on WG and health have been carried out mainly in North American and European population, recent studies have also provided evidence that WG foods could be part of a healthy dietary template in other parts of the world. Recent dietary pattern analysis observations have suggested that WG foods are part of a healthy dietary template in other regions of the world, including South America[64], Africa[65] and Asia[66,67].

In relation to the findings of these recent dietary pattern studies, it is important to consider the generalisability of WG-based public health messages in the target population. Health messages should be based on what the target population consume, what health challenges they face or are expected to face and what the quality of evidence is in relation to the association of WG food intake with health outcomes in this population group.

While not all intervention studies have shown positive outcomes in relation to health, very few (if any) of these studies have shown negative impacts on the health outcomes tested, as evidenced by recent meta-analyses. As such, messages targeted at increasing WG at a population level are still relevant and attempts by individuals to include more WG in their diets (assuming they have no allergy or intolerance to grain-based foods) are also justified.

One overarching concern that is likely to impact researchers, public health bodies and other government agencies, consumers and WG food manufacturers alike is the lack of the adoption of transparent and standardised definitions for the terms ‘whole grains’ and ‘whole-grain foods’. These terms must be clearly delineated and policy provided in terms of a uniform definition. With the increasing internationalisation of the food market and differences in labelling and other requirements in different regions of the world, this may be more challenging at a global level although it may be feasible in regions with more harmonised food regulation such as the EU, North America and the ASEAN countries.

The recent Scientific Advisory Committee for Nutrition draft report on dietary carbohydrates has stated that ‘The evidence ….. endorses a dietary pattern concerning carbohydrates that is based on whole grains, pulses (e.g. kidney beans, haricot beans, lentils), potatoes, vegetables and fruits’ and also makes note that intake of free sugars from all sources should be limited[14]. While this reinforces the idea that WG are an important part of a healthy dietary pattern, the latter recommendation on free sugars may also be important to consider in relation to choice of WG foods and the development of new WG food products. A single serving of certain ready-to-eat breakfast cereals may contain higher amounts of free sugars than the 5 % of daily energy intake suggested by Scientific Advisory Committee on Nutrition[14]. A single serving of WG snacks, such as flapjacks and cereal bars is likely to exceed this amount. The recommendation suggested by Ferruzzi *et al.*[8] would encourage development of products that provided biologically relevant amounts of WG to the consumer and should be used for development of products based on replacement or substitution of refined grain for WG in product formulations. This reformulation should also consider the overall nutrient profile of the product so that the consumer can be confident that ‘whole-grain’ foods are clearly a healthier food option.

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Conflicts of Interest

The authors declare no conflicts of interest and the views expressed within this paper are entirely their own.

Authorship

I. A. B. and C. J. S. contributed equally to the collation of evidence, and design of content and writing of the paper.

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