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WholEUGrain project

A European Action on Whole Grain Partnerships

Funded under the Annual Work Plan 2018 (grant agreement 874482)

Deliverable number 4.1

Evidence base for the health benefits of whole grains including sustainability aspects

Whole grain:

definition, evidence base review, sustainability aspects and considerations for a dietary guideline.

Description: Report on the updated evidence base for health effect and sustainability aspects of whole grains

User Guide: The purpose of this deliverable is to ensure the knowledge base as one of the prerequisites for establishing a national whole grain partnership

WP 4: *Implementation tools for whole grain Partnerships*

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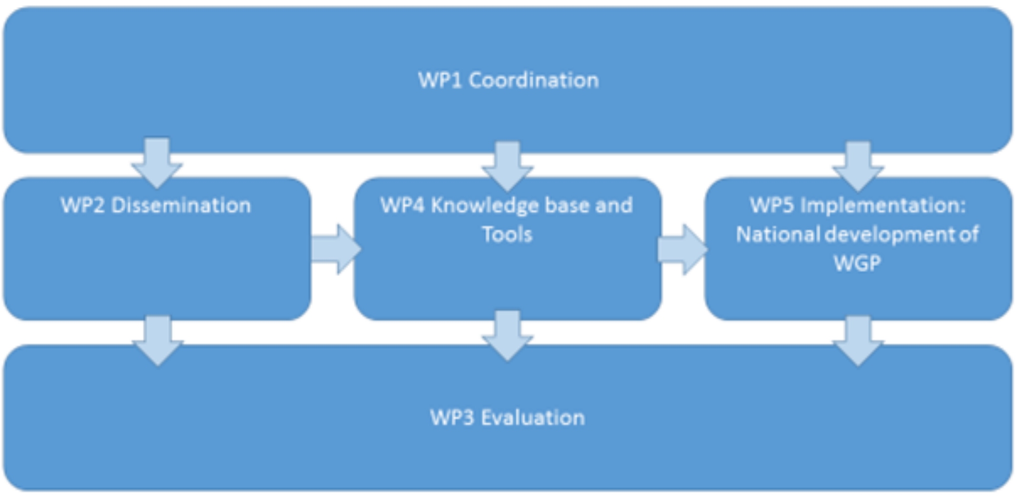
The WholEUGrain project

WholEUGrain – A European Action on Whole Grain Partnerships

Four countries are partners in a 3-year project with the aim to transfer Danish experiences with a national whole grain partnership (WGP) to other European countries. In less than 10 years, the public/private partnership in Denmark succeeded in nearly doubling whole-grain intake among the Danish population. The consortium consists of Romania, Slovenia, Bosnia and Herzegovina and Denmark; however, other countries are able to follow the project and can also benefit from this action.
The overall objectives are to promote good health through healthy diets, prevent diseases, reduce inequalities and establish supportive environments for healthy lifestyles by developing country-based whole grain public/private partnerships.
The task of transferring the experiences of the Danish whole grain partnership consists of three phases: Feasibility check, Education, and Adaptation leading to the formation of the national WGPs. Besides leading to the establishment of WGP's in the countries directly involved, the project provides important knowledge in the form of a publicly available updated evidence base of the health effects of whole grain, including sustainability aspects, as well as an EU Guideline for Whole Grain Promotion.

The project activities are carried out within five work packages: Coordination (WP1), Dissemination (WP2), Evaluation (WP3), Implementation tools for WGP (WP4), and national/sub-national development of a WGP (WP5):



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INTRODUCTION

In 2019, under the auspices of the 3rd EU Health Programme, a consortium between Denmark, Slovenia, Bosnia-Herzegovina, and Romania was granted support for the WholEUGrain project – A European Action on Whole Grain Partnerships.

The aim of the WholEUGrain project is to share the experience of the Danish Whole Grain Partnership with other European countries, in order to help build up the necessary competencies and knowledge on how to establish and run a national public-private partnership, and through its work and actions promote an increase of whole-grain intake in other European countries' populations.

Part of the necessary knowledge encompasses a clear understanding of the definition of whole grains and whole-grain products, knowledge of the evidence base for the health benefits of whole-grain consumption, and knowledge of relevant aspects regarding the establishment of a quantitative recommendation at a national level. A report addressing such themes was published in 2008 in the Danish language, before the official launch of the Danish Whole Grain Partnership.

The present report is inspired by the aforementioned Danish report and gathers the most recent and updated knowledge on this subjects, as well as new knowledge on sustainability aspects regarding whole grains, and aims to make such knowledge available for other European countries.

This report contains:

- An executive summary of findings.
- A chapter on relevant aspects regarding the establishment of definitions of "whole grains" and "whole-grain food products" that other European countries can use if they decide to establish nationally accepted definitions.
- A chapter with an overview of whole-grains' composition and nutrients.
- A chapter that gathers the latest and best level of evidence available concerning the associations between whole-grain intake on the development of cardiovascular diseases, type 2 diabetes, cancer, risk of overall mortality, overweight and effects on adiposity measures.
- A chapter describing unwanted substances and contaminants in whole grains.
- A chapter describing insights into the sustainability of whole grains in terms of environmental impact, and the role of whole grains regarding sustainability of the total diet.
- A chapter on relevant aspects regarding the establishment of a quantitative recommendation for whole-grain intake that other European countries can use for a national accepted recommendation.

SUMMARY

This report aims to give a clear understanding of relevant aspects regarding the definition of whole grains and whole-grain products, as well as review the evidence base for the health benefits of whole-grain consumption, and gather knowledge of relevant aspects regarding the establishment of a quantitative recommendation at a national level, as well as provide an insight into sustainability aspects of whole grains.

Seeds from grass species – also called grains or caryopses – are composed of three main compartments: the starchy endosperm, the germ (embryo), and the bran (consisting of the aleurone cell layer and a fibre-rich seed coat). Whole grains are defined as intact grains or processed grains (e.g. ground, cracked or flaked) where the three fractions endosperm, germ and bran are present in the same relative proportion as in the intact grains.

The most widely consumed grains (cereals) belong to the grass family *Poaceae*, which includes e.g. wheat, rice, barley, maize (corn), rye, oats and millets. Theoretically, intact seeds from all plants from the grass family could be defined as whole grains. However, scientific evidence for beneficial health effects is almost entirely based on the most commonly consumed grains. So-called "pseudo-cereals" (amaranth, buckwheat, quinoa) can be used in similar ways as cereal grains, since their culinary use is comparable. Their nutrient content is somewhat similar, so the nutritional impact of replacing cereal grains in the diet with pseudo-cereals is probably limited. However, seeds from pseudo-cereals do not contain the mixed-linkage beta-glucans typical of true cereals; the xylan structures are also substantially different between the two groups and xyloglucan content will generally be higher in pseudo-cereals' cell walls compared with those of true cereals.

To avoid misleading consumers, whole-grain food products should contain a specified minimum amount of whole grains. Preferably, whole grains should be the primary ingredient in a whole-grain food product. Also, the designation "whole grain" could be reserved to specific food categories, e.g. bread, pasta, and breakfast cereals, which are natural components of a healthy diet. We suggest that foods consisting of only one ingredient, e.g. flour or rolled oats, should be 100% whole grain to use the designation "whole grain". In composite foods, more than 50% of the dry matter should be whole grains. In multicomponent foods (consisting of more than one food group) such as meals, the whole-grain criteria should refer to the cereal part, e.g. the bun in a burger or the crust in a pizza.

To ensure the concept of whole grain is associated with human health benefits, processing the grains, e.g. by cleaning, germination or fermentation, is acceptable only if it causes a total loss of less than 2% of the grain and 10% of the bran. Since many consumers may regard foods labelled "whole grain" as healthy, it is further advisable that such foods should meet accepted standards for healthy foods, e.g. nutrient profiles on sodium, fat and sugars.

Of the three main compartments, the bran and germ parts have the highest concentrations of vitamins, minerals, dietary fibre, and a series of other bioactive compounds. Hence, whole grains and whole-grain products contain these nutrients and bioactive compounds in significantly higher proportions than refined-

grain products. Many of these nutrients and bioactive compounds are either shown to or hypothesized to be associated with the health benefits of whole-grain consumption.

An umbrella review was conducted, with the aim of gathering the latest and best level of evidence available concerning the associations between whole-grain intake and the development of cardiovascular diseases, type 2 diabetes, cancer, risk of overall mortality, and overweight.

The results of recent good quality meta-analyses, expert reports and of the WholEUGrain umbrella review show there is consistent evidence that an intake of about 90 g of whole-grain products per day (equivalent to 3 servings of whole-grain products, or 48 grams of whole grain as an ingredient) significantly reduces the risk of these diseases and overall mortality. In general, stronger improvements in risk reductions are observed for the shift between none to relatively low levels of intake, with significant benefits being achieved with as little as one-two servings of whole-grain products per day. Furthermore, protective effects are clearly seen for higher whole-grain intakes, with clear dose-response associations showing further risk reductions with intakes as high as 200-225 g whole-grain products per day (6.5–7.5 servings, equivalent to 104-120 grams of whole grain as an ingredient) for some of the observed associations.

There is strong epidemiological evidence that consumption of higher amounts of whole grains is associated with a lower risk of overall cardiovascular and coronary heart disease. Dose-response analyses show that the biggest differences in risk are found for those consuming at least one serving of whole grains (30 g whole-grain products/day) compared to those who consume none to very low doses, but with further risk reductions observable for intakes up to 100-210 g whole-grain products/day (approximately 3-7 servings). In addition, there is good evidence for the mechanisms explaining this relationship in humans.
For heart failure, not much evidence is available so far, but one good quality meta-analysis indicates a possible lower risk with a higher intake of whole grains. For stroke, the evidence is not clear, possibly due to a small number of studies conducted.

There is strong evidence that consumption of higher amounts of whole grains is associated with a lower risk of type 2 diabetes. Dose-response analyses further confirm this association, showing a significant lower risk for those consuming at least half a serving of whole grains (15 g whole-grain products/day) compared to those who consumed none to very low doses. Further risk reductions were observable for intakes up to 90 g whole-grain products/day (3 servings). In addition, there is fairly good evidence for the mechanisms explaining this relationship in humans.

There is strong evidence of a protective role of whole grains for colorectal cancer. This conclusion is based on consistent data from several prospective cohort studies that show a statistically significant and clear dose-response relationship showing a lower risk of cancer with higher consumption of whole grains, with low heterogeneity. Furthermore, there is robust evidence for the mechanisms explaining this relationship in humans. There is, so far, not enough data to draw conclusions regarding a potential protective effect of whole grains and the risk of other types of cancer.

There is strong evidence that a high whole-grain intake is associated with a lower risk of all-cause mortality. Dose-response analyses further confirm the robustness of this association, showing steeper risk reductions for those with a whole-grain intake in the lower range compared to those who do not consume whole grains. Further risk reductions were observable in those consuming higher amounts, with considerable risk reductions for intakes up to 5.5 servings of whole-grain products per day (165 grams).

There is rather limited evidence suggestive of a protective role of whole grains on the risk of weight gain, overweight and obesity. Even though the evidence is limited at present, it is generally consistent and shows a trend towards an inverse, albeit very small, risk reduction. There is evidence of biological plausibility through a number of different mechanisms related to energy balance. For adiposity parameters like waist circumference, body fat percentage, fat mass and fat-free mass the evidence is scarce, and results are conflicting.

A variety of unwanted substances and/or contaminants from different sources can, similarly to other foods, be found in whole grains and whole-grain products. For whole grains and whole-grain products, levels of such substances do not differ considerably from the levels found in refined grains or refined-grain products. As long as the maximum levels stipulated by the EU for different groups of foods are not exceeded, unwanted substances and contaminants in whole grains and whole-grain products pose very few food safety or health concerns, but awareness must be kept regarding potential problems deriving mainly from arsenic, but also aflatoxins and acrylamide to some extent. Furthermore, consumer education programs and campaigns must provide consumers and professionals with knowledge on how to use cereals in safe manners.

Grains and cereals are, together with vegetables, fruits, legumes and pulses, among the food groups with the lowest climate impact per kg of food. When comparing the different types of grains and cereals, rice tends to have a higher impact than wheat, rye and oats.
Few studies have compared whole-grain products with products made from refined grains, but whole-grain bread might have a slightly lower climate impact per kg than bread made from refined grains. Further, it is not clear to which degree the studies take possibly extra grinding and the use of the separated grain parts in other foods or animal feed into account.

When using estimates of the environmental impact of foods, differences in e.g. system boundaries, life cycle assessment methods and production conditions must be taken into account. Fortunately, reviews and databases with environmental data typically adjust for these differences. When evaluating the environmental impact of specific foods, it is not enough to evaluate foods separately. It is essential to consider how they are included in the overall diet because foods are included in different quantities, contribute with different combinations and amounts of nutrients, and there are significant differences in intake between populations.

Although grains make up a relatively large proportion of the typical European diet, they only contribute a smaller part of the climate impact from a total diet due to the high climate impact from most animal products. Regardless of diet type, whole grains can always play a significant role and can help improve the nutritional content of a diet. When transitioning to a more healthy and sustainable plant-based diet with fewer animal products, whole-grain products become even more important. Together with legumes, grains contribute essential amino acids. Further, whole-grain products have a significant content of those minerals that may be limited in a more plant-based diet, e.g. iron and zinc.

Establishing a recommendation for whole-grain intake should be based on the scientific evidence for associations between whole-grain intake and incidence of non-communicable diseases and mortality. The amount of whole grains (established in grams, grams of products or number of servings/portions) associated with reduced disease incidence should be identified from high-quality cohort studies.

The amount of whole grains that is shown to provide health benefits should be evaluated in the context of local dietary habits and nutrient recommendations. Adding a sustainable perspective is expected to increase the whole-grain recommendation at the expense of animal-based foods, since the contribution of essential nutrients from whole-grain food products in a healthier and more sustainable diet becomes highly relevant. It should be emphasised that different types of whole grains should be consumed, since they contribute with different nutrients and other compounds.

Whether a whole-grain recommendation is communicated to consumers in grams, grams of products or no. of servings/portions, and whether it is expressed per energy unit or per day, is for the responsible health authority to decide based on local practice.

CHAPTER 1
Definition of whole grains and whole-grain food products

By Heddie Mejborn, National Food Institute, Technical University of Denmark

1.1. INTRODUCTION

This chapter aims to clarify relevant aspects regarding the establishment of definitions of “whole grains” and “whole-grain food products” that other European countries can use if they decide to establish nationally accepted definitions.

Several countries have defined “whole grains” and “whole-grain food products” in their legislation. In some countries, the authorities accept a “code of practice” for use of the term “whole grain” by private organisations, e.g. if bakers’ associations have defined whole-grain food products.

Definitions are often established to help inform consumers about possible health benefits of whole grains and to make it easier for consumers to distinguish whole-grain food products in a shopping situation. A lack of officially recognised definitions by food and health authorities opens the door for food producers or health non-governmental organizations to establish their own definitions.

Since whole grains are often included as ingredients in composite foods, it is difficult for consumers to identify whole grains. Thus, consumers may lose confidence in whole-grain food products, if they cannot be certain to get what they expect, when buying a food labelled “whole grain”. Besides, this lack of definition makes it difficult for food producers to communicate to consumers through labels and claims, and to sell whole-grain food products in different countries. Thus, standardized definitions of whole grains and whole-grain food products established by food and health authorities benefit both consumers and food producers.

It is important to distinguish between “whole grain”, which is the total plant seed, and “whole-grain food products”, which are foods containing a minimum of whole grains as an ingredient.

This chapter discusses existing definitions and points out aspects to consider when defining whole grains and whole-grain food products.

1.2. WHAT IS WHOLE GRAIN?

Seeds from grass species – also called grains or caryopses – are composed of a starchy endosperm, a germ (the embryo), an aleurone cell layer, and a fibre-rich seed coat (pericarp, testa). The aleurone layer and the seed coat are often collectively called the bran. Whole grains are defined as intact grains or processed grains (e.g. ground, cracked or flaked) where the three fractions endosperm, germ and bran are present in the same relative proportion as in the intact grains. Some grains have an inedible outer layer called the hull or the husk. Removing the hull does not affect the grains' status as whole grains.

The most widely consumed grains (cereals) belong to the grass family, *Poaceae*. The grass family consists of twelve subfamilies, of which the seeds of some are part of the human diet, e.g. *Chloridoideae* (includes some millet species and teff), *Oryzoideae* (syn. *Ehrhartoideae*, includes rice), *Panicoideae* (includes maize, sorghum and some millet species), and *Pooideae* (which includes the major cereal grains wheat, barley, oat and rye) [1,2].

The term "millet" covers a group of highly variable species, which may not be closely related, since they can belong to different subfamilies. The most commonly cultivated are pearl millet (*Pennisetum glaucum*), proso millet (*Panicum miliaceum*, also known as common millet, broomcorn millet, hog millet, or white millet), and foxtail millet (*Setaria italic*c), all from the subfamily *Panicoideae*, and finger millet (*Eleusine coracana*) from the *Chloridoideae* subfamily [3]. The grass species most commonly eaten by humans are shown in table 1.1.

Table 1.1 – Commonly eaten species from the grass family (*Poaceae*).

Common name	Genus	Species
Barley	*Hordeum*	*Hordeum vulgare* L.
Oat	*Avena*	*Avena sativa* L.
Rye	*Secale*	*Secale cereale* L.
Wheat	*Triticum*	*Triticum aestivum* L. (common wheat)
		Triticum spelta L. (spelt or dinkel wheat)
		Triticum dicoccum Schrank ex Schübl. (emmer)
		Triticum monococcum L. (einkorn)
		Triticum durum Desf. (durum)
Maize	*Zea*	*Zea mays* L.
Rice	*Oryza*	*Oryza sativa* L. (Asian rice)
Millet	*Eleusine*	*Eleusine coracana* Gaertn. (finger millet)
	Panicum	*Panicum miliaceum* L. (common millet)
	Pennisetum	*Pennisetum glaucum* (L.) R.Br. (pearl millet)
	Setaria	*Setaria italica* (L.) P. Beauvois (foxtail millet)
Sorghum/durra	*Sorghum*	*Sorghum bicolor* (L.) Moench (alm. durra)
Teff	*Eragrostis*	*Eragrostis tef* (Zucc.) Trotter
Wild rice	*Zizania*	*Zizania aquatica* L.

Theoretically, intact seeds from all plants from the grass family could be defined as whole grains. However, scientific evidence for beneficial effects related to either human health or the environment should restrict the definition to species that are commonly eaten by humans, or species acceptable as part of a human diet, whose intake should be increased in a sustainable diet. Since the definition preferably should be suitable for use within the whole European Union, it is appropriate that all species mentioned in table 1.1 are defined as whole grains, including varieties and hybrids. Thus, e.g. the wheat variety *T. aestivum* 'Epos', and the hybrid *T. aestivum* x *S. cereale* = *X Triticosecale* (triticale) are whole grains. Table 1.1 should be updated whenever new information is obtained.

In countries where fresh maize is commonly eaten as a vegetable and not as a staple food, fresh maize should not be considered a whole grain, but dried maize, e.g. maize flour, should if it contains all three fractions of the grain present in the same relative proportion as in the intact grain.

Pseudo-cereals

So-called "pseudo-cereals" can be used as foods in similar ways as cereal grains, since their culinary use is comparable. Their nutrient content is somewhat similar as well [4] (see also https://frida.fooddata.dk/?lang=en or https://fdc.nal.usda.gov/), so the nutritional impact of replacing cereal grains in the diet with pseudo-cereals is limited. However, it should be pointed out that pseudo-cereal seeds do not contain the mixed-linkage beta-glucans typical of true cereals; the xylan structures are also substantially different between the two groups and xyloglucan content will generally be higher in the pseudo-cereal cell walls compared with those of true cereals [5].

Normally three plants are defined as pseudo-cereals: amaranth, buckwheat and quinoa (see table 1.2). Three species of amaranth are cultivated as food source [6].

Table 1.2 – Commonly eaten species of "pseudo-cereals", included in some whole-grain definitions.*

Common name	Family	Genus	Species
Amaranth	*Amaranthaceae*	*Amaranthus*	*Amaranthus caudatus* L.
			Amaranthus cruentus L.
			Amaranthus hypochondriacus L.
Buckwheat	*Polygonaceae*	*Fagopyrum*	*Fagopyrum esculentum* Moench
Quinoa	*Amaranthaceae*	*Chenopodium*	*Chenopodium quinoa* Willd.

* Austria, Croatia, Hungary, UK, Canada, USA, American Association of Cereal Chemists, Healthgrain Forum, Whole Grain Initiative.

1.3. PROCESSING OF WHOLE GRAINS AND EFFECT ON WHOLE-GRAIN STATUS

Grains may undergo a light cleaning such as removing of stones and dirt before they are consumed. Some whole-grain definitions specify this (see below). To reduce the loss of nutrients during cleaning, an acceptable cleaning loss should be defined.

Grains are normally cooked or heated before they are consumed by humans. They may also undergo other types of processing such as milling, sprouting or fermentation. Depending on how the processing affects the grains, they may no longer qualify as whole grains. Issues related to further processing such as baking and extrusion are outside the scope of the definition of whole grain as a food ingredient.

Milling

Grains can be eaten as whole kernels but most grains are milled, before they are used in food production. Whole grains may be ground, cracked or flaked. To be defined as whole grains after milling, the three fractions endosperm, germ and bran must be present in the same relative proportion as in the intact kernels.

Milling can vary from the simplest form, where each single grain is cracked or cut into few pieces, to more thorough milling or even finely ground flour. Depending on the type of mill, the different grain fractions may or may not be separated during milling. In stone mills whole grains are crushed without separation of the fractions. In roller mills grains are ground and separated by sieving, and when all fractions have obtained the desired particle size, they are reconstituted to form whole-grain flour. It is not possible to define a standard ratio between the three grain fractions, since it varies within and between species, and it is affected by grain size. Therefore, it is recommended that the recombination of fractions after milling be done at the mill.

During milling grains can be ground very finely. That may affect the health effects of whole grains (e.g. effects on nutrient availability, satiety, and human gut microbiota). Increased availability of micronutrients from finely ground whole grains may benefit human health, but it is possible the fine grinding may also reduce their health effects. This has not yet been studied in detail, so at this point we can merely propose a hypothesis: that once the intact cellular structures that are readily visible in coarsely ground flour using bright-field light microscopy are no longer prevalent, then neither are the whole-grain properties, health effects included. Testing this hypothesis and inferring a quantitative statement about the fraction of intact cellular structures, requires experimental work.

Behall and colleagues (2013) found no difference in plasma glucose or gluco-regulatory hormone responses after intake of refined grains, conventionally-ground whole grains, or ultra-finely ground whole grains in non-diabetic adult men and women [7]. A study in diabetic adults showed that consuming less-ground whole-grain food products improved postprandial glycaemic control compared with consuming whole-grain food products where the grain particle size was further reduced through milling [8]. Likewise, Reynolds and colleagues (2020) found the consumption of whole-grain bread made with more intact and coarsely-ground whole grains reduced postprandial glycaemia in adults with type 2 diabetes when compared with whole-grain bread made with finely roller-milled whole grains, while bread made with more coarsely ground stone-milled flour did not follow this trend [9]. No studies on effects of level of milling of whole grains on other health parameters were identified.

Thus, whole grain’s structural integrity determines nutrient availability including starch, so any process that disrupts the physical or botanical structure may be important for those who need to control their blood glucose. Therefore, if the term whole grain is used to imply a health benefit, the definition should also consider the degree of processing.

Currently, no studies give indications of a level of milling, where there is still a positive health effect of whole grains, but the studies by Reynolds et al. (2020) and Åberg et al. (2020) suggest that maintaining the structural integrity of whole grains will likely have long-term health benefits [8,9]. Grains that are so finely ground that no positive health effects persist should no longer be called whole grains. Until studies are available to set such a limit, it could be set where the grains are milled so finely that no intact cellular structures can be recognised in a bright-field light microscope.

Germination

Grains are normally used in foods in a dried state but grains can be germinated (sprouted) before they are used as food ingredients. The process is equivalent to the process of malting used in beer brewing. To start germination, the grains must be soaked in water, so they absorb moisture. Depending on the water content, temperature, and time, the embryo will start forming a new plant. During the process, the composition of the kernel will change: starch is hydrolysed by endogenous enzymes to glucose to provide energy for the growing embryo. Other compounds are degraded or synthesised, changing the nutrient content and availability and possibly the effects on health, including the human gut microbiota. When starch is metabolised by the plant to CO_2 and water, the relative amount of fibres in the grains increases relatively. Besides, fibres are synthesised during cell wall formation in the germinating plant. For a comprehensive overview of the impact of germination on nutrient content in grains, see Lemmens et al. (2019) [10].

Only limited studies in humans have shown positive health effects of germinated grains [10]. The moist environment during germination can promote bacterial growth, which should be taken into consideration, as it may affect food safety.

Thus, we suggest that germinated grains can be included in the definition of whole grains, if the level of germination is well defined, e.g. the germination time or the length of the sprout in proportion to the kernel length, and the acceptable impact on nutrient content. More studies on health effects are required to determine if germinated grains possess health benefits for humans similar to non-germinated whole grains.

Fermenting/enzyme treatment

In bread production, composition of grains and flour in the dough are subject to changes during the raising of the bread caused by enzymes from naturally occurring or added yeast or bacteria. This fermentation results in changes in grain composition and nutrient availability, which may affect the health effects of the whole grains included. Whole grains that are subject to the standard fermentation which is part of a normal bread production should be considered whole grains, since bread is part of the whole-grain food products that are shown to have health benefits to humans.

A range of enzymes are used in baking industry. These comprise proteases, lipases, amylases, and xylanases as the most common activities. Increased bread volume, improved shelf-life or modulation of dough rheological properties are the usual purposes of these enzyme technologies. However, it is possible to purchase very specific, potent enzymes, e.g. cellulases, which can break down fibres in whole grains to sugars. In some bakeries it is common practice to apply a pre-treatment to the grains, flour or a grain fraction, e.g. the bran, before reconstitution to whole grains. If enzymes are added as part of the pre-treatment, a large part of the grains in principle may be converted to sugars. Such grains no longer contain all of the original bran, germ and endosperm.

Since several studies have shown that cereal fibres possess health benefits [11-15], it is essential that the main part of the fibres are intact when whole-grain food products are consumed. Thus, use of fibre-degrading enzymes before or during fermentation leading to degradation of a significant part of the fibres before the grains are used as food ingredients, is not compatible with the whole-grain definition, since the grains no longer contain the endosperm, germ, and bran in the same relative proportions as the intact grains.

There are, to the best of our knowledge, no published studies of how far enzyme digestion can be taken before the health benefits of whole grains are lost. We propose that the content of cellulose as measured by the Updegraff method [16] shall be substantially equivalent to that of the starting material, and that loss of the hemicellulosic fraction should remain below an experimentally determined threshold to ascertain that the health effects are not compromised.

We suggest that, in general, grains that are fermented before they are used as ingredients in composite foods are not considered whole grains, because such grains no longer contain all of the original bran, germ and endosperm in the same relative proportions as the intact grains.

1.4. WHOLE-GRAIN FOOD PRODUCTS

To avoid misleading consumers, whole-grain food products should contain a specified minimum amount of whole grains. Preferably, whole grains should be the primary ingredient in a whole-grain food product. Besides, the designation “whole grain” could be reserved to specific food categories, e.g. bread, pasta, and breakfast cereals, which are natural components of a healthy diet.

Whole-grain food products may contain different levels of water, e.g. bread and breakfast cereals. Thus, to set comparable criteria for minimum whole-grain content in whole-grain food products, the whole-grain content should preferably be expressed as a percentage of the food’s dry matter.
We suggest, foods consisting of only one ingredient, e.g. flour or rolled oats, should be 100% whole grain to use the designation “whole grain”. In composite foods, more than 50% of the dry matter should be whole grains. In multicomponent foods (consisting of more than one food group) such as meals, the whole-grain criteria should refer to the cereal part, e.g. the bun in a burger or the crust in a pizza.

As pointed out by Ross and colleagues (2017), sensory aspects of whole-grain food products are not universally appreciated by consumers [17]. To encourage consumers in countries not accustomed to whole grains to enjoy their taste and their health benefits, it may be necessary to set the requirements for whole-grain content in foods lower than in countries where whole grains are part of the traditional diet. The Healthgrain Forum – an Europe-based partnership between cereal scientists from academia and industry – has discussed the subject thoroughly and suggests whole-grain food products contain at least 30% whole-grain ingredients on a dry-weight basis and more whole-grain ingredients than refined-grain ingredients [17]. However, it is stated by the authors that if national regulation regarding whole-grain food product definitions exist, they should be paramount to this definition.

The Whole Grain Initiative (WGI) – a worldwide interdisciplinary collaboration with the aim to increase whole-grain intake worldwide – has suggested that whole-grain food products shall contain at least 50% whole grains on dry-weight basis. However, they also suggest that foods containing at least 25% whole grains on dry-weight basis may make a front of pack claim of the presence of whole grains but cannot designate “whole grain” in the product name [18].

According to the EU Regulative 1169/2011, article 22, an ingredient that appears in the name of the food or is usually associated with that name by the consumer, e.g. foods claiming “made with/contains

whole grains", are required to provide a quantitative indication of ingredients (QUID) of whole grains on the packaging [19]. This rule also applies to foods carrying a whole-grain label.
Since many consumers may regard foods labelled "whole grain" as healthy, it is advisable that such foods meet accepted standards for healthy foods, e.g. nutrient profiles on sodium, fat and sugars.

1.5. WHOLE-GRAIN DEFINITIONS IN DIFFERENT COUNTRIES AND ORGANISATIONS

Worldwide, several countries, organisations, or scientists have defined whole grains and whole-grain food products either in national legislation or as a code of conduct, e.g. guidelines for the food industry or scientists. In this chapter we present the most important contributions to the discussions on unique worldwide definitions (see table 1.3). Definitions from individual countries and organisations are presented in Appendix A.

Table 1.3 – Important worldwide contributions to the discussion of definitions of whole grains and whole-grain food products.

Issuing body	Species included in definition	Whole-grain food products definition
AACC	All seeds from the *Poaceae* family and pseudo-cereals (amaranth, buckwheat and quinoa)	27 g whole grain/100 g product
Healthgrain Forum	Commonly known cereal species (wheat, oats, rye, barley, maize, rice, millets, sorghum, teff, and wild rice), more uncommon cereals (Canary seeds, Job's tears, Fonio), and pseudo-cereals (amaranth, buckwheat and quinoa)	At least 30% whole-grain ingredients on a dry-weight basis and more whole-grain ingredients than refined-grain ingredients
Whole Grain Initiative	Cereal grains from the *Poaceae* family and pseudo-cereals (amaranth, buckwheat and quinoa) used for human consumption	Suggested, not adopted: Contain at least 50% whole grains on dry-weight basis. Foods containing at least 25% whole grains on dry-weight basis may make a front-of-pack claim on the presence of whole grains but cannot designate "whole grain" in the product name.

American Association of Cereal Chemists

In 1999 the American Association of Cereal Chemists (AACC) defined whole grains as follows: "Whole grains shall consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components — the starchy endosperm, germ and bran — are present in the same relative proportions as they exist in the intact caryopsis" [20].

In a letter from the AACC (later named AACC International) to the American Food and Drug Administration, it is stated: "Cereals are generally considered to be the seeds of grasses from the

Poaceae family. Pseudocereals are seed heads of a number of different species of plants that do not belong to the grass family and do not include legumes or oilseeds". "Pseudocereals should be included with the cereals because the grain heads of pseudocereals are used in the same traditional ways that cereals are used, such as in the making of bread, starch staples and side dishes. In addition, the overall macronutrient composition (proportions of carbohydrate, protein and fat) of cereals and pseudocereals is similar" [21]. Pseudo-cereals are listed as amaranth, buckwheat, quinoa and wild rice.

This definition was later extended to specify whole-grain food products: "A whole grain food must contain 8 grams or more of whole grain per 30 grams of product" (27 g/100 g) [22]. The distinction of 8 grams of whole grains per 30 grams of product was made to take into account food products that include refined grains, which currently enjoy higher levels of consumer acceptance.

The AACCI has also approved a statement on sprouted grains: "Malted or sprouted grains containing all of the original bran, germ, and endosperm shall be considered whole grains as long as sprout growth does not exceed kernel length and nutrient values have not diminished. These grains should be labelled as malted or sprouted whole grain" [23].

Healthgrain Forum

The Healthgrain Forum, a collaboration between scientists from academia and food industry, developed a definition of whole grain including a specification of included grains and milling processes: "Whole grains shall consist of the intact, ground, cracked or flaked kernel after the removal of inedible parts such as the hull and husk. The principal anatomical components - the starchy endosperm, germ and bran - are present in the same relative proportions, as they exist in the intact kernel. Small losses of components – that is, less than 2% of the grain/10% of the bran – that occur through processing methods consistent with safety and quality are allowed." [24].
The definition includes commonly known cereal species (wheat, oats, rye, barley, maize, rice, millets, sorghum, teff, and wild rice), more uncommon cereals (Canary seeds, Job's tears, Fonio), and pseudo-cereals (amaranth, buckwheat and quinoa).

The Healthgrain Forum suggests that whole-grain food products should contain at least 30% whole-grain ingredients on a dry-weight basis and more whole-grain ingredients than refined-grain ingredients [17].

Whole Grain Initiative

Recently, WGI suggested a definition of whole grain: "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." [25]. The term "whole grains" applies to cereal grains from the *Poaceae* family and the pseudo-cereals (amaranth, buckwheat and quinoa) that are used for human consumption.

In the WGI definition, grain processing is not specified but it is mentioned that "processing of cereals and their fractions includes dry and wet methods which should be executed according to good manufacturing principles and consider the following points: 1) A batch of grain consisting of one or more varieties or classes of a single species may be temporarily separated into fractions and considered whole grain if the fractions are recombined in the original proportions. 2) Grain fractions from one or more varieties or classes of a single species that originated from different batches and combined to reflect the original proportions are considered whole grain. 3) Small, generally unavoidable losses of components, that occur through processing consistent with safety and quality standards are allowed. 4) Fermented, malted or sprouted grains containing all of the original bran, germ and endosperm shall be considered whole grains as long as nutrient values have not diminished; for malted or sprouted grains the length of the sprout should not exceed kernel length" [25].

1.6. CONCLUSION

Which species should be included in a whole-grain definition

Whole grains are defined as intact grains or processed grains (e.g. ground, cracked or flaked) where the three fractions – endosperm, germ and bran – are present in the same relative proportion as in the intact grains. Some grains have an inedible outer layer called the hull. Removing the hull does not affect the grains' status as whole grains.

Inclusion of seeds from species of the grass family, *Poaceae,* shown to have beneficial effects related to either human health or the environment in the definition of whole grains should be restricted to species that are commonly eaten by humans, or species acceptable as part of a human diet whose intake should be increased as part of a healthy diet.

Documentation for pseudo-cereals' health benefits to humans is uncertain, since most prospective cohort studies that show a positive association between whole-grain intake and health did not investigate associations with pseudo-cereals. However, as pseudo-cereals (amaranth, buckwheat and quinoa) are used as foods in similar ways as cereal grains, and their nutrient content is somewhat similar (except for fibre composition), they may be considered whole grains.

How much processing is acceptable?

For safety reasons, whole grains may undergo a light cleaning such as removing of stones and dirt.

It is not possible to define a standard ratio between the three grain fractions, endosperm, germ and bran, since it varies within and between species, and it is affected by grain size. During milling, the grains can be ground very fine. That may affect health effects, e.g. the effect on digestion, satiety and composition of human gut microbiota. Currently, no studies give indications of a level of milling, where there is still a positive health effect of whole grains. Until enough studies are available to set such a limit, it could be set where the grains are ground so finely that no intact cellular structures can be recognised in a bright-field light microscope.

It is recommended that the recombination of fractions after milling on roller mills be done at the mill.

Germinated (sprouted) grains can be included in the definition of whole grains if the level of germination is well defined, e.g. the germination time or the length of the sprout in proportion to the kernel length, and an acceptable impact on nutrient content.

Fermentation of whole grains (or part of the grains) before they are used as ingredients in food products is only compatible with the whole-grain concept if nutrient loss, in particular fibre loss, can be kept within an acceptable limit.

The use of fibre-degrading enzymes before or during fermentation, leading to degradation of a significant part of the fibres, is not compatible with the whole grain concept.

To ensure the concept "whole grain" can be associated with human health benefits, more studies are required for setting criteria for particle size after grinding and acceptable nutrient loss during sprouting and fermentation.
Our proposition is that an acceptable loss due to processing, including cleaning should be less than 2% of the grain and 10% of the bran.

How much whole grain should be included in a whole-grain food product?

Whole grains should be the main ingredient in whole-grain food products, i.e. whole grains should constitute more than 50% of the dry matter. However, in countries where consumers are not accustomed to whole grains it may be necessary to set a lower requirement for whole-grain food products to be accepted as part of a regular healthy diet. If national regulations regarding whole-grain definitions exist, they should be paramount to a common European definition.

Consumers may regard foods labelled "whole grain" as healthy. Thus, from a health perspective such foods should also meet accepted standards for healthy foods, e.g. nutrient profiles.

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CHAPTER 2
Whole grain: composition and nutrients

Adapted and translated from "Nutrients and other constituents of whole grains" by Helle Nygaard Lærke & Knud Erik Bach Knudsen in "Whole grain: definition and evidence base for the recommendation of whole-grain intake in Denmark" [1].

By Sofia de Moura Lourenço, Danish Cancer Society

The aim of this chapter is to give a short introduction to and an overview of the generic composition of whole grains and their nutrients, micronutrients, and bioactive compounds.

2.1. COMPOSITION AND STRUCTURE

Overall, grain kernels have the same anatomical structure and include three distinct fractions: bran, endosperm, and germ (see figure 2.1.).

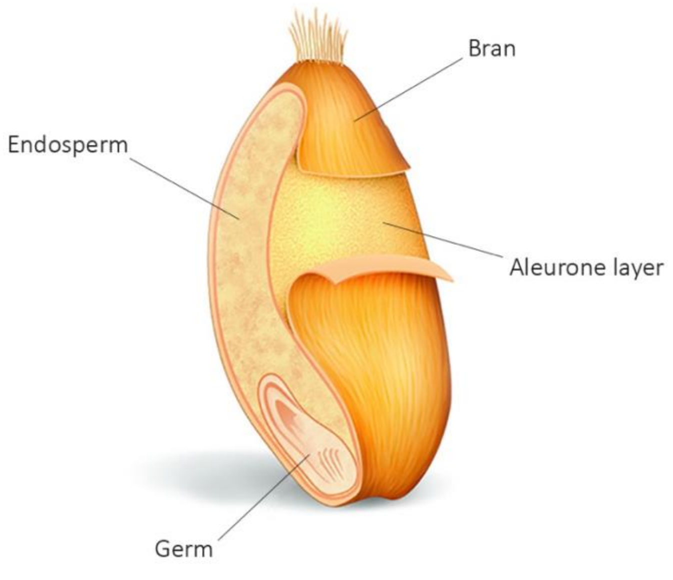

Figure 2.1 – Anatomy of the grain kernel. Illustration by Dalhoff Design, courtesy of the Danish Whole Grain Partnership.

The bran is the seed coat of the edible grain kernel, and is composed by 1-2 layers: both the outer layer (pericarp) and the inner layer (testa) are composed primarily by strongly lignified cell walls with a high content of cellulose and arabinoxylans. It is rich in antioxidants, minerals, vitamins and dietary fibres.

The endosperm is the nutrient storage fraction, and is the largest fraction of the kernel. It is composed by an outer aleurone layer with thick cell walls, and a higher content of dietary fibres, essential amino acids, and minerals. The aleurone layer also has a high concentration of fats and B-vitamins. The remaining endosperm fraction is composed by thin cell walls and stores high quantities of starch embedded in a protein matrix [2]. During milling, the aleurone layer is separated from the endosperm and gets mixed up with the bran fraction. Thus, the aleurone layer is not included in refined grain products.

The germ is the cereal plant embryo, with thin cell walls and a high content of protein and fat. This fraction is also rich in vitamins, minerals, and a number of other phenolic and bioactive compounds.

2.2. NUTRIENTS, MICRONUTRIENTS, AND BIOACTIVE COMPOUNDS

For the most part, grain kernels of cereals have the same anatomy, but there are slight differences in structure and nutrient content between species and variants, e.g. a higher lipid content in oats and lower dietary fibre content in millet and rice [3]. It is important to have such differences in mind in terms of the nutritional value and culinary properties of both whole kernels (either intact or ground) and different milled fractions like flour or bran.

Grains are primarily a source of carbohydrates with a high content of starch and dietary fibre, and low contents of sugars and fructans. Starch is concentrated in the endosperm, and dietary fibres are concentrated in the bran and the aleurone layer. The germ and the bran are the fractions that contain most of the vitamins, minerals, as well as a series of phenolic and other bioactive compounds. Furthermore, the germ has a high content of fats with a high proportion of mono- and polyunsaturated fatty acids, and a high content of plant sterols.

Most of the kernel's enzymes are concentrated in the germ and the bran fraction. The type and amount of enzymes in flour influence its technological properties, as well as its food shelf life. In addition, the extraction rate[a] and degree of grinding[b] are important for the content of different nutrients and bioactive components.

Though botanically distinct, pseudo-cereals and pseudo-cereal products can be used culinarily in a similar fashion as cereal grains and cereal-based products [4]. There are some differences between kernels of cereals and pseudo-cereals in terms of anatomical composition, but their nutrient content is somewhat similar [5]. Thus the nutritional impact of replacing cereal grains in the diet with pseudo-cereals is limited. However, there is considerable difference between cereals and pseudo-cereals in the content and proportion of different types of dietary fibre (see also Chapter 1).

[a] Extraction rate is the percentage of finished product obtained from the milling of a cereal. An extraction rate of 100% expresses that the whole kernel is milled and used. An extraction rate of 72%, e.g. as in white flour, expresses that only 72% of the kernel – starting from the kernel core – is part of the flour or other product, and that the outer 28% has been removed.

[b] The degree of grinding expresses the size of the particles resultant from the grinding process. The higher the degree of grinding, the smaller the particles in the final product.

An overview of nutrients, phenolic and other bioactive compounds common in cereal grains is presented in Table 2.1.

Table 2.1. – Overview of nutrients and other bioactive compounds present in grain kernels of cereals. A majority of the same nutrients and bioactive compounds are also found in pseudo-cereals, but might differ in terms of the proportions presented here, since this overview is based on the nutrient content of cereals alone.

MACRONUTRIENTS	
Carbohydrates	**Starch** Starch is the grain seed's primary energy source. Starch encapsulated in intact cell walls (e.g. due to a coarser/lower degree of grinding or in whole kernels) is digested more slowly than starch from products with a higher degree of grinding (hence smaller particles). It is mainly concentrated in the endosperm. Hence, the starch content is higher in products with a lower extraction rate (e.g. white wheat flour).
Carbohydrates	**Dietary fibre** The majority of dietary fibre in cereals is composed by non-starchy polysaccharides and lignin. The most important polysaccharides in dietary fibre are arabinoxylans, β-glucans and cellulose. There are two types of dietary fibre: soluble and insoluble. Soluble dietary fibre increase the viscosity in the intestines, hereby influencing their emptying rate as well as digestion and absorption processes. One example is seen with the cholesterol-reducing properties of oats largely due to the amount of soluble fibre (mainly viscosity-enhancing β-glucans) [6]. Soluble fibre is digested very little in the small intestine, and is instead metabolised by the microorganisms in the colon. Insoluble fibre are more resistant to digestion by microbiota in the colon, and act primarily as undigested filler that influences the intestines' peristaltic movements. All cereals contain the same type of cell wall polysaccharides, but the proportions between types are different between cereal species. Lignin and cellulose are concentrated in the outer layers (pericarp and testa), while arabinoxylans and β-glucans are concentrated in the aleurone and sub-aleurone layers as well as in the endosperm. Since the majority of dietary fibre is concentrated in the bran and aleurone fractions, an extraction rate of 80% or more results in a higher content of dietary fibre in cereal products.
Protein For the majority of cereals, approximately 70% of protein is found in the endosperm fraction. Protein quality – determined by the digestibility [c] and quantity of essential amino acids – is typically low in cereals, due to the limited content of some essential amino acids, mostly lysine, but also tryptophan, methionine, isoleucine, valine and threonine. E.g., oats have a better protein quality than most other cereals, since the lysine content in this species is higher. Nonetheless, since a large part of the human diet is composed by cereal-based products, whole grains and whole-grain products can be good protein sources, particularly if consumed as part of a varied diet.	
Fat The majority of grain kernels have a fat content of 1,5-4%, but oats are an exception with a fat content of 5-9%.	

[c] Amount of nutrient absorbed by the individual.

These fats are mostly concentrated in the germ fraction, but there is also a considerable concentration of fats in the aleurone layer [2]. Fats in grain kernels are composed by both oleic acid and polyunsaturated fatty acids (mostly linolenic acid).

MICRONUTRIENTS

Minerals

Whole grains contribute to the human diet with a range of minerals like iron, magnesium, phosphorus, zinc, copper, manganese, and selenium. Calcium, potassium and sodium are also present in smaller amounts [7].

Minerals are mostly concentrated in the kernel's bran fraction. As such, the mineral content in flour is highly dependent of the extraction rate. A higher extraction rate (e.g. whole-grain wheat flour) can result in a 2-4 times higher mineral content than a lower extraction rate (e.g. refined wheat flour).

The processing or preparation of whole grains is important for the bioavailability of minerals. Grain kernels contain phytic acid, which binds and impairs the absorption of minerals like iron, zinc and magnesium. Phytic acid is digested by the enzyme phytase, which is naturally present in cereals during batter or dough preparation. Lactic acid bacteria can also digest phytic acid, which increases the bioavailability of minerals in bread prepared with sourdough. Hence, a longer rising time or an effective fermenting of the cereals will increase the digestion of phytic acid and consequently increase the bioavailability of minerals from whole grains.

Vitamins

Grains are characterized by a high content of both B-vitamins (B1: thiamine; B2: riboflavin; B3: niacin; B5: pantothenic acid; B6: pyridoxin; B7: biotin; and B9: folate) and E-vitamins (tocopherols and tocotrienols).

The aleurone layer is rich in several B-vitamins, which is why a high extraction rate is important for the content of B-vitamins in whole grains and whole-grain products.
E-vitamins are primarily antioxidants that inhibit lipid oxidation in biological membranes. The germ fraction is rich in E-vitamins in all cereals, but the proportion of tocopherols and tocotrienols varies between species. E.g., oats contain twice as much E-vitamins than durum wheat or spelt.

Since both germ and bran are removed in milling processes for refined flours, a higher extraction rate (typical for whole-grain flours) gives a higher content of these vitamins.

BIOACTIVE COMPOUNDS

Lignans

Lignans are bioactive compounds that act as plants' natural defence substances. Lignans of plant origin are digested by microbiota in the human gut and become enterolignans which are absorbed by the human body. Research suggests enterolignans might decrease the risk of certain forms of cancer (see Chapter 3).

Lignans are primarily concentrated in the bran fraction of cereals, and as such whole grains and whole-grain products are rich in these compounds. Rye products are especially rich in lignans, but all cereals species contain these compounds, and up to 20 different types have been identified.

Alkylresorcinols

Alkylresorcinols are phenolic lipids composed by long aliphatic chains and resorcinol-type phenolic rings [8]. These compounds are concentrated in the bran fraction and aleurone layer of some species of cereals (e.g. rye, wheat), and are otherwise rare in nature. Hence, alkylresorcinols are good biomarkers of diets rich in whole-grain rye and whole-grain wheat products [9].

Other phenolic compounds

The bran fraction and particularly the aleurone layer are also rich in antioxidants like ferulic acid, coumaric acid and other derivates from cinnamic acid, as well as flavonoids, avenanthramides and similar compounds. The composition and content levels of such phenolic compounds in the outer layers of grains varies significantly between cereals species.

Phytosterols

Phytosterols are secondary metabolites known primarily for their cholesterol lowering effect [10] (see also Chapter 3). Phytosterols are mainly found in the bran and germ fractions of the kernels, hence a higher extraction rate results in higher contents in whole-grain products [11].

The profiles of phytosterols vary considerably between cereal species, and in-between species variations depend on both genotypes, environmental factors, growing locations, and cultivation methods [11].

2.3. CONCLUSION

Of the three main compartments, the bran and germ parts have the highest concentrations of vitamins, minerals, dietary fibre, and a series of other bioactive compounds. Hence, whole grains and whole-grain products contain these nutrients and bioactive compounds in significantly higher proportions than refined grain products. Many of these nutrients and bioactive compounds are either shown to or hypothesized to be associated with the health benefits of whole-grain consumption, as is described further in Chapter 3 of this report.

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CHAPTER 3
Whole-grain intake and risk of disease, mortality and overweight

By Sofia de Moura Lourenço and Anne-Sofie Q. Lund, Danish Cancer Society

3.1. INTRODUCTION

Noncommunicable diseases (NCDs) like cardiovascular diseases (CVDs), cancer, and type 2 diabetes, are among the leading causes of morbidity and mortality in the European Region [1]. In addition, 30-80% of adults in the countries in this region have overweight or obesity [1], which are well established risk factors for these NCDs [2] and are associated with higher overall mortality [3].
Poor quality diets, characterized by a low intake of fruit and vegetables, whole grains, nuts, seeds and fish, but a high intake of sodium, sugar sweetened beverages, fast food and other high-calorie foods, contribute significantly to the global burden of disease, and increase the risk of NCDs [4].
Associations between whole-grain intake and its potential risk reduction regarding CVDs, type 2 diabetes, some cancer types, and mortality have been investigated previously, as well as the impact of whole-grain intake in weight changes and adiposity measures [5–9].

This chapter aims to provide an update on the latest and highest level of evidence available concerning the associations between whole-grain intake and the development of CVDs, type 2 diabetes, cancer, risk of overall mortality, and overweight.

3.2. METHODOLOGY

Search strategy and selection of studies

First, we searched for recent meta-analyses and expert reports evaluating the influence of whole-grain intake in the development of CVDs, type 2 diabetes, cancer, overall mortality, and overweight. We then conducted a systematic literature review of evidence published after the cut-off dates for the systematic searches conducted under the scope of these reports and meta-analyses (from here on referred to as either "WholEUGrain project search" or "WholEUGrain umbrella review").

The WholEUGrain review was conducted as an umbrella review due to the number of themes revised, and hence the large amount of published evidence. This method provides a summary of existing published systematic reviews and meta-analyses, and compares whether different studies posing similar research questions independently reach similar results, and draw similar conclusions. For a detailed description of the search protocol, search terms, inclusion and exclusion criteria see Appendix B.

In the evidence hierarchy, meta-analyses and systematic literature reviews range as the highest levels of evidence, preferably based on data from randomized controlled trials (RCTs), followed by prospective cohort studies if no relevant RCTs have been conducted. However, noncommunicable diseases like cancer, type 2 diabetes or CVDs develop over decades, and it is not feasible to conduct RCTs for such a long time span [10]. The same applies to the effects of whole-grain intake in assessing the risk of overall mortality. Meta-analyses and systematic reviews based on data from epidemiological studies (e.g. prospective cohort studies) are thus more relevant for the evaluation of the influence of long-term intake of high vs. low quantities of whole grains in the development of such conditions.

For this reason, the systematic WholEUGrain umbrella review is limited to systematic reviews and meta-analyses of data from cohort studies for the sections on CVDs, type 2 diabetes, cancer, and mortality. In the overweight section, the review includes systematic reviews and meta-analyses of both RCTs and prospective cohort studies, since RCTs can be conducted for periods of time long enough to detect changes in different body weight parameters of relevance.

The two authors of the WholEUGrain umbrella review worked independently, and performed searches that yielded two separate lists of title-abstract records. Both authors screened these records and applied inclusion criteria previously agreed upon. Copies of full-text articles for title-abstract records coded as 'provisionally eligible' were retrieved, and an independently duplicate screening of full-text articles was then performed. Any disagreements were identified and discussed between the authors until consensus was reached, and a final list of included full text articles was complete for each section.

The quality and risk of bias of the included studies was assessed with two quality tools. For studies pertaining the sections on diseases and mortality a quality-grading scheme was developed adapted from the guidelines of the USA's National Institutes of Health [11]. For studies pertaining the section on overweight a quality-grading scheme was adapted from the approach of the World Cancer Research Fund International (WCRF) [12,13] (see Appendix C for details regarding these tools).

Data analysis and evidence judgement

For the included systematic reviews and meta-analyses in the WholEUGrain umbrella review, the following predefined information and data were extracted and consolidated into overview tables. These data included: study characteristics (type, number, country of origin); exposure (whole grains or whole-grain food products – see Box 3.1); outcomes; type of analyses and sub-analyses performed; total number of cases or participants in intervention arms; summary of risk measures pertaining disease/mortality/overweight parameter; and heterogeneity measures.

BOX 3.1 – Whole grains and whole-grain products (see also Chapter 1)

Whole grains are defined as intact grains or processed grains (e.g. ground, cracked or flaked) where the three fractions endosperm, germ and bran are present in the same relative proportion as in the intact grains. These are 100% whole grains.

Whole-grain food products are products with whole grains as the primary ingredient, but other ingredients (e.g. water, salt or others) are also present.

1 serving = 16 g whole grains = 30 g whole-grain product *

*From: The Whole Grains Council. U.S Dietary Guidelines and Whole Grain. Available at: https://wholegrainscouncil.org/whole-grains-101/how-much-enough/us-dietary-guidelines-and-wg. This is a commonly agreed-upon rule-of-thumb among experts, and this definition of serving-size is used in the present report.

Heterogeneity was considered low when accounting for less than 30% of the variability in point estimates, medium-level for 30-50%, and high for statistically significant levels above 50% variability, in accordance to the WCRF's Continuous Update Project (CUP) approach [10].

Results for the studies retrieved through the WholEUGrain umbrella review were gathered and consolidated, and compared to the previously retrieved meta-analyses and expert reports on the different themes, and evaluated in the light of the evidence quality and conciliation with possible explanatory mechanisms. The overall evidence judgement was based on the criteria listed by the WCRF's CUP project in their Third Expert Report [10]. A summary of these criteria is available in Appendix D.

3.3. CARDIOVASCULAR DISEASES

Background

Cardiovascular diseases (CVDs) are a group of ailments related to the heart and blood vessels. The most common are coronary heart disease (CHD)[a], and cerebrovascular disease (commonly known as stroke). Other types include heart failure, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism [14]. CVDs are the leading cause of death globally. In 2016, an estimated 17.9 million people died from CVDs worldwide. 85% of those deaths were due to heart attack and stroke [14].

The most important behavioural risk factors of CVDs are unhealthy diet patterns, physical inactivity, tobacco, and excessive alcohol consumption [14], and an estimated 80% of all cardiovascular diseases could be prevented [15].
It is well established that a diet high in saturated fat, trans-fatty acids, and salt, combined with a low intake of fruits, vegetables, and fish increases the risk of cardiovascular diseases [16]. Research focus on the preventive effects of whole-grain intake is rather more recent.

Epidemiological evidence of whole grains and CVDs

The evidence presented here is based on:

1. A systematic literature review and meta-analysis by Aune and colleagues, that includes a summary of evidence gathered until April 3, 2016 [6].
2. The WholEUGrain umbrella review including data from systematic reviews and meta-analyses of prospective cohorts, conducted for the period April 4, 2016 through February 2020. For a detailed description of search terms and inclusion criteria see Appendix B.

The flow chart of the search and selection of studies for the CVD section of the WholEUGrain umbrella review is presented in Figure 3.3.1. A total of four new relevant publications were retrieved for this section, of which two were good quality systematic reviews that included meta-analyses [17,18], and two were systematic reviews alone of fair quality [19,20]. A descriptive overview of the included studies is available in Table E.1 in Appendix E.

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[a] Also referred to as coronary artery disease (CAD) or ischaemic heart disease [80].

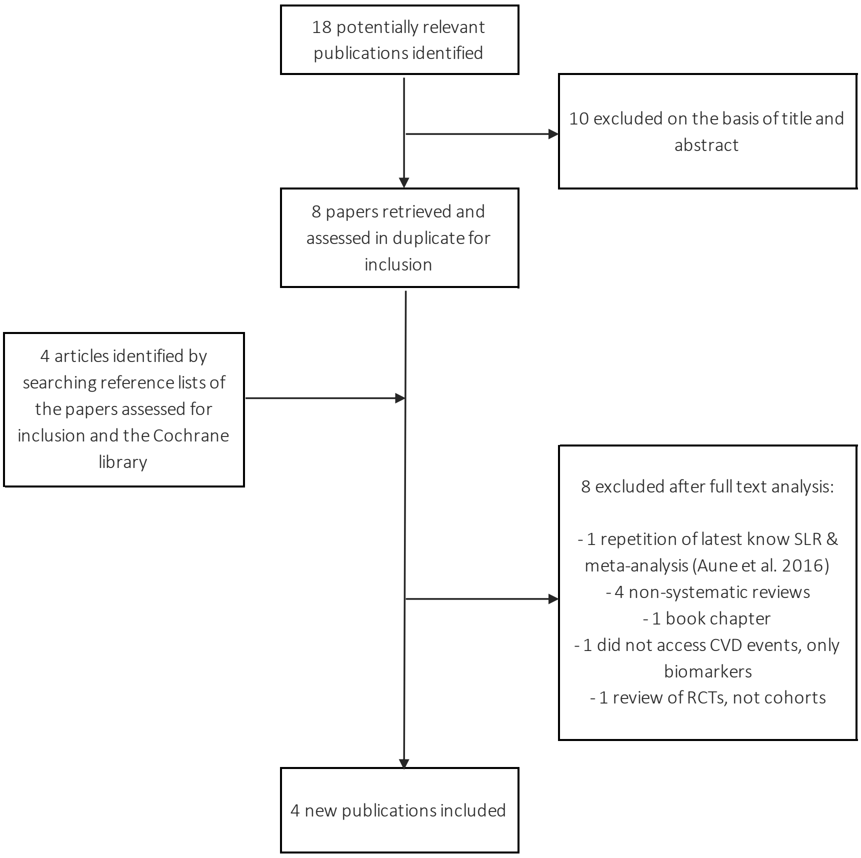

Figure 3.3.1 – Flow chart of the search for the CVD section in the WholEUGrain umbrella review.

Cardiovascular disease (overall risk)

The meta-analysis by Aune and colleagues confirmed conclusions of previous studies, showing that a high intake of whole grains is associated with a lower risk of overall CVD (relative risk (RR) 0.84; 95% confidence interval (CI) 0.80-0.87]; 25,436 cases from 9 cohorts), with no heterogeneity [6]. The summary RR for 90 g whole-grain products/day (3 servings) confirmed this association (RR 0.78; 95% CI 0.73-0.85; 26,243 cases from 10 cohorts), and even though the strongest association was observed for an intake up to 50 g whole-grain products/day ($p_{non\text{-}linearity} < 0.001$, 9 cohorts), higher intakes up to 200 g whole-grain products/day (6.5 servings) were also associated with lower risk, with medium heterogeneity [6].

The WholEUGrain umbrella review identified two new references reviewing relevant data for overall risk of CVD [18,19]. One good quality meta-analysis showed an inverse association between the highest intake of whole grains and the risk of CVD, without heterogeneity [18]. This association was further confirmed by a dose-response analysis that showed a 2% decrease in risk per 15 g whole-grain products a day (Table 3.3.1), and very low, non-significant heterogeneity [18]. However, it should be noted that results from this meta-analysis are based on data from only three prospective studies, two of which already incur in the previous review by Aune and colleagues (2016), as shown in figure 3.3.2. Hence, the similarity of results is explained by the repetition of data sources.

Table 3.3.1 – Summary of findings from the included meta-analyses in the CVD section.

	High *vs.* low analysis						Dose-response analysis					
	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value		Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
Reynolds 2019 [18]	3	4,357	0.89 (0.81–0.98)	0%	0.684		15	3	4,357	0.98 (0.96–0.99)	15%	0.948
Aune 2016 [6]	9	25,436	0.84 (0.80–0.87)	0%	0.48		90	10	26,243	0.78 (0.73–0.85)	40%	0.09

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het}: significance value for the heterogeneity level; WG-products: whole-grain products.

Furthermore, one fair quality systematic review was identified, that describes results from studies with different types of outcomes, spanning between markers of metabolic risk to incidence and outcomes of CVD. Of the 20 articles included in the review 17 found a significant inverse association between whole-grain intake and at least one CVD-related outcome [19]. However, data stems from a mix of both prospective cohorts and cross-sectional studies, and no dose-response meta-analyses were conducted.

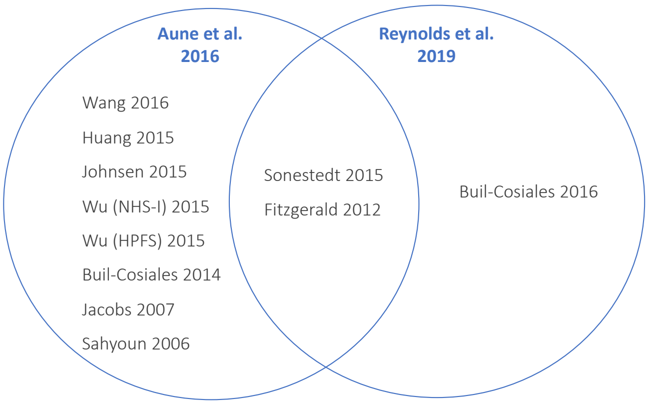

Figure 3.3.2 – Prospective cohort studies included in the meta-analyses of data for cardiovascular diseases.

Coronary heart disease

The meta-analysis by Aune and colleagues confirmed conclusions of previous studies, showing that a high intake of whole grains is associated with a lower risk of CHD (RR 0.79; 95% CI 0.73-0.86; 6,713 cases from 6 cohorts) [6]. The summary relative risk for 90 g whole-grain products/day confirmed this association (RR 0.81; 95% CI 0.75-0.87; 7,068 cases from 7 cohorts), and even though the strongest inverse association was found from 0 to 90 g of whole-grain products per day (3 servings), the inverse association was also found for up to 210 g/day (7 servings) ($p_{non\text{-}linearity} < 0.0001$, 7 studies) [6]. The heterogeneity was low for these analyses.

The WholEUGrain umbrella review identified three new references reviewing relevant data [17–19]. Two good quality meta-analyses showed inverse associations between the highest intake of whole grains and the risk of CHD [17,18]. This association was further confirmed by dose-response analyses, that showed a decrease in risk of CHD for each additional 15-30 g whole-grain products per day [17,18] (Table 3.3.2), and there was also evidence of a non-linear dose-response association in one of the studies [17]. The risk of CHD decreased by

17% with increasing intake of whole grains up to ~100 g whole-grain products/day ($p_{non\text{-}linearity} < 0.001$, 5 studies) [17]. Heterogeneity was high in one of the meta-analysis [18], but low to medium for the other [17].

Table 3.3.2 – Summary of findings from the included meta-analyses in the CHD section.

	High *vs.* low analysis					Dose-response analysis					
	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
Reynolds 2019 [18]	6	7,697	0.80 (0.70–0.91)	79%	< 0.001	15	6	6,587	0.93 (0.89–0.98)	67%	< 0.001
Bechthold 2019 [17]	7	8,652	0.85 (0.81–0.90)	0%	0.72	30	5	6,557	0.95 (0.92–0.98)	46%	0.11
Aune 2016 [6]	6	6,713	0.79 (0.73–0.86)	0%	0.63	90	7	7,068	0.81 (0.75–0.87)	9%	0.36

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het}: significance value for the heterogeneity level; WG-products: whole-grain products.

However, it should be noted that data from the same four prospective cohorts is included in all the meta-analyses summarized here, and data from one recent prospective cohort is included in two of them, as shown in figure 3.3.3. Hence, the similarity of results might be driven by the use of some of the same data.

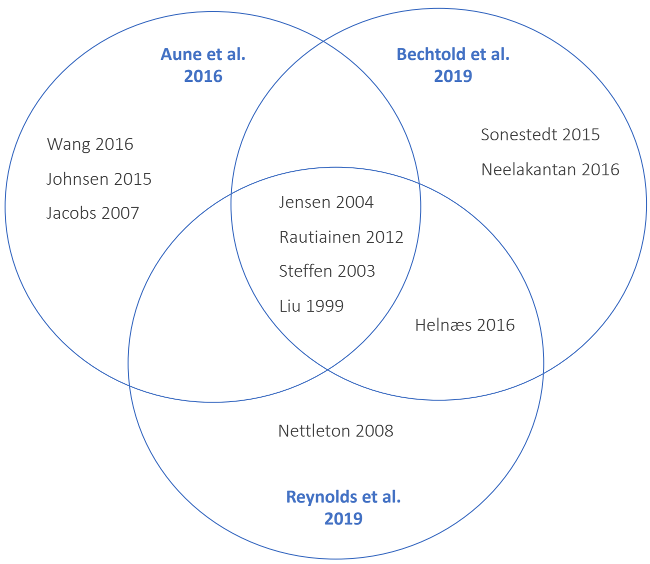

Figure 3.3.3 – Prospective cohort studies included in the meta-analyses of data for coronary heart disease.

One systematic review reported data from only one prospective study that found a lower risk of CHD associated with a higher whole-grain intake [19]. However, the prospective study in case is also included both in the WholEUGrain umbrella review and the review by Aune and colleagues (2016), hence not contributing new data to the results already described.

Stroke

In the meta-analysis by Aune and colleagues, neither the high vs. low nor the dose-response analyses showed a significant association with the risk of stroke [6]. However, the same study reported evidence of non-linearity between whole-grain intake and risk of stroke ($p < 0.001$) up to 120-150 g whole-grain products/day [6].

Table 3.3.3 – Summary of findings from the included meta-analyses in the stroke section.

	High *vs.* low analysis					Dose-response analysis					
	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
Reynolds 2019 [18]	3	1,247	0.86 (0.61–1.21)	65%	0.057	15	3	1,247	0.97 (0.92–1.02)	70%	0.028
Bechthold 2019 [17]	7	11,116	0.91 (0.82–1.02)	53%	0.05	30	4	5,863	0.99 (0.95–1.03)	65%	0.04
Deng 2017 [20] *	4	NR	0.83 (0.69–1.02)	NR	NR	--	--	--	--	--	--
Aune 2016 [6]	5	1,885	0.87 (0.72–1.05)	32%	0.21	90	6	2,337	0.88 (0.75–1.03)	56%	0.04

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het}: significance value for the heterogeneity level; WG-products: whole-grain products; NA: not reported. * This is in fact the result for the MA performed by Mellen et al. (2008). Whole grain intake and cardiovascular disease: a meta-analysis. Nutr Metab Cardiovasc Dis 18:283-290.

The WholEUGrain umbrella review identified three new references reviewing relevant data on stroke [17,18,20]. Two good quality meta-analyses showed a non-significant inverse association between the highest intake of whole grains and the risk of stroke, with high heterogeneity between studies [17,18]. This association was not observed in neither the dose-response analyses (Table 3.3.3) nor the non-linear dose-response analyses. However, it should be noted that data from three of the same prospective cohorts is included in both meta-analyses identified by the WholEUGrain umbrella review and the meta-analysis by Aune and colleagues, as shown in figure 3.3.4. Hence, the similarity of results might be driven by the use of some of the same data.

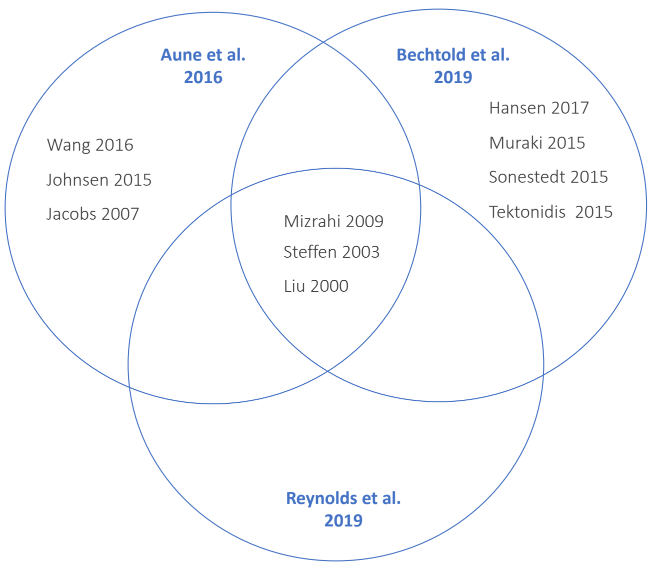

Figure 3.3.4 – Prospective cohort studies included in the meta-analyses of data for stroke.

One systematic review reported the results of one meta-analysis[b] previously conducted by other authors, that showed no association with the risk of stroke [20].

Heart failure

The review by Aune and colleagues from 2016 did not discuss the association between whole-grain intake and heart failure.

The WholEUGrain umbrella review identified one reference reviewing relevant data [17]. This was a good quality meta-analysis that showed an inverse association between the highest intake of whole grains and the risk of heart failure, with low heterogeneity [17]. This association was further confirmed by a dose-response analysis, that showed a decrease in risk of heart failure for each additional 30 g of whole-grain products/day (1 serving) without heterogeneity between the included studies (Table 3.3.4) [17].

Table 3.3.4 – Summary of findings from the included meta-analyses in the heart failure section.

	High *vs.* low analysis						Dose-response analysis					
	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value		Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
Bechthold 2019 [17]	5	6,455	0.91 (0.85–0.97)	35%	0.19		30	2	2,158	0.96 (0.95–0.97)	0%	0.36

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het}: significance value for the heterogeneity level; WG-products: whole-grain products.

Mechanisms

There is a number of biologically probable mechanisms that can explain cardio-protective associations observed with a higher whole-grain intake.

Fermentation of dietary fibre in the bowel

Whole grains and whole-grain products are rich in dietary fibre, which is fermented by the microbiota in the bowel into short chain fatty acids (SCFAs) [21,22]. Dietary fibre inhibits the reabsorption of bile acids in the gut, which helps regulate cholesterol levels in the body [6,17]. Of notice are β-glucans found in oats, a type of soluble fibre particularly effective in reducing blood LDL-cholesterol, which may reduce the risk of CHD, and are therefore appraised with an EU health claim [23]. In addition, SCFAs inhibit cholesterol synthesis in the liver, further contributing to a down-regulation of LDL-cholesterol levels in the body [6].

Antioxidant and anti-inflammatory properties

Whole grains are a good source of various bioactive compounds, like vitamins, minerals, phytoestrogens and phenolic compounds, many of which have antioxidant properties [17,22,24]. The antioxidant capacity of e.g. phenolic compounds reduces the risk of several cardiovascular risk factors [17,25]. Lower levels of cardiovascular risk factors like hypertension, hypertriglyceridaemia, and lower concentrations of both total and LDL-cholesterol have also been associated with higher whole-grain intake [6]. Whole grains have further

[b] The meta-analysis in question had an "acceptable" quality score (5/11 on the AMSTAR-score).

been associated with reduced levels of inflammatory markers and liver enzymes, which have been associated with a lower risk of CVD as well [6].

Glycaemic response

The high content of dietary fibre in whole grains regulates and improves the postprandial glycaemic response, thus decreasing the development of insulin resistance, which is a risk factor for type 2 diabetes, which in turn is a risk factor for CVD [6,17,18]. A higher whole-grain intake has also been associated with higher levels of the hormone adiponectin, which improves insulin sensitivity and reduces the level of low-grade inflammation in the body [6].

Adiposity regulation

An excessive accumulation of fat in the body increases the risk of CVDs in general [6]. The structure of whole grains and their high dietary fibre content promote increased chewing and yield higher levels of satiation [18]. Also, whole-grain foods typically have a lower energy density and help manage caloric intake [22]. Previous studies have also shown inverse associations between a high intake of whole grains and different adiposity measures [22], which could well be a direct effect of a high whole-grain intake since epidemiological evidence most often has adjusted for body mass index (BMI), suggesting the association seen for whole grains is independent of this adiposity measure [6]. Additionally, an indirect effect of whole grains through the displacement of unhealthy foods or drinks in the diet is also a possible explanation [6]. For instance, Aune and colleagues report that the inverse associations seen for CVD remain significant in studies that adjusted for other known influential dietary components, like intake of red and processed meat, or sugar sweetened beverages [6]. However, we cannot exclude the possibility that high levels of whole-grain intake can also be associated with better diet quality and an overall healthier lifestyle, which can contribute some confounding to the results for whole grains alone [19].

Conclusion – CVDs

The most comprehensive meta-analyses published in recent years confirm there is strong epidemiological evidence that consumption of higher amounts of whole grains is associated with a lower risk of overall CVD and CHD. The dose-response analyses further show that the biggest differences in risk are found for those consuming at least one serving of whole grains (30 g whole-grain products/day) compared to those who consumed none to very low doses, but with further risk reductions observable in those consuming up to 100-210 g whole-grain products/day (approximately 3-7 servings) [6,17]. Also, there is good evidence for the mechanisms explaining this relationship in humans.

For heart failure not as much evidence is available so far, but one good quality meta-analysis with a high number of cases indicates a possible risk reduction with a higher intake of whole grains [17]. Further research including data from more good-quality prospective studies is needed in order to substantiate these results. For stroke the evidence is not clear, possibly due to a small number of studies conducted.

3.4. TYPE 2 DIABETES

Background

Type 2 diabetes (diabetes mellitus) is a metabolic disorder generally characterized by insulin resistance, a condition in which the body does not fully respond to insulin [26]. Due to the impaired insulin response, blood glucose levels continue to rise, releasing even more insulin. In some cases this eventually exhausts the pancreas and insulin production falls significantly, causing even higher blood sugar levels (hyperglycaemia) [26].

Type 2 diabetes is the most common type of diabetes, and accounts for approximately 90% of all diabetes cases [27]. The prevalence of type 2 diabetes has risen severely since 1980. In 2019, an estimated 463 million adults worldwide lived with diabetes (both type 1 and type 2), and this number is projected to increase by 25% in 2030 [28]. Over time, this disease can cause damage to the heart, blood vessels, eyes, kidneys, and nerves. Adults with diabetes have two to three times higher risk of suffering heart attacks and stroke [29], and diabetes also increases the risk of cancer [30].

The most important behavioural risk factors of type 2 diabetes are unhealthy diet patterns, physical inactivity, excessive body fatness, and tobacco [31], and up to an estimated 80% of type 2 diabetes cases could be prevented through healthy diet and regular physical activity [26].

A diet rich in dietary fibre from fruits, vegetables, and whole grains, as well as low intakes of saturated fat, and added sugar, is recommended for the prevention of type 2 diabetes [26]. Research focus on the preventive effects of whole-grain intake independent of dietary fibre is not altogether new.

Epidemiological evidence of whole grains and type 2 diabetes

The evidence presented here is based on:

3. A systematic literature review conducted under the scope of the Cochrane collaboration, that includes a summary of evidence gathered until May 2006 [7].
4. The WholEUGrain umbrella review including data from systematic reviews and meta-analyses of prospective cohorts, conducted for the period May 2006 through February 2020. For a detailed description of search terms and inclusion criteria see Appendix B.

The flow chart of the search and selection of studies for the type 2 diabetes section of the WholEUGrain umbrella review is presented in Figure 3.4.1. A total of six new relevant publications were retrieved for this section, of which five were systematic reviews that included meta-analyses: two of good quality [18,32], and three of fair quality [8,33,34]. The sixth study was a systematic review alone of fair quality [35]. A descriptive overview of the included studies is available in Table E.2 in Appendix E. A summary of findings from the included meta-analyses is presented in Table 3.4.1.

The Cochrane collaboration systematic review reported that five prospective cohort studies consistently found that a high intake of whole grains was associated with lower risk of type 2 diabetes [7]. However, the reviewers considered the evidence to be of week quality, and did not perform dose-response analyses with the available data.

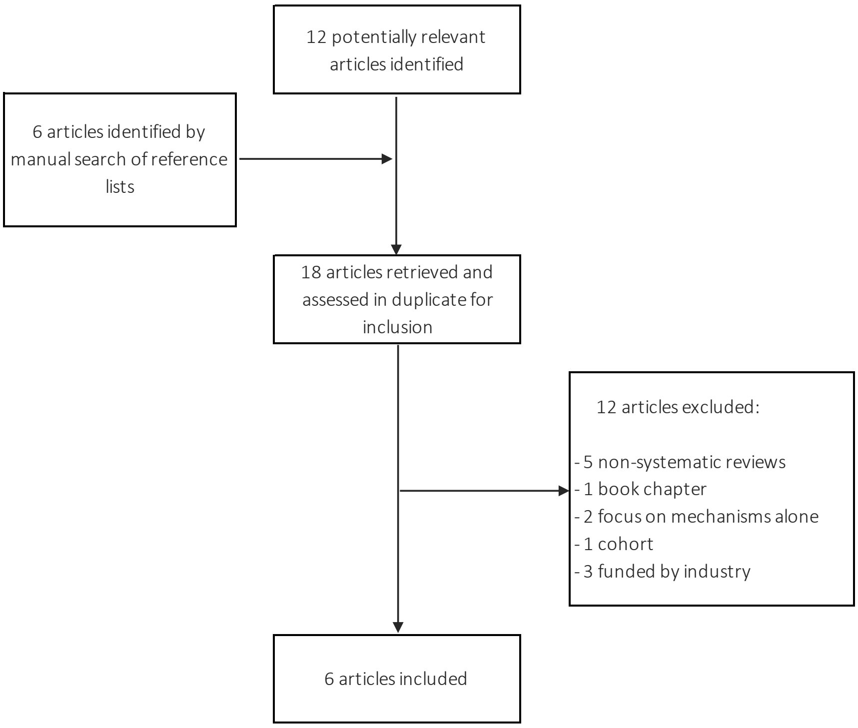

Figure 3.4.1 – Flow chart of the search for the type 2 diabetes WholEUGrain umbrella review.

Table 3.4.1 – Summary of findings from the included meta-analyses in the type 2 diabetes section.

	High vs. low analysis					Dose-response analysis					
	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
de Munter 2007 [33]	--	--	--	--	--	40	6	10,944	0.79 (0.72–0.87)	68%	0.009
Ye 2012 [34]	6	NR	0.74 (0.69–0.80)	0%	0.44	--	--	--	--	--	--
Aune 2013 [8]	9	19,105	0.74 (0.71–0.78)	0%	0.43	90	10	19,829	0.68 (0.58–0.81)	82%	< 0.0001
							5	13,857	0.69 (0.60–0.80) Adjusted for BMI	58%	0.05
									0.53 (0.41–0.69) No BMI adjustment	88%	< 0.001
Schwingshackl 2017 [36]	13	29,633	0.77 (0.71–0.84)	86%	<0.00001	30	12	22,267	0.87 (0.82–0.93)	91%	<0.00001
Reynolds 2019 [18]	8	14,686	0.67 (0.58–0.78)	82%	<0.001	15	7	13,147	0.88 (0.81–0.95)	89%	< 0.001

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het}: significance value for the heterogeneity level; WG-products: whole-grain products; NR: not reported.

The WholEUGrain umbrella review identified 5 meta-analyses that show a significant lower risk of type 2 diabetes (21% to 33%) with the highest levels of whole-grain intake [8,18,33,34,36], with 2 of them finding no heterogeneity for these results [8,34], while the most recent meta-analyses did find considerable heterogeneity [18,33,36]. These results were further confirmed by dose-response analyses performed in 4 of the meta-analyses [8,18,33,36], spanning from a 12% lower risk for an intake of 15 g whole-grain products/day (half serving) [18] up to a 32% lower risk for an intake of 90 g whole-grain products/day (3 servings) [8]. The heterogeneity was high for all dose-response results found [8,18,33,36]. There was also evidence of a non-linear dose-response association with inverse associations (25% to 28%) up to 50-60 g whole-grain products/day (25% lower risk with $p_{non\text{-}linearity} < 0.001$, n=12 cohorts [36]; 28% lower risk with $p_{non\text{-}linearity} < 0.0001$, n=10 cohorts [8]) in two references of good quality.

The WholEUGrain umbrella review also identified one systematic review of fair quality, that did not conduct a meta-analysis [35]. This review reports that the results of six prospective cohorts indicate a consistent inverse association between consumption of mixtures of whole grains and bran (five cohorts) or whole grains alone (one cohort) and the risk of type 2 diabetes [35]. These results are in line with the findings of the meta-analyses included in the WholEUGrain umbrella review.

The WholEUGrain project reviewed studies that had identified additional prospective cohorts and datasets to the ones included in the Cochrane collaboration review, hence adding to the body of evidence regarding whole grains and the risk of type 2 diabetes. At the same time, it should be noted that data reviewed stems from many of the same prospective cohort studies, and several overlaps exist for all the meta-analyses (see Table E.3 in Appendix E). Hence, the similarity of results between the different meta-analyses might be driven by the use of much of the same data.

Mechanisms

There is a number of biologically probable mechanisms that can explain the type 2 diabetes-protective associations observed with a higher whole-grain intake.

Glycaemic response

The high content of soluble dietary fibre, found especially in oats and rye, regulates and improves the postprandial glycaemic response, thus decreasing the development of insulin resistance, which is a risk factor for type 2 diabetes [6–8,17,18,34]. A higher whole-grain intake has also been associated with higher levels of the hormone adiponectin, which improves insulin sensitivity and reduces the level of low-grade inflammation in the body [6,8].

Antioxidant and anti-inflammatory properties

Whole grains are a good source of various bioactive compounds, like vitamins, minerals, phytoestrogens and phenolic compounds, many of which have antioxidant properties [17,22,24,34], and there is evidence suggesting the pathogenesis of diabetes could be associated with increased oxidative stress [7]. Whole grains have further been associated with reduced levels of inflammatory markers and liver enzymes, that decrease the risk of type 2 diabetes as well [8].

Adiposity regulation

An excessive accumulation of fat in the body increases the risk of type 2 diabetes. The structure of whole grains and their high dietary fibre content promote increased chewing and yield higher levels of satiation [18]. In addition, whole-grain foods typically have a higher volume but lower energy density and help manage caloric intake [7,22]. Previous studies have also shown inverse associations between a high intake of whole grains and different adiposity measures, including risk of weight gain over time [22], which could well be a direct effect of a high whole-grain intake since epidemiological evidence most often has adjusted for body mass index (BMI), suggesting the association seen for whole grains is independent of this adiposity measure [6,8]. Furthermore, the greater content of dietary fibre in whole grains reduces the rate of gastric emptying [8] and increases faecal weight, which in turn may contribute to a lower risk of weight gain [34]. Additionally, an indirect effect of whole grains through the displacement of unhealthy foods or drinks in the diet is also a possible explanation [6]. However, we cannot exclude the possibility that high levels of whole-grain intake can also be associated with better diet quality and an overall healthier lifestyle, which can contribute some confounding to the results for whole grains alone [19].

Conclusion – type 2 diabetes

The most comprehensive meta-analyses published in recent years confirm there is strong epidemiological evidence that consumption of higher amounts of whole grains is associated with a lower risk of type 2 diabetes. Dose-response analyses further confirm this association, showing a significant lower risk for those consuming at least half a serving of whole grains (15 g whole-grain products/day) compared to those who consumed none to very low doses. Further risk reductions were observable in those consuming up to 90 g whole-grain products/day (3 servings). In addition, there is fairly good evidence for the mechanisms explaining this relationship in humans.

The current body of evidence for whole grains and the risk of type 2 diabetes builds up on data from a large number of prospective studies. However, it should be noted that the consistency of results found in the included meta-analyses might be driven by a repetition of data from several of the same prospective cohorts.

3.5. CANCER

Background

Cancer is the common generic name for a large group of diseases characterized by the transformation of normal cells into tumour cells in a tissue or organ that grow rapidly and can invade neighbouring organs or even spread to other parts of the body [37].

Cancer is the second leading cause of mortality worldwide [37], and responsible for 20% of deaths in the European region [38]. In Europe 3.9 million new cancer cases were registered in 2018, and cancers of the lung, breast and colorectum are the most common in this region [39]. However, an estimated 40% of all cancer cases in Europe are attributable to potentially modifiable risk factors [40], and could potentially be prevented.

It has previously been established that a high intake of dietary fibre is associated with a lower risk colorectal cancer [41], but only more recently has there been a more specific research focus on the preventive effects of whole-grain intake alone [5]. In addition to dietary fibre, whole grains are also rich in bioactive compounds (see Chapter 2) that may pose cancer preventive effects.

Epidemiological evidence of whole grains and cancer

The evidence presented here is based on:

5. The systematic literature review and meta-analysis by the World Cancer Research Fund's Continuous Update Project (CUP report), that includes a summary of evidence gathered until April 2015 [42].
6. The WholEUGrain umbrella review including data from systematic reviews and meta-analyses of prospective cohorts, conducted for the period May 1, 2015 through February 2020. For a detailed description of search terms and inclusion criteria see Appendix B.

The flow chart of the search and selection of studies for the WholEUGrain project cancer section is presented in Figure 3.5.1.
A total of five relevant publications were retrieved for this section, of which four were systematic reviews that included meta-analyses [18,24,43,44], and one was a systematic review alone [22]. Of these, one was of good quality [18], and four were of fair quality [22,24,43,44]. A descriptive overview of the included studies is available in Table E.4 in Appendix E.

The results reported by these recent publications show that data regarding the intake of whole grains and its potential preventive effects for some types of cancer continues to emerge and add to previously available data. However, the available data is still limited to just a few cohorts, and the meta-analyses we found included a mix of data from both prospective cohorts and case-control studies.

Breast and female reproductive cancers

The WCRF's CUP reports did not discuss the association between whole-grain intake and breast and female reproductive cancers, since there were either too few studies providing relevant data, or the available data was either too inconsistent or of too low quality [45–49].

For breast cancer, the WholEUGrain umbrella review identified two references reviewing relevant data [22,24][c]. A systematic review conducted in 2016 identified three prospective cohort studies, but no significant associations between whole-grain intake and risk of breast cancer were found [22].
The evidence reviewed by a systematic review and meta-analysis published in 2018 indicates a preventive effect of a higher intake of whole grains, and a dose-response analysis found a statistically significant 17 percent decrease in risk of breast cancer per 50 grams increase in whole grains[d] consumed per day (relative risk [RR] 0.83; 95% CI 0.73-0.93]; 4,757 cases from 3 cohorts, and 978 cases from 3 case-control studies) [24]. However, the heterogeneity for this analysis was high (I^2 = 70.5%), probably due to the mix of results from both cohorts and case-control studies. Furthermore, when separate analyses were conducted for cohort and

[c] The systematic review by Schwingshackl et al. (2017) is mainly focused on the preventive effects of the Mediterranean Diet. In this study, a meta-analysis was conducted with data from a sub-group of nine studies (seven cohorts and two case-control studies) reporting specifically on the intake of whole grains [43].

[d] It was unclear whether this result is reported as 50 g of pure whole grains (ingredients) or as 50 g of whole-grain products.

case-control studies, the results were non-significant for the meta-analysis of cohort studies (see Table 3.5.1). This indicates that the inverse associations obtained are mainly driven by results from case-control studies, which are more prone to bias than cohort studies (e.g. recall bias). Hence, further data from cohort studies is needed, before firm conclusions regarding the preventive potential of whole-grain intake for breast cancer can be established.

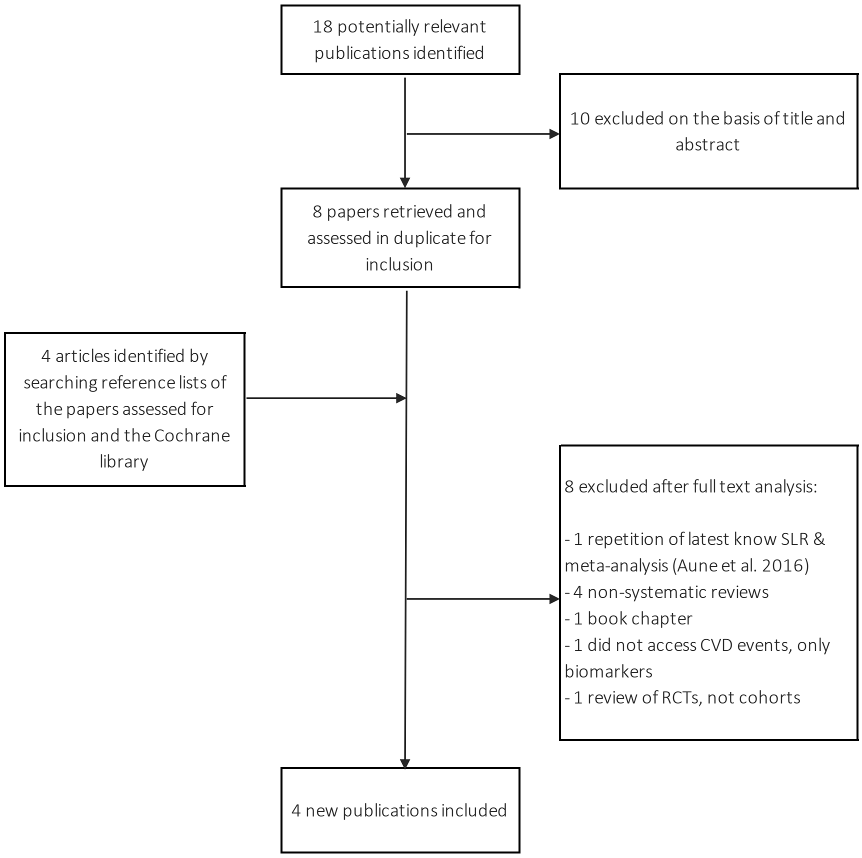

Figure 3.5.1 – Flow chart of the search for the cancer section of the WholEUGrain umbrella review.

For endometrial cancer, the WholEUGrain umbrella review identified a systematic review from 2016 including 2 prospective cohort studies (382 cases from an American cohort, and 217 cases from a Danish cohort), but no significant associations between whole-grain intake and risk of endometrial cancer were found [22].

The WholEUGrain umbrella review did not identify references that reviewed the association between whole-grain intake and risk of other female reproductive cancers, like ovarian or cervical cancers.

Genitourinary cancers

The WCRF's CUP report did not discuss the association between whole-grain intake and genitourinary cancers, since there were too few studies providing relevant data, or the available data was either too inconsistent or of too low quality [45,50–52].

Table 3.5.1 – Summary of findings from the included meta-analyses regarding breast cancer.

	High vs. low analysis					Dose-response analysis					
	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value
Xiao 2018 [24]	4 cohorts	5,734	0.96 (0.82–1.14)	66.7%	0.029	--	--	--	--	--	--
	7 case-control	5,855	0.69 (0.56–0.87)	58.2%	0.026	--	--	--	--	--	--
	11 (4 cohorts + 7 case-control)	11,589	0.84 (0.74–0.96)	63.8%	0.002	50 *	6 (3 cohorts + 3 case-control)	5,735	0.83 (0.73–0.93)	70%	0.005
			Highest vs. lowest								
			0.85 (0.76–0.95)	66.6%	0.001	--	--	--	--	--	--
			Intermediate vs. lowest								
			0.90 (0.86–0.95)	0%	0.525	--	--	--	--	--	--

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; WG-products: whole-grain products. *It is unclear whether this result is reported as 50 g of pure whole grains (ingredients) or as 50 g of whole-grain products.

The WholEUGrain umbrella review identified one reference that reviewed the evidence for kidney cancer (renal cell carcinoma). This systematic review from 2016 identified one prospective study that found a statistically significant 16% lower risk of renal cell carcinoma for participants in the highest vs. lowest quintile of whole-grain consumption (hazard ratio [HR] 0.84; 95% CI 0.73-0.98, p = 0.05; 1,816 cases) [22].

The same review identified three prospective cohort studies evaluating the risk of prostate cancer in relation to whole grains. Two of the studies reported null associations, and one study found a 13% higher risk of prostate cancer with a higher consumption of whole grains (RR/HR 1.13; 95% CI 1.03-1.24, p = 0.001; 5,112 cases) [22]. The evidence reviewed by a systematic review and meta-analysis published in 2019 found a 10% increase in the risk of prostate cancer for participants in the highest vs. lowest quintile of whole-grain consumption (RR 1.10; 95% CI 1.02-1.19; 7,010 cases) [18] (see Table 3.5.2). However, this good quality review pinpoints that the certainty of such results is low so far, due to the limited number of cohorts included [18].

None of the identified references from the WholEUGrain umbrella review had gathered evidence for neither bladder cancer nor cancers of the testicle and penis.

Table 3.5.2 – Summary of findings from the included meta-analyses regarding prostate cancer.

	Highest vs. lowest					Dose-response analysis					
	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value
Reynolds 2019 [18]	3 cohorts	7,010	1.10 (1.02–1.19)	0%	0.497	--	--	--	--	--	--

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity WG-products: whole-grain products.

Gastrointestinal cancers

The WCRF's CUP report did not discuss the association between whole-grain intake and the majority of gastrointestinal cancers, since there were too few studies providing relevant data, or the available data was either too inconsistent or of too low quality [45,53–57]. For the WCRF's CUP report results on the association between whole-grain intake and colorectal cancer see further below.

The WholEUGrain umbrella review identified one systematic review reporting evidence for a protective effect of whole grains on upper aerodigestive tract cancers (oesophagus and stomach cancers), but data was provided for one cohort alone (n=169 cases) [22].

For pancreatic cancer, the WholEUGrain umbrella review identified one systematic review and meta-analysis. The evidence reviewed indicates a preventive effect of a higher intake of whole grains [44]. However, when separate analyses were conducted for cohort and case-control studies, the results were non-significant for the meta-analysis of the only cohort study included [44] (see Table 3.5.3). This indicates that the positive results obtained are mainly driven by results from case-control studies, and the need for further data from cohort studies, before firm conclusions regarding the preventive potential of whole grains for pancreatic cancer can be established.

The WholEUGrain umbrella review identified one systematic review reporting no statistically significant association between whole grains and small intestine cancer, but the evidence is built solely upon the results of one prospective cohort [22].

The WholEUGrain umbrella review did not retrieve any references reviewing evidence for cancers of the liver, spleen, gallbladder nor anus.

In 2018, the latest review of the association between whole-grain intake and cancer risk by the WCRF's CUP report concluded there is strong evidence that whole grains decrease the risk of colorectal cancer [5]. The meta-analysis performed under the scope of the CUP report showed a significant 17% decrease in risk per 90 g of whole-grain products/day (RR 0.83; 95% CI 0.78-0.89; 8,320 cases) with low heterogeneity [5].

The WholEUGrain umbrella review identified one systematic review reporting evidence regarding colorectal cancer. This study reports a statistically significant 6%-53% reduction in colorectal cancer risk in 4 out of 7 prospective cohorts with higher intake of whole grain [22]. A systematic review and meta-analysis from 2019 showed a statistically significant reduction (13%) in colorectal cancer risk for participants in the highest vs. lowest quintile of whole grain consumption (RR 0.87; 95% CI 0.79-0.96; 8,803 cases), but the quality of the evidence was considered low by the study's authors [18].
However, it should be noted that data from the cohorts included in these studies is already included in the WCRF's CUP report [5,45]. Hence, no new evidence for the relation between whole grain intake and colorectal cancer risk was found through the WholEUGrain umbrella review.

Table 3.5.3 – Summary of findings from the included meta-analyses regarding gastrointestinal cancers.

	High vs. low analysis					Dose-response analysis					
	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value
Colorectal cancer			Highest vs. lowest								
Reynolds 2019 [18]	7 cohorts	8,803	0.87 (0.79–0.96)	51.8%	0.053	15	8	6,056	0.97 (0.95–0.99)	45%	0.009
CUP Colorectal SLR 2016 [5]	13 cohorts	8,081	0.92 [a] (0.84–1.00)	NA	NA	90	6	8,320	0.83 (0.78–0.89)	18%	0.295
Pancreatic cancer											
Lei 2016 [44]	1 cohort	163	OR: 1.23 (0.73–2.05)	NA	NA	--	--	--	--	--	--
	4 case-control	2,385	OR: 0.72 (0.60–0.85)	0%	0.872	--	--	--	--	--	--
	5 (1 cohort + 4 case-control)	2,548	OR: 0.76 (0.64–0.91)	11.7%	0.339	--	--	--	--	--	--

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; WG-products: whole-grain products; NR: not reported; OR: odds ratio.

Head and neck cancers

The WCRF's CUP report did not discuss the association between whole-grain intake and head and neck cancers, since there were too few studies providing relevant data, or the available data was either too inconsistent or of too low quality [45,58,59].

The WholEUGrain umbrella review identified one systematic review reporting evidence suggestive of a protective effect of whole grains on head and neck cancers, but data stems from only two cohorts (2,036 cases), and results were not significant for men [22].

Hematologic cancers

The WCRF's CUP report did not discuss the association between whole-grain intake and hematologic cancers, since there were too few studies providing relevant data, or the available data was either too inconsistent or of too low quality [45].

The WholEUGrain umbrella review identified one systematic review that included one prospective cohort study focusing on the preventive effects of whole grains for hematologic cancers, but a null association was reported for non-Hodgkin's lymphoma [22].

Total cancer

For total cancer, the evidence reviewed under the scope of the WholEUGrain umbrella review indicates a preventive effect of a higher intake of whole grains, based on a meta-analysis of 7 cohort studies (number of cases not reported) and 2 case-control studies (652 cases) [43]. Once more, the results are from a meta-analysis where data from both cohort studies and case-control studies are pooled, but no separate analyses were performed, and the number of cases from cohort studies was not reported, making it difficult to assess what type of data might drive the results obtained. Also, the data comes from cohorts reporting several types of cancer, and as such we are not able to assess whether data from cohorts reporting more common cancer types (e.g. colorectal or breast cancer) are the driver for these results. Hence, we need further good quality data and analyses from a larger number of cohorts before firm conclusions can be established.

Table 3.5.4 – Summary of findings from the included meta-analyses for total cancer.

	High vs. low analysis						Dose-response analysis					
	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value		Dose WG-products (g/day)	No. of studies	No. of cases	RR (95% CI)	I^2	P_{het} value
Schwingshackl 2017 [43]	9 (7 cohorts + 2 case-control)	NA	0.91 (0.87–0.95)	31%	NR		--	--	--	--	--	--

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; WG-products: whole-grain products; NA: not available; NR: not reported.

Mechanisms

There is a number of biologically probable mechanisms through which the consumption of whole grains may contribute to a decreased risk of cancer development. Overall, we agree with the WCRF's assessment [5] that there is plausible mechanistic evidence for a preventive effect of whole grains on colorectal cancer. Possible mechanistic pathways related to other forms of cancer are also briefly described, but the data is limited.

Dietary fibre content and fermentation in the bowel

Whole grains and whole-grain products are rich in dietary fibre, which is fermented by the microbiota in the bowel into SCFAs [21,22]. SCFAs like butyrate have shown anti-proliferative effects in experimental studies, which could explain their contribution for the prevention of colorectal cancer [5,22]. Furthermore, SCFAs influence the metabolism of both glucose and lipids, and stimulate the production of gut hormones (like peptide-tyrosine-tyrosine and GLP-1) that increase gastrointestinal transit time and increase faecal bulk [6,9,18,21,22]. This reduces the interaction time of faecal mutagens with the colon mucosa, and reduces the production of secondary bile acids, which in turn reduces cell proliferation and the chance of mutations [5,24]. Dietary fibre can also bind and dilute carcinogens, as well as remove damaged cells from the digestive tract [6,22,24]. Additionally, dietary fibre can bind oestrogens in the colon increasing the faecal excretion of these components, which might contribute to a reduction of risk for breast cancer [24].

Glycaemic response

Whole grains improve the glycaemic response, and this decreases the development of insulin resistance, which is a risk factor for colorectal cancer [5]. Also, an association between higher levels of serum insulin and breast cancer has been observed in epidemiological studies [24].

Bioactive compounds

Whole grains are a good source of various bioactive compounds, many of which have plausible anticarcinogenic properties [5]. These include vitamins (e.g. vitamin C, vitamin E, and β-carotene) and minerals (e.g. selenium, zinc, copper, and manganese) are components of enzymes with antioxidant functions, for instance by preventing the formation of carcinogens or blocking interactions between carcinogens and the cells [22,24]. Other bioactive compounds include essential non-nutrients like lignans, phytoestrogens, and phenolic compounds, that also act as antioxidants, inhibit cell proliferation and angiogenesis[e], and even induce cell apoptosis[f] [24].

Hormone regulation

Whole grains may also play a role in hormone regulation. For instance, phytoestrogens (e.g. lignans and isoflavones) regulate the production and metabolism of sex hormones, which results in a reduction of circulating oestrogen levels, inhibition of tumour initiation and growth, and a reduction in early markers of risk for mammary and colon carcinogenesis [6,22]. Whole grains have also been associated with reduced levels of inflammatory markers and liver enzymes, which in turn are associated with a lower risk of cancer [6,24].

Adiposity regulation

An excessive accumulation of fat in the body increases the risk for several cancer forms. Whole grains might play a role in the regulation of adiposity, hereby contributing to an indirect reduction in the risk of adiposity-related cancers [22]. The structure of whole grains and their high dietary fibre content promote increased chewing and yield higher levels of satiation [18]. Also, whole-grain foods typically have a lower energy density and help manage caloric intake [22]. Previous studies have also shown inverse associations between a high intake of whole grains and different adiposity measures [22].

Conclusion – cancer

Based on the current body of evidence for whole grains and the risk of cancer, there is strong evidence of a protective role of whole grains for colorectal cancer based both on the WCRF's conclusion and the WholEUGrain umbrella review. This conclusion is based on consistent data from several prospective cohort studies that show a statistically significant and clear dose-response relationship showing a decreased risk of cancer with increased consumption of whole grains, with low heterogeneity. Also, there is robust evidence for the mechanisms explaining this relationship in humans.
There is, so far, not enough data to draw conclusions regarding a potential protective effect of whole grains and the risk of other types of cancer.

3.6. MORTALITY

Background

The establishment of nutrition guidelines and quantitative recommendations regarding the intake of whole grains is guided by an evaluation of the health benefits and potential disease-preventive effects associated with the consumption of whole grains. A potential risk reduction in all-cause mortality is an integral part of such an evaluation, since it is closely intertwined with the previously reviewed risk reductions of disease

[e] Angiogenesis is the process by which new blood vessels form from pre-existing vessels. It is a normal and vital process, e.g. in growth and development, as well as in wound healing. However, it is also a crucial step in the transition of tumours from a benign to a malignant character [81].

[f] Programmed cell death.

incidence of major NCDs like CVD, cancer, and type 2 diabetes. For instance, the Global Burden of Disease (GBD) study estimated that a diet low in whole grains resulted in more than 260,000 avoidable deaths from all causes in 2017 in the EU, of which a vast majority is due to CVDs [60]. Low whole-grain intake was, in this study, considered the leading dietary risk factor for mortality in both Eastern and Western Europe, and was surpassed only in Central Europe by a high intake of sodium [60].

Epidemiological evidence of whole grains and mortality

The evidence presented here is based on:

7. A systematic literature review and meta-analysis by Aune and colleagues, that includes a summary of evidence gathered until April 3, 2016 [6].
8. The WholEUGrain umbrella review including data from systematic reviews and meta-analyses of prospective cohorts, conducted for the period April 4, 2016 through February 2020. For a detailed description of search terms and inclusion criteria see Appendix B.

The flow chart of the search and selection of studies for the WholEUGrain umbrella review is presented in Figure 3.6.1.

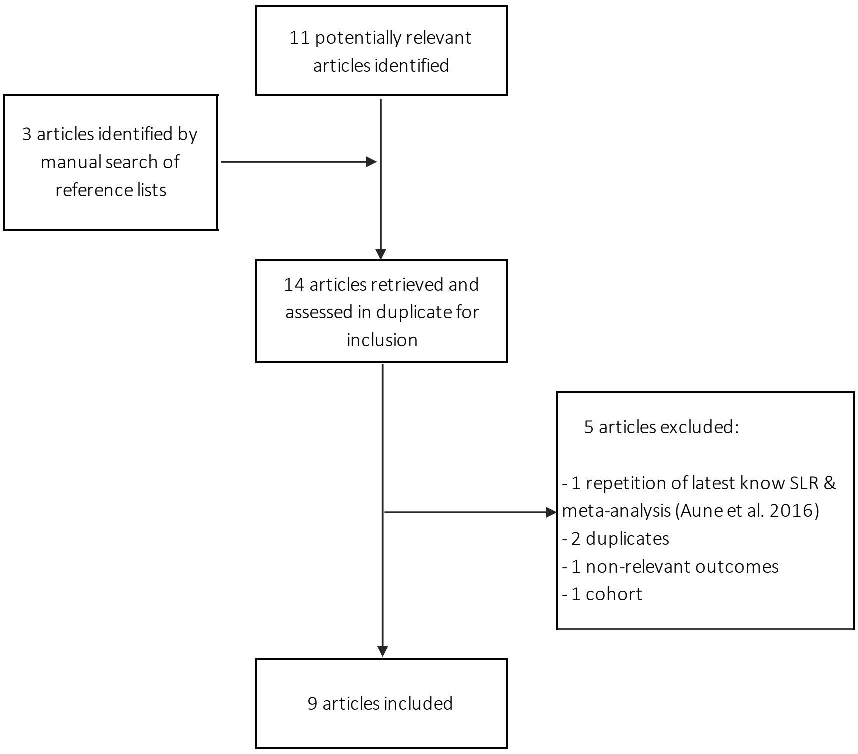

Figure 3.6.1 – Flow chart of the search for the mortality section of the WholEUGrain umbrella review.

A total of nine new relevant systematic reviews including meta-analyses were retrieved for this section, eight of which were of good quality [18,32,61–66] and one of fair quality [67]. A descriptive overview of the included studies is available in Table E.5 in Appendix E. A summary of findings from the included meta-analyses is presented in Table 3.6.1.

Table 3.6.1 – Summary of findings from the included meta-analyses in the mortality section.

	High vs. low analysis					Dose-response analysis					
	No. of cohorts	No. of deaths	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of cohorts	No. of deaths	RR (95% CI)	I^2	P_{het} value
Zong 2016 [61]	12	97,870	0.84 (0.80–0.88)	74%	<0.001	70	8	84,984	0.78 (0.74–0.82)	NR	NR
Chen 2016 [62]	12	96,218	0.83 (0.80–0.88)	71%	<0.001	50	10	100,653	0.78 (0.67–0.91)	94%	<0.001
Wei 2016 [63]	11	94,638	0.87 (0.84–0.90)	67%	<0.001	90	9	92,647	0.81 (0.76–0.85)	79%	<0.001
Li 2016 [64]	--	--	--	--	--	30	10	92,647	0.93 (0.91–0.95)	79%	<0.001
Ma 2016 [65]	10	91,591	0.82 (0.78–0.87)	77%	<0.001	30	10	99,224	0.93 (0.89–0.97)	92%	<0.001
Benisi-Kohansal 2016 [66]	11	92,288	0.87 (0.84–0.91)	57%	0.006	90	5	79,831	0.83 (0.79–0.88)	56%	<0.001
Schwing-shackl 2017 [32]	19	121,141	0.88 (0.84–0.92)	91%	<0.001	30	11	94,128	0.92 (0.89–0.95)	80%	<0.001
Zhang 2018 [67]	9	84,464	0.84 (0.81–0.88)	47%	0.055	28	9	84,464	0.91 (0.90–0.93)	NR	NR
Reynolds 2019 [18]	9	99,224	0.81 (0.72–0.90)	97%	<0.001	15	7	88,348	0.94 (0.92–0.95)	80%	<0.001
Aune 2016 [6]	9	89,534	0.82 (0.77–0.88)	83%	<0.001	90	11	100,726	0.83 (0.77–0.90)	83%	<0.001

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance level for heterogeneity; WG-products: whole-grain products; NR: not reported.

The systematic literature review and meta-analysis by Aune and colleagues reported a 17% lower risk for all-cause mortality for a whole-grain intake of 90 g whole-grain products/day (3 servings), with high heterogeneity [6]. The authors further found a significant non-linear risk reduction, with steeper reductions in risk observed at lower intakes, but the highest risk reduction of 30% was observed for an intake of 225 g whole-grain products/day (7,5 servings) [6].

The WholEUGrain umbrella review identified eight meta-analyses that compared a high versus a low whole-grain intake. All 8 meta-analyses showed a consistent and significant lower all-cause mortality (12% to 19%) with the highest versus the lowest levels of whole-grain intake, with moderate heterogeneity for the results of 1 study [67], but high heterogeneity for the remaining 7 studies [18,32,61–63,65,66]. These findings were further confirmed by all 9 dose-response analyses performed [18,32,61–67], spanning from a 6% lower risk for a whole-grain intake of 15 g whole-grain products/day (half serving) [18], up to a 17-19% lower risk for a whole-grain intake of 90 g whole-grain products/day (3 servings) [63,66]. The heterogeneity was high for nearly all dose-response results, albeit not reported for 2 of the studies (see Table 3.6.1).

Seven of the included meta-analyses reported results for non-linear dose-response calculations. One reference found no evidence of a non-linear relation [66]. The remaining 6 studies reported evidence of a non-linear dose-response association with lower mortality risk [18,32,62–64,67] with as much as 25-42% lower risk of mortality for intakes of 100-168 g whole-grain products/day in 2 studies [32,67].

These findings are in line with the results from Aune and colleagues (2016). However, it should be noted that data from included in the meta-analyses retrieved under the scope of the WholEUGrain project review above stems from many of the same prospective cohort studies, and several overlaps exist for all the meta-analyses, as well as with the meta-analysis by Aune and colleagues (see Table E.6 in Appendix 6). Hence, the similarity of results between the different meta-analyses might be driven by the use of much of the same data.

Conclusion – mortality

The WholEUGrain umbrella review gathered good quality and comprehensive meta-analyses published in recent years that confirm previous results showing there is strong evidence that a high whole-grain intake is associated with a lower risk of overall mortality. Dose-response analyses further confirm the robustness of this association, showing that the highest benefit was found for an increase from no intake to low intake levels. Looking at higher intakes of up to 5.5 servings/day (165 grams of whole-grain products), there was still an association, although not as strong, which is very much in line with the results previously reported by Aune and colleagues (2016), and confirming that added benefits are observed for higher intakes of whole grains.

The current body of evidence for whole grains and the risk of all-cause mortality builds up on data from a large number of prospective studies. However, it should be noted that the consistency of results found might be driven by a repetition of data from several of the same prospective cohorts.

3.7. OVERWEIGHT

Background

Overweight and obesity are defined by an excessive accumulation of fat in the body that may impair health [2]. Overweight and obesity pose one of the greatest public health challenges of the 21st century, as they cause several physical disabilities and psychological problems, but also because these conditions significantly increase the risk of developing serious NCDs, like cancer, CVDs, and type 2 diabetes [68].

The prevalence of overweight and obesity in the WHO European Region has been steadily increasing over the last 4 decades, with an average of 39% for overweight among adults in 1975 rising to 59% in 2016 (range: 45-67%) [69]. For obesity the average rose from 10% in 1975 to 23% in 2016 (range: 14-32%) [70]. Overweight and obesity among children in the WHO European Region is unequally distributed between and within countries and population groups. But although a decrease in the prevalence of both overweight and obesity was documented between 2007 and 2017 among school children 6-9 years old in some countries (e.g. Greece, Italy, Portugal and Slovenia), several other countries report opposite trends [71].
Thus, prevention of overweight and obesity is paramount, and a multitude of strategies must be considered to help maintain a healthy weight among both adults and children.

An important contributor to weight gain is a long-term imbalance between energy intake and energy expenditure. A diet characterized by a low intake of high-energy-dense foods (e.g. sugar-sweetened beverages and highly processed foods) and a high intake of fruit, vegetables and whole-grain products (low-energy-dense foods) is known to counteract such an energy imbalance, and to be associated with lower risk of weight gain over time [72].

It has long been hypothesized that a high whole-grain intake might play a crucial role in the maintenance of a stable weight and lower adiposity measures (e.g. BMI, body fat mass, waist circumference), but overall evidence seems inconsistent.
The latest review of the association between whole-grain intake and risk of weight gain performed by the World Cancer Research Fund International found there is limited but suggestive evidence that whole grains decrease the risk of weight gain [9].

Epidemiological and trial-based evidence for whole grains and overweight

The evidence presented here is based on:
1. The systematic literature review by the World Cancer Research Fund's Continuous Update Project (CUP report), that includes a summary of evidence gathered until August 2016 [9].
2. The WholEUGrain umbrella review including reviews of data from both prospective cohorts and randomised controlled trials (RCTs), conducted for the period September 2016 through December 2020. For a detailed description of search terms and inclusion criteria see Appendix B.

The flow chart of the search for the overweight section is presented in Figure 3.7.1.

A total of seven new relevant publications were retrieved in this literature search, of which three were good quality systematic reviews that included meta-analyses [18,21,73], one was a systematic review alone of good quality [74], one was an umbrella review of meta-analyses of fair quality [75], and two were fair quality systematic reviews that included meta-analyses [76,77]. A short description of characteristics of the included studies is available in Table E.7 in Appendix E.

The results presented concern evidence regarding effects and associations observed for adults, unless otherwise described.

Weight changes
The CUP report identified 2 meta-analyses of RCTs evaluating the effect of whole-grain intake in weight changes. One reported a protective effect, and the other a negative effect, but none was statistically significant [9].

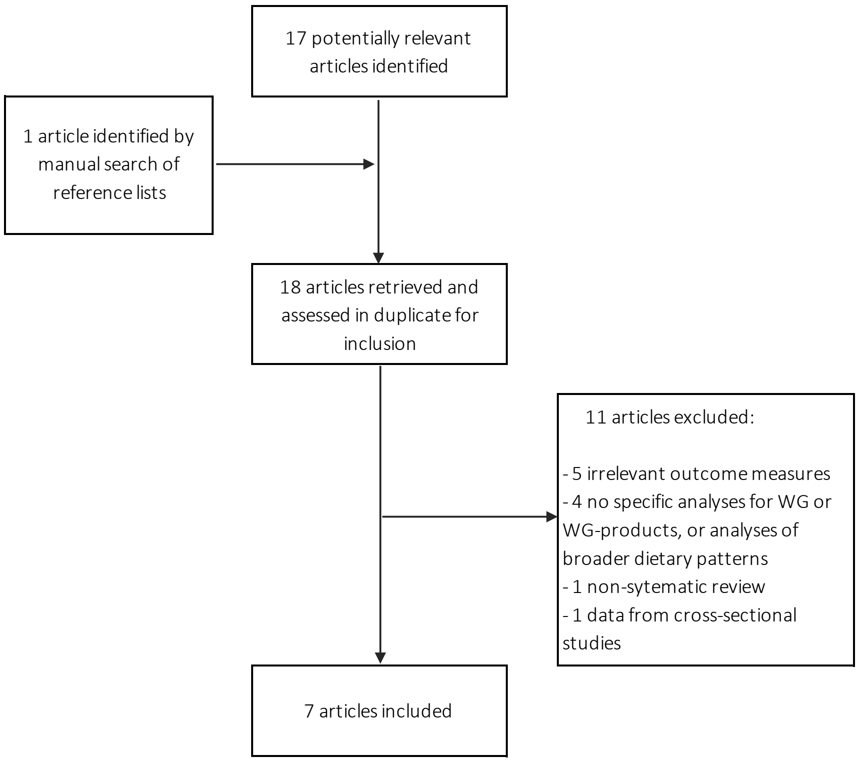

Figure 3.7.1 – Flow chart of the search for the overweight section of the WholEUGrain umbrella review.

The WholEUgrain umbrella review identified five systematic reviews including meta-analyses of RCTs assessing the effect of whole-grain intake on weight changes (see Table 3.7.1). Two meta-analyses showed significant but very small reductions in body weight (under 0.65 kg) for intervention groups with a high intake of whole-grain products with medium heterogeneity [18,76], while 3 meta-analyses reported minimal but non-significant reductions in body weight (under 0.1 kg) [21,75,77].

Table 3.7.1 – Summary of findings from the included meta-analyses of RCTs evaluating body weight changes.

	High *vs.* low analysis				
	No. of RCTs in the MA	No. of subjects	RR (95% CI)	I^2	P_{het} value
Wang 2020 [76]	19	Int. = 767 + Cont. = 763	MD = - 0.50 kg (-0.74, -0.25)	35%	0.07
Sadeghi 2020 [21]	19	T = 1,698	WMD = - 0.09 (-0.26, 0.07)	0%	0.99
Maki 2019 [77]	9	Int. = 472 + Cont. = 501	SMD = -0.049 kg (-0.297, 0.199)	71.5%	0.698
Reynolds 2019 [18]	11	Int. = 498 + Cont. = 421	MD = -0.62 kg (-1.19, -0.05)	50%	0.03
McRae 2017 [75]	26 Pol et al. 2013	T = 2,060	WMD = -0.06 kg (-0.09, 0.20)	0%	0.45

RCT: randomised controlled trial; MA: meta-analysis; Int.: intervention arm; Cont.: control arm; T: total population; RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; MD: mean difference; WMD: weighted mean difference; SMD: standardized mean difference.

The CUP report also reviewed results of two prospective cohorts, of which one reported significant inverse trends for odds of weight gain when comparing the highest and lowest categories of whole-grain intake. The other cohort found a non-significant lower relative risk of overweight among participants consuming more than 30 g per day (one serving) of whole-grain cereal when compared to participants who rarely or never consumed it [9].

The WholEUgrain umbrella review identified three reviews of prospective studies assessing risk of weight gain over time (see Table 3.7.2). One meta-analysis found a significant 17% lower risk of weight gain when comparing high vs. low intakes of whole-grain products (2,747 participants), with low heterogeneity [73]. The dose-response sub-analysis showed a 9% lower risk of weight gain for each increase of 30 g in the intake of whole-grain products, but this result was not statistically significant [73].
One systematic review of six prospective cohorts reported that in five of the six studies reviewed aging was shown to be associated with weight gain. The authors of the review underline that a general observation of weight gain is the norm in prospective studies, and thus conclude that the inverse association between whole-grain intake and weight gain reflects an attenuating effect of whole-grain intake over longer periods. Also, this attenuating effect should not be mistaken for a weight-loss effect [77]. Another systematic review reported mixed results from two prospective cohorts with data for children and/or adolescents. In one study no differences were observed, while the other study found that whole-grain intake was associated with a significantly lower weight gain [74].

Table 3.7.2 – Summary of findings from prospective cohorts retrieved for the WholEUGrain umbrella review.

META-ANALYSES											
	High vs. low analysis					Dose-response analysis					
	No. of cohorts	No. of subjects	RR (95% CI)	I^2	P_{het} value	Dose WG-products (g/day)	No. of cohorts	No. of cases	RR (95% CI)	I^2	P_{het} value
Risk of overweight/obesity (defined as BMI ≥ 25 kg/m^2)											
Schlesinger 2019 [73]	5	17,547	0.85 (0.79-0.91)	0%	0.70	30	3	10,056	0.93* (0.89-0.96)	0%	0.82
Risk of weight gain (defined as gain in weight during a predefined time period) a)											
Schlesinger 2019 [73]	3	2,747	0.83 (0.70-0.97)	16%	0.31	30	3	2,747	0.91** (0.82-1.02)	69%	0.04
SYSTEMATIC REVIEWS											
Risk of weight gain (defined as gain in weight during a predefined time period)											
Reynolds 2020 [74]	2	373 4,646	. No difference observed between high vs. low intake of whole grains. . Whole-grain intake was associated with lower weight gain after 5 years of follow-up.								
Maki 2019 [77]	6	74,091 27,082 17,881 120,877 9,267 15,995	"In five of the six prospective studies assessed, aging was shown to be associated with weight gain; thus, results reported on the level of weight gain attenuation rather than weight loss. (…) age-related weight gain is the norm in these prospective cohort studies, and generally, higher intake of WG-foods was associated with attenuation of weight gain."								

RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; WG-products: whole-grain products. a) The included cohorts define weigh gain differently as >2 kg during a mean period of 4 years, ≥10 kg during 13 years, or ≥25 kg during an average period of 12 years.
* There is low confidence for the effect estimate with the NutriGrade rating system; further research will provide important evidence on the confidence and likely change the effect estimate.
** There is very low confidence for the effect estimate with the NutriGrade rating system; meta-evidence is very limited and uncertain.

BMI

The WholEUgrain umbrella review identified three studies reporting results of meta-analyses of RCTs that assessed the effect of whole-grain intake in BMI changes (see Table 3.7.3). Two meta-analyses showed significant but small reductions in BMI (under 0.65 kg/m^2) for intervention groups with a high intake of whole-grain products [18,75], while the third meta-analysis did not find significant changes in BMI [21]. The heterogeneity was either high or not reported.

The CUP report reviewed results from one cohort assessing the association of whole-grain intake with the odds of obesity (defined as BMI ≥ 30 kg/m^2), that found a significant inverse trend when comparing the highest and lowest categories of whole-grain intake [9].

Table 3.7.3 – Summary of findings from the included meta-analyses of RCTs evaluating BMI changes.

	High *vs.* low analysis				
	No. of RCTs in the MA	No. of subjects	RR (95% CI)	I^2	P_{het} value
Sadeghi 2020 [21]	10	T = 769	WMD = -0.04 (-0.62, 0.70)	90%	< 0.001
Reynolds 2019 [18]	5	NR	MD = -0.36 (-0.69, -0.02)	67%	0.02
McRae 2017 [75]	15 Harland & Garton 2008	T = 207,005	WMD = -0.63 (-0.46, -0.80)	NR	< 0.0001

BMI: body mass index; RCT: randomised controlled trial; MA: meta-analysis; T: total population; RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; MD: mean difference; WMD: weighted mean difference; NR: not reported.

The WholEUgrain umbrella review identified one meta-analysis of prospective cohorts that assessed the association of whole-grain intake with risk of overweight (defined as BMI ≥ 25 kg/m^2). This study found a significant 15% lower risk when comparing high vs. low intakes of whole-grain products (17,547 participants) [73]. This result was further confirmed by a dose-response analysis, that showed a significant 7% lower risk of overweight for each increase of 30 g in the intake of whole-grain products [73]. Both results had low heterogeneity, but also a low number of cohorts included in the meta-analyses (Table 3.7.2).
One systematic literature review included only one cohort reporting on BMI changes, that found a significant inverse association for BMI change in men for higher intakes of whole grains, but results for women were not statistically significant [77].

Waist circumference

The WholEUgrain umbrella review identified five systematic reviews including six meta-analyses of RCTs assessing the effects of whole-grain intake on waist circumference (WC) changes (see Table 3.7.4). Only one meta-analysis reported a significant decrease in WC size for the intervention group with a high intake of whole-grain products [75]. The other five meta-analyses showed no changes in WC between intervention and control groups [18,21,75–77].

The CUP report reviewed results from 2 cohorts assessing the association of whole-grain intake with WC. Results from one cohort showed an inverse association between intake of whole-grain bread and WC, while the other cohort showed a positive (adverse) association when measuring megajoules per day of whole-grain products [9].

Table 3.7.4 – Summary of findings from the included meta-analyses of RCTs evaluating changes in waist circumference.

	High *vs.* low analysis				
	No. of RCTs in the MA	No. of subjects	RR (95% CI)	I^2	P_{het} value
Wang 2020 [76]	14	Int. = 564 Cont. = 553 T = 1,117	MD = -0.12 cm (-0.92, 0.68)	44%	0.04
Sadeghi 2020 [21]	10	T = 823	WMD = 0.06 cm (-0.50, 0.63)	0%	0.56
Maki 2019 [77]	5	T = 482	SMD = 0.276 cm (-0.44, 0.99)	NR	0.447
Reynolds 2019 [18]	6	NR	MD = 0 cm (-0.58, 0.580)	26%	0.24
McRae 2017 [75]	6 Harland & Garton 2008	T = 4,178	MD = -2.7 cm (-0.2, -5.2)	NR	NR
	4 Pol et al. 2013	T = 371	MD = -0.1 cm (-0.25, 0.04)	67%	0.001

RCT: randomised controlled trial; MA: meta-analysis; Int.: intervention arm; Cont.: control arm; T: total population; RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; MD: mean difference; SMD: standardized mean difference; WMD: weighted mean difference; NR: not reported.

The literature search under the scope of the WholEUgrain umbrella review did not identify any systematic reviews nor meta-analyses of prospective cohorts reporting effects of whole-grain intake in WC measures.

Body fat percentage, fat mass, and fat-free mass

The WholEUgrain umbrella review identified three systematic reviews including meta-analyses of RCTs assessing the effects of whole-grain intake in changes in body fat percentage, but none reported significant changes [21,75,77] (see Table 3.7.5). Furthermore, no significant results were found for meta-analyses of effects of whole-grain intake in fat mass [18,21] nor in fat-free mass [21].

Mechanisms

There is a number of possible mechanisms through which the consumption of wholegrain may contribute to energy balance, and thus a decreased risk of weight gain and improvements in adiposity measures over time.

Satiation

Whole grain contributes to an increased feeling of fullness – satiation – after a meal [21]. This may be due to the high content of dietary fibre in whole grains and whole-grain products, but might also be related to the structure of these foods, that require a longer chewing time to be broken down [9,18]. The dietary fibre in whole grains form gel-like structures that slow down gastric emptying, hence leading to an increased intestinal transit time and subsequent lower appetite [21]. The satiation feeling registered after eating whole grains and whole-grain products will naturally vary, depending on the degree of processing (either industrial or preparation at the consumer end) these foods are subjected to.

Table 3.7.5 – Summary of findings from the included meta-analyses of RCTs evaluating changes in body fat percentage, fat mass and fat-free mass.

	High *vs.* low analysis				
	No. of RCTs in the MA	No. of subjects	RR (95% CI)	I^2	P_{het} value
Body fat percentage (%)					
Sadeghi 2020 [21]	9	T = 853	WMD = 0.26 (-0.08, 0.59)	9.5%	0.35
Maki 2019 [77]	6	T = 666	SMD = 0.042 (-0.57, 0.66)	NR	0.895
McRae 2017 [75]	3 Pol et al. 2013	T = 394	MD = -0.48% (-0.95, -0.01)	0%	0.99
Fat mass (FM) & Fat-free mass (FFM) (kg)					
Sadeghi 2020 [21]	4 (FM)	T = 298	WMD = 0.45 kg (-0.12, 1.02)	0%	0.674
	4 (FFM)	T = 247	WMD = 0.31 kg (-0.67, 0.06)	0%	0.443
Reynolds 2019 [18]	2 (FM)	NR	MD = -0.68 kg (-1.63, 0.28)	50%	0.16

RCT: randomised controlled trial; MA: meta-analysis; Int.: intervention arm; Cont.: control arm; T: total population; RR: relative risk; CI: confidence interval; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; MD: mean difference; SMD: standardized mean difference; WMD: weighted mean difference; NR: not reported.

Energy density

Whole grains and whole-grain products are rich in dietary fibre. Foods with a high content of dietary fibre (e.g. fruit and vegetables or whole grains) tend to be low in energy density, i.e. the amount of calories in these foods is low compared to their volume. Hence, the consumption of low energy density foods rich in dietary fibres or other indigestible components reduces the risk of passive overconsumption [9,21], and might help reduce the absorption of other energy-containing nutrients in the gut [21].

Influence on gastrointestinal hormones

It is proposed that whole grains lead to an increased release of glucagon-like peptide 1 (GLP-1) [9], which leads to a delay in gastric emptying and gut motility [78], which might contribute to a lower energy intake and lower hunger feeling in subsequent meals [9,77]. This response might not be observed for the ingestion of all types of whole grains though.

Glycaemic response

The glycaemic response is the postprandial blood glucose response (the change in blood glucose concentration after a meal) elicited by the consumption of carbohydrates. It is agreed that a reduced postprandial glycaemia is a healthier effect, than an increased glycaemia [79]. Some evidence suggests that consumption of whole grains can reduce postprandial glycaemia in subsequent meals [9,18]. This can contribute to reductions in body fat mass and improvements in weight management over time [79].

Fermentation in the bowel

It has been proposed that fermentation in the bowel of complex carbohydrates from whole grains regulates appetite. Gut microbiota ferment dietary fibre from whole grains and produce SCFAs [21]. SCFAs influence the metabolism of both glucose and lipids, and stimulate the productions of gut hormones (like peptide-tyrosine-tyrosine and GLP-1) that regulate appetite, increase gastrointestinal transit time, and regulate glucose metabolism [9,18,21]. It has also been shown, that the composition of the gut microbiome is different for people in different BMI categories. However, whether this is a result of higher/lower levels of body fat or whether people with different gut microbiota profiles are at a higher risk of accumulating an excess of fat in the body is not well established [9].

Conclusion – overweight

Based on the included body of evidence for whole grains and the risk of weight gain, overweight and obesity, there is rather limited evidence suggestive of a protective role of whole grains. Even though the evidence is limited at the moment, it is generally consistent and shows a trend towards an inverse, albeit very small, risk reduction. This might be explained in part, by the short duration of most of the trials included in the reviewed meta-analyses (the majority up to 16 weeks, a few up to 26 weeks, and only one trial more than a year), and by a lack of research analysing the specific association between the intake of whole grains and body weight measures in good quality cohorts.

For adiposity parameters like WC, body fat percentage, fat mass and fat-free mass the evidence is very scarce, and results are conflicting.

There is evidence of biological plausibility through a number of different mechanisms related to energy balance.

3.8. CONCLUSION

An umbrella review was conducted, with the aim of gathering the latest and highest level of evidence available concerning the associations between whole-grain intake and the development of cardiovascular diseases, type 2 diabetes, cancer, risk of overall mortality, and overweight. The umbrella review shows that new reviews and meta-analyses on these subjects continue to emerge and add to previously available expert reports and reviews, but that these subjects are far from being fully covered.

Based on the collected results from the WholEUGrain umbrella review and results from previously published good quality expert reports and meta-analyses, an overview of conclusions is presented in the matrix in figure 3.8.1. In short, there is strong epidemiological evidence of a protective role of whole grains and the risk of cardiovascular diseases, coronary heart disease, type 2 diabetes, colorectal cancer, and mortality.

There is consistent evidence that an intake of about 90 g of whole-grain products per day (equivalent to 3 servings of whole-grain products, or 48 grams of whole grain as an ingredient) significantly reduces the risk of these diseases and overall mortality. In general, stronger improvements in risk reductions are observed for the shift between none to relatively low levels of intake, with significant benefits being achieved with as little as one-two servings of whole-grain products per day. Furthermore, protective effects are clearly seen for higher whole-grain intakes, with clear dose-response associations showing further risk reductions with intakes as high as 200-225 g whole-grain products per day (6.5–7.5 servings, equivalent to 104-120 grams of whole grain as an ingredient) for some of the observed associations.

There is limited evidence suggestive of a protective role of whole grains on the risk of weight gain, overweight and obesity. There is limited evidence available regarding the role of whole grains on the risk of other types of cancer, stroke, heart failure, and whole grain's effects on a series of adiposity-related measures.

Whole-grain intake and CVD, type 2 diabetes, cancer, mortality, and overweight		
2021		DECREASES RISK
STRONG EVIDENCE	Convincing	CVD, CHD Type 2 diabetes Mortality
	Probable	Colorectal cancer
LIMITED EVIDENCE	Limited - suggestive	Weight gain, overweight, and obesity
	Limited – no conclusion	Other types of cancer Stroke & Heart failure Adiposity parameters

Figure 3.8.1 – Matrix of conclusions regarding the role of whole grains in the development of major NCDs, overall mortality, overweight and adiposity measures.

These conclusions are based mainly on reviews and meta-analyses of prospective cohort studies. Risk of bias through confounding can never be completely eliminated in cohort studies, either due to imperfect adjustments of known confounders, or due to residual confounding, e.g. the influence of a possible but unknown confounder. However, the majority of reviews at the base of these conclusions were of good quality, and clearly reported statistical adjustments for a large number of known confounders. Furthermore, these reviews and reports include data from a large number of prospective studies with high numbers of relevant cases, originating from several different countries, and the large majority reached similar conclusions. Hence, risk of confounding is rather improbable.

The conclusions presented in this report show that the evidence base for dietary guidelines regarding the consumption of whole grains and whole-grain products has been strengthened in relation to the previous review published under the Danish definition and evidence report from 2008.
Despite a broad consensus among researchers and health authorities worldwide that whole grains are to be preferred rather than refined grains, the majority of people in most European and other Western countries have a rather low whole-grain intake. At the same time, a large majority might have a total grain and grain-products intake of three or more servings per day, consisting mostly of refined-grain products. Hence, replacement of at least a proportion of such servings – but preferably a majority – with whole grains and whole-grain products could potentially contribute to a substantial reduction in the number of major NCDs like CVDs, type 2 diabetes, colorectal cancer, as well as contribute to a reduction in premature mortality, thus having a considerable impact in public health.

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CHAPTER 4
Unwanted substances and contaminants in whole grains

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4.1. INTRODUCTION

This chapter gives a brief presentation of different unwanted substances and potential contaminants in whole grains and whole-grain products.
A variety of unwanted substances and contaminants can be found in whole grains and whole-grain products. Such substances and contaminants find their way into whole grains either through environmental pollution (of air, water, and soil), or through technological processes occurring in different phases of grain storage, processing and end-user consumption (including product storage and preparation), as shown in figure 4.1. Some of these substances and contaminants also occur naturally in the environment.

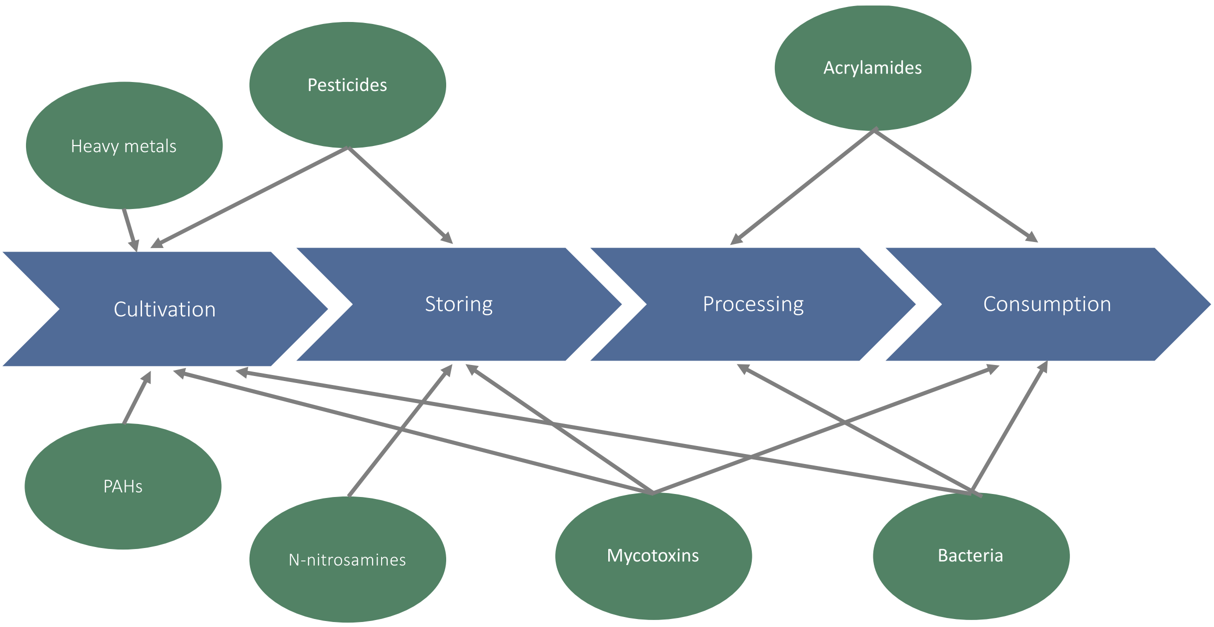

Figure 4.1 - From farm to fork: Overview of entry points for unwanted substances and contaminants that can be found in whole grains and whole-grain products. PAHs: polycyclic aromatic hydrocarbons.

These substances and contaminants are problematic due to their varied adverse health effects, that can range from skin rashes, to seizures, neurotoxicity, impaired fetal and infant development, kidney and liver dysfunction, reproductive deficiencies, hepatoxicity, or even a higher risk of noncommunicable diseases like certain types of cancer, cardiovascular diseases and type 2 diabetes.

The joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Panel on Contaminants in the Food Chain (CONTAM) under the European Food Safety Authority (EFSA) provide scientific health-risk assessments associated with the consumption of such substances, that help define safe exposure levels with the aim of protecting consumers' health and ensure fair trade practices [1-3]. These committees and panels use the concepts of provisional tolerable weekly intake (PTWI) and benchmark dose lower confidence limit (BMDL), that provide the scientific base for the establishment of maximum levels (MLs) allowed in products by the European Union [4].

4.2. HEAVY METALS AND METALLOIDS

Heavy metals and metalloids that can be found in cereals are arsenic, cadmium, lead, mercury and nickel. These are common contaminants, occurring both naturally in the environment or as a result of anthropogenic activity, e.g. crops and water contamintation. A summary is presented in table 4.1.

Arsenic

Arsenic accumulates mostly in the outer layers of rice grains. Hence, whole-grain rice can have 50-80% more arsenic than white rice [8]. A very high consumption of rice and rice-products can result in an arsenic intake that exceeds the PTWI for inorganic arsenic. Children under three years of age are the most exposed group to inorganic arsenic, since they naturally eat more in relation to their bodyweight, thereby risking a relatively higher intake of arsenic than adults. National food and health authorities can address this potential risk through consumer education. This is the case e.g. in Denmark, where the dietary recommendations for children 0-2 years of age underline the importance of using a variety of different cereals in porridges, and of avoiding rice drinks and rice biscuits or crackers [9].

In 2020, EFSA concluded it is generally safe for adults to eat whole-grain rice, but children under three years of age and other high-level consumers are at risk of exceeding the PTWI. Consequently, the EU has started a monitoring programme on the occurrence of arsenic in foods and drinks [10].

Cadmium

Cadmium is mainly stored in the endosperm fraction of the grain. Thus, whole-grain products contain a more diluted cadmium content than refined-grain products.

In 2010, JECFA conducted an evaluation of cadmium dietary exposure for all age groups, including consumers with high exposure and subgroups with special dietary habits (e.g. vegetarians), and concluded that they are all below the PTMI [11]. Although available data indicated that most individuals had intake levels below the PTMI, several international bodies recognize that the margin between the PTMI and the actual monthly intake of cadmium by the general population is small and in some populations may even be non-existent [12]. Hence, there are no indications that the consumption of whole grains and whole-grain products poses a higher risk for toxic cadmium intake than the consumption of refined-grain products.

Lead

Lead is nearly eavenly distributed in all grain-kernel compartments, and as such whole grains and whole-grain products do not contribute significantly more to lead exposure than refined grains and refined-grain products.
However, for both adults, children and infants, the margins of exposure are such that the possibility of a toxic effect from lead in some consumers, particularly in children 1-7 years of age, cannot be

excluded. Lead is absorbed more in children than in adults and accumulates in soft tissues and, over time, in bones. Protection of children against the potential risk of neurodevelopmental effects caused by a toxic level of lead intake would be preventive in regard to all other adverse effects of toxic lead intake, in all populations. In 2011, JECFA withdrew the established PTWI and concluded that it was not possible to establish a new one that could be considered health protective [13-15].

Table 4.1. Summary of heavy metals and metalloids that can be found in cereals, their adverse health consequences, tolerable intakes and maximum levels allowed in products.

Name	Adverse health consequences & tolerable intakes	Maximum Level in products
Arsenic [5] (organic and inorganic forms)	Chronic arsenic poisoning (weakness, debility, loss of hair, hoarseness and weight loss); skin lesions; higher risk of cancer; neurotoxicity; higher risk of cardiovascular diseases; abnormal glucose metabolism and higher risk of type 2 diabetes; impaired fetal and infant development; reduced birth weight. BMDL01 = 0.3 and 8 µg/kg/day for cancers PTWI withdrawn[a]	Rice: 200 µg/kg Baby food: 100 µg/kg
Cadmium [7]	Kidney and liver dysfunction; osteoporosis; reproductive deficiencies; higher risk of cancer PTMI: 25 µg/kg/month	Cereal grains (except for wheat and rice): 100 µg/kg Wheat and rice: 200 µg/kg
Lead (organic and inorganic forms)	Chronic lead poisoning (colic, constipation and anemia); neurotoxicity and fetal neuro-developmental adverse effects; reduced learning capacity in children and youth; hypertension, other adverse cardiovascular effects; nephrotoxicity in adults. Current PTWI = 25 µg/kg no longer appropriate (no evidence of threshold for critical lead-induced effects)	Cereal grains: 200 µg/kg
Mercury, primarily methylmercury	Nephrotoxicity; hepatotoxicity; neurotoxicity; immunotoxicity; reproductive and developmental toxicity. PTWI = 4 µg/kg/week	None for cereals
Nickel	Systemic contact dermatitis in nickel-sensitized people; possible reproductive and developmental toxicity. TDI of 13 µg/kg b.w	None established

ML: maximum level; BMDL: benchmark dose lower confidence limit; PTWI: provisional tolerable weekly intake; PTMI: provisional tolerable monthly intake; TDI: tolerable daily intake.

[a] In 2011, JECFA concluded that the PTWI for Arsenic (2,1 µg/kg body weight per day) was no longer health protective as the BMDL0.5 value was in the same range as the PTWI value. The PTWI for inorganic arsenic has therefore been withdrawn [6].

Mercury

In general, mean dietary exposures do not exceed the tolerable weekly intake (TWI) for methylmercury across age groups in Europe, with exceptions in all age groups that are close to or above the TWI (e.g. high consumers of fish may exceed the TWI by up to approximately six-fold). Methylmercury is able to enter the hair follicle, and to cross the placenta as well as the blood-brain and blood-cerebrospinal fluid barriers, allowing accumulation in hair, the fetus and the brain. Thus, unborn children are the most vulnerable group for developmental adverse effects of methylmercury exposure, and pregnant women can be present in the group of high and frequent fish consumers, and therefore advised to limit their intake of fatty-fish types [16,17]. Cereal products are only considered a secondary source of mercury.

Nickel

In 2020, EFSA concluded that nickel in foods and drinking water primarily poses a risk for nickel-sensitized persons [18]. Since nickel is accumulated in the bran, whole grains and whole-grain products might pose a larger risk for nickel-sensitized persons, and should be avoided. However, this is only a concern for very small fractions of European populations.

4.3. PESTICIDES

Pesticides are applied to crops with the purpose of reducing unwanted weeds, fungi, insects and other pests that can affect crop yields negatively. While pesticides can be necessary to combat pests, pesticides' residues in foods are unwanted substances [19].

Application of pesticides in grains is heavily regulated by both EU and UN organizations [20,21]. Rules and regulations prescribe which pesticides can be used in different crops and how, in which concentrations, and when they can be applied in relation to harvest time [22].

The risk of pesticide residues in grains is low since pesticides are mainly applied during spring and in the beginning of the growing season, through which pesticides gradually degrade before harvest. Some pesticides are used during storage of the grains. Any pesticide residues will predominantly be present on the surface of the grain, i.e. the bran of the grain. Thus, whole-grain products are more likely to contain pesticide residues compared to refined-grain products. During storage and processing any remaining pesticide residues will further decompose. A 30-100 per cent residue reduction is expected for the end product, e.g. whole-grain flour [23,24].

Organic products are generally lower in pesticide residues, since pesticides are not used on organic crops, but a certain risk of contamination and spillover from the surrounding environment remains.

It is well accepted that acute pesticide poisonings has several adverse health consequences, such as seizures, rashes, and gastrointestinal illness, and in particular persons applying pesticides to the crops are at risk of such acute effects. Chronic effects, such as a higher risk of cancer and adverse reproductive outcomes, have also been reported.

The EFSA uses a special computerized model to estimate the dietary exposure of European consumers to pesticide residues. The expected exposure is then compared with acceptable exposure levels, known as toxicological reference values, to assess the risk to consumers. In 2014, the EU-coordinated control program (EUCP) concluded that the probability of European citizens being exposed to pesticide residues in concentrations that may lead to negative health outcomes was low for the 12 food categories evaluated, but for a limited number of samples a possible short-term health risk could not be ruled out. The long-term exposure estimations were negligible or within acceptable levels. Thus, residues of pesticides are not likely to pose long-term consumer health risks in regard to the consumption of whole grains or whole-grain products [25-27].

4.4. POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous pollutants formed by incomplete combustion (pyrolysis) of several organic materials. PAHs occur as complex mixtures, never as individual components. They are chemically stable and highly lipophilic in nature and occur as contaminants in different food categories, including cereals. The two highest contributors to the human diet are cereals and sea food and products thereof [28].

The occurrence of PAHs in cereals can be due to fallouts from polluted air at the growing site of crops, or through contamination by drying harvested crops with impure air. Studies have shown a higher content of PAHs in crops grown in highly industrialized areas or near heavily trafficked areas and roads. In contrast, PAHs are unlikely to be absorbed via the root network of plants grown in a PAH-contaminated soil. The concentration of PAHs is naturally highest in the bran of the grains. Although only low levels of PAHs occur in cereals and cereal products, they are estimated to make a significant contribution (approximately one third) to total PAH intake through diet, because cereals constitute a large part of the human diet [29]. However, the low lewels of PAHs in whole grains are not considered a public health concern.

Experimental studies on animals show that several of the PAH compounds are genotoxic, carcinogenic, or affect the immune and the resproductive systems. The most carcinogenic of these substances, benz[a]pyrene (BaP), is often used as a marker for all carcinogenic PAHs. In 2008, the CONTAM Panel concluded that BaP is not a suitable indicator for the occurrence of PAHs in food. Based on the currently available data relating to occurrence and toxicity, the CONTAM Panel concluded that PAH4 and PAH8 are the most suitable indicators of PAHs in food, with PAH8 not providing much added value compared to PAH4 [29]. Minor contamination of crops with PAHs is difficult to avoid completely, hence measures to control and monitor PAHs are necessary. The European Commission's Scientific Committee on Food (SCF) recommends that the content of PAHs in foods should not be detectable. If found in a measurable amount, the food is unacceptable. Even so, the commission has established a ML of 1 µg/kg for the presence of PAHs in cereal-based products [30,31].

4.5. MYCOTOXINS

Mycotoxins are toxins that can be formed when fungi (e.g. *Penicillium* and *Aspergillus*) grow on crops and foods. Several fungi occur naturally in a variety of plant products such as cereals. Mycotoxins can be formed in grain products during storage, especially in years when the harvesting period is wet, and the grain is not dried sufficiently before storage.

Visible growth of fungi is known by most as mold stains on bread. Moldy foods are unsuitable for human consumption, and porous or watery foods such as bread or jam with mold must always be discarded, because toxins may be dispersed throughout the food. The lack of or the amount of visible mold is not a good indicator of either presence or concentration of mycotoxins in a food. Foods without visible mold can contain mycotoxins, either because the growth of the fungi is invisible or because the fungi is no longer present in the food after processing. However, mycotoxins are generally very stable substances that are not readily degraded during processing and food preparation.

Table 4.2. Summary of mycotoxins that can be found in cereals, their adverse health consequences, and maximum levels.

Name	Adverse health consequences	Maximum levels
Aflatoxins B1, B2, G1 and G2	Carcinogenic (liver) [34]; genotoxic Less than 1 ng/kg/day increases risk of liver cancer	Cereals: 4 µg/kg Baby food: 0.1 µg aflatoxin B1/kg
Ochratoxin A	Nephrotoxic; possibly carcinogenic (kidney) [35]; teratogenic (abnormal development); adverse immunological effects. TWI = 120 ng/kg Non-neoplastic effects BMDL10 = 4.73 µg/kg/day Neoplastic effects BMDL10 = 14.5 µg/kg/day	Cereals: 3 µg/kg Baby food: 0.5 µg aflatoxin B1/kg
Deoxynivalenol	Human toxicoses, e.g. nausea, vomiting, diarrhea, headache, fever	Flour and pasta: 750 µg/kg Bread and breakfast cereals: 500 µg/kg
Fumonisin B1	Suspected to be a human carcinogen by IARC	Maize products: 1000 µg/kg Breakfast cereals: 800 µg/kg Baby food: 200 µg/kg
Zearalenone	Identified as possible human carcinogen by IARC	Flour: 75 µg/kg Bread: 50 µg/kg Baby food: 20 µg/kg
Ergot-alkaloids	Vasoconstrictive effects, that can lead to hallucinations, atrophy, gangrene and ultimately death. ARD: 1 µg/kg Group TDI = 0.6 µg/kg	Cereals: provisional limit value 500 mg/kg

TWI: tolerable weekly intake; BMDL: benchmark dose lower confidence limit; ARD: acute reference dose; TDI: tolerable daily intake; IARC: International Agency for Research on Cancer.

The European Commission regulates MLs for mycotoxins in foods [1], and the WHO has performed risk assessments of mycotoxins [32]. Mycotoxins can cause diseases as they can damage the liver, kidneys and the nervous system. The potential carcinogenicity of mycotoxins in humans has been subject to extensive evaluation, with focus on associations between mycotoxin exposure and primary cancers of the liver, breast, and cervix [33]. The most common mycotoxins present in foods are aflatoxins B1, B2, G1, G2, ochratoxin A and ergot- alkaloids [33]. A summary of common mycotoxins in cereal foods is presented in table 4.2.

Mycotoxins in cereals can be an issue of public health concern, why monitoring of human exposure is important. The EU has set MLs for these five groups of mycotoxins, and EFSA's comsumption databases monitor exposures. Recent analyses of exposure levels reveal that they are below the tolerable weekly intakes in the adult European populations. Currently, it is not possible to indicate whether whole-grain products pose a higher risk for mycotoxin exposure than other types of foods, even though naturally occurring aflatoxins might be present in whole grains, and these contaminants increase the risk of liver cancer [34].

4.6. N-NITROSAMINES

N-nitrosamines are formed in food as a result of natural chemical interactions, but mainly through food processing activity. Most are potent carcinogens and their detection and elimination is therefore of considerable importance [36].

N-nitrosamines are formed by reaction between secondary amines and nitrogen oxides. This can happen, for example, if grain products come into direct contact with drying combustion gas.

In grains, bread or breakfast products nitrosamines are rarely detected or detected only in very low concentrations near the analytical detection limit.

4.7. ACRYLAMIDE

Acrylamide is a low-molecular weight, highly water soluble, organic compound developed during heat treatment at particularly high temperatures, such as during frying and baking of carbohydrate-rich foods. The higher the temperature used (above 120 °C), the more acrylamide is usually formed. Likewise, longer cooking time gives rise to more acrylamide as the formation increases greatly as the water content decreases. Therefore, the acrylamide content in crispbread and toasted rye bread is significantly higher than in baked bread, where the proportion of browned surface is smaller. In wheat bread, levels are lower than in rye bread. Levels in porridge are five times lower than in breakfast cereals overall. Bran, wheat and rye-based breakfast cereal levels are about double those for maize, oat, spelt, barley and rice [27,37].

Acrylamide can damage the nerves, interfere with cell division processes and reproductive capacity. Experimental studies in animals have shown that acrylamide is carcinogenic [38]. However, the evidence of a carcinogenic effect in humans is not well established, and several questions regarding associations found in some studies but not in others remain unanswered [39,40].

The CONTAM panel concluded that the current levels of human dietary exposure to acrylamide are not of concern with respect to non-neoplastic effects. Still, whole-grain bread and cakes baked with whole-grain flour may contain 50-100% more acrylamide than refine-grain variants. However, these differences are highly dependent on grain variant, baking time and temperature, as well as liquid content in foods [41]. In addition, exposure to acrylamide in food can range from 20 times the exposure level considered of low concern for average adult consumers, to 200 times the level of concern for high consuming toddlers [27]. Therefore, the EU Commission has passed regulation establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in different food groups [42].

4.8. BACTERIAL CONTAMINANTS

Only a few species of pathogenic bacteria occur in cereals and cereal products, but particularly *Bacillus* bacteria are relevant. Several species of *Bacillus* bacteria have been described in association with food poisoning, especially after intake of meals with cooked or fried rice or flour (e.g. gravy, cream with cornmeal, and flour-containing meats) [43]. Such food poisoning can occur because raw cereal products (e.g. rice or flour) can be contaminated with *Bacillus* spores, that are quite common in earth and dust, and are rather resilient to common cooking temperatures. If not properly cleaned and cooked, potential *Bacillus* spores in such foods can become active bacteria and be the cause of food poisoning. Symptoms of a *Bacillus* poisoning (e.g. vomiting, diarrhea) occur relatively quickly, namely after five hours. The course of poisoning rarely extends beyond 12-48 hours [44].

However, most infections with Bacillus can be prevented if foods are handled according to good hygiene standards, namely properly cleaning of raw foods/ingredients, correct cooking temperature and time, as well as fast cooling and fridge-storing after finishing the cooking process.
The latest European Union One Health 2018 Zoonoses Report from EFSA and ECDC states that *Bacillus* infections are rarely reported, since they are overshadowed by *Salmonella* infections [45]. Hence, such contaminants are not more widespread in whole grains and whole-grain products than in many other food categories, and pose no special concern.

4.9. CONCLUSION

A variety of unwanted substances and/or contaminants from different sources can, similarly to other foods, be found in whole grains and whole-grain products. For whole grains and whole-grain products, levels of such substances do not differ considerably from the levels found in refined grains or refined-grain products. As long as the maximum levels stipulated by the EU for different groups of foods are not exceeded, unwanted substances and contaminants in whole grains and whole-grain products pose very few food safety or health concerns, but awareness must be kept regarding potential problems deriving mainly from arsenic, but also aflatoxins and acrylamide to some extent. Furthermore, consumer education programs and campaigns must provide consumers and professionals with knowledge on how to use cereals in safe manners.

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CHAPTER 5
Sustainability aspects of whole-grain consumption

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5.1. INTRODUCTION

This chapter aims to provide an insight into the sustainability of whole grains in terms of environmental impact, and the role of whole grains regarding sustainability of the total diet that can be considered when developing a recommendation for whole-grain intake.

Environmental impact and nutritional adequacy are central elements in the definition of sustainable diets. Thus, the Food and Agriculture Organization of the United Nations (FAO) defines sustainable diets as "…those diets with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations. Sustainable diets are protective and respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable; nutritionally adequate, safe and healthy; while optimizing natural and human resources" [1].

The environmental impact of food is described by parameters such as greenhouse gas emission (climate impact), land use, water use, biodiversity, toxic impact, acidification and eutrophication [2].

Food production is estimated to account for up to 30% of the global climate impact in Western countries [3,4], and for a significant proportion of the environmental impact on the planet [5]. Especially with regard to loss of biodiversity and the nitrogen and phosphorus emissions the proposed planetary boundaries have been exceed, whereas the levels of climate change and land system change are in zone of uncertainty but with increasing risk of reaching planetary boundaries [6].

To be able to address these increasing serious environmental impacts and at the same time ensure adequate food production for a global growing population there is a need to reduce the environmental impact at all stages of the food supply chain – from primary production and processing to retailers, consumer's dietary composition and food waste [4,7].

To help governments and other actors in policy-making to implement sustainability in their Food Based Dietary Guidelines (FBDG), FAO and the World Health Organization (WHO) have developed a set of "Guiding Principles for Sustainable Healthy Diets". It is emphasised that a sustainable diet includes whole grains, legumes, nuts, fruits and vegetables and that it can include moderate amounts of eggs, dairy, poultry and fish; and small amounts of red meat due to both the health and environmental properties of the foods [8].

Since whole grains play a role in healthy diets (see chapter 3), it is relevant to examine the significance of the environmental impact of different kinds of grains and whole grains, and the environmental impact of grains in the diet. The current chapter also discusses the nutritional significance of grains and whole grains in plant-based diets. The content is partly inspired by the scientific work of including sustainability in the Danish food-based dietary guidelines [9,10].

5.2. ENVIRONMENTAL FACTORS, SYSTEM BOUNDARIES AND DATABASES

The climate impact is often expressed in CO_2-equivalents (eq), which is a common unit for all greenhouse gases. It is typically expressed as kg CO_2-eq per unit weight of food, but estimates expressed per protein or energy content may also be used [11].

Land use (LU) is the area used to farm the crops that are used to provide a unit (e.g. in kg) of the product. In the case of animal products, the land used for animal feed is also calculated. In addition, it is relevant to distinguish between arable land and non-arable land with regard to land use for grassing [12].

The contribution from land use changes (LUC) to the climate impact of food or food groups is included in some studies [12]. The impact is estimated either as direct LUC (dLUC) or as indirect LUC (iLUC). It is based on the estimates of changes in food demand that will affect agricultural land demand at the global level. An increase of agricultural land for food, feed or biomass (for energy production) in replacement of native vegetation such as forest will decrease the amount of carbon that could be stored and thereby increase the CO_2-eqv emissions [13]. The standard PAS 2050 [14] and the carbon opportunity cost method by Searchinger and colleagues (2018) are examples of dLUC, where the climate impact of the specific LUC is assigned to the specific crop grown at the areas of LUC [15]. Especially the data from Searchinger and colleagues result in a several times higher climate impact of the foods, e.g. more than three times for beef. Indirect LUC effects is a change in land use caused indirectly as a consequence of a direct LUC taking place somewhere else in the world. The total effect of LUC is in iLUC assigned to all food depending of LU. The estimates differ depending on the specific method of estimating iLUC. One method for including iLUC has been suggested by Audsley and colleagues (2009) [16]. They found an average iLUC emission factor of 143 g CO_2-eq per m^2 (arable) used for crop production [16], while other estimates of iLUC provides other values [17,18]. The European Product Environmental Footprint guidelines has suggested, that LUC is not currently included in the climate calculations, due to the uncertainty of methods and data [19].

The use of water in the production of a product is expressed as the so-called "water footprint" (e.g. in litres per kg). It can be divided into the blue water footprint (represents the use of groundwater and surface water) and the green water footprint (represents the use of rainfall) [20]. This may be particularly important in areas with declining groundwater or surface water availability and therefor inclusion of water scarcity in the footprint has been suggested [20,21].

Water eutrophication occurs when a high concentration of nutrients such as nitrogen and phosphor is present. Fertilizers with nitrogen and phosphorus are commonly used in plant production. The excess nitrogen and phosphorus can run off in the aquatic systems resulting in excessive growth of algae, oxygen-depletion and water toxicity, which can disturb normal ecosystem function [22,23].

Biodiversity can be described by genetic and functional diversity [6]. Genetic diversity is about the number of species as well as the genetic variation within species, while functional diversity is about the function that the species performs in the ecosystem. Quantifying the impact on biodiversity from food production is challenging. For example, biodiversity impacts arise from several impact pathways (e.g. land use, use of pesticides, water pollution, climate change), and biodiversity includes a diversity of ecosystems, species, breeds and genes [24].

Other environmental parameters are also relevant e.g. pesticide emissions and different contaminants which influence both environmental and human toxicity [8].

In this chapter we primarily focus on the effect of the consumption of grains (and cereals) on climate (greenhouse gas emissions), but also partly on land use and water use.

For individual foods within the food groups, estimates of the environmental impact can vary widely, partly because they rely on data from different life cycle assessments (LCA) and partly because they involve different contributions from farm to fork and different areas and production conditions. In figure 5.1, an example of the system boundaries for the consumption of bread shows the many steps affecting the environmental impact of consumption of bread.

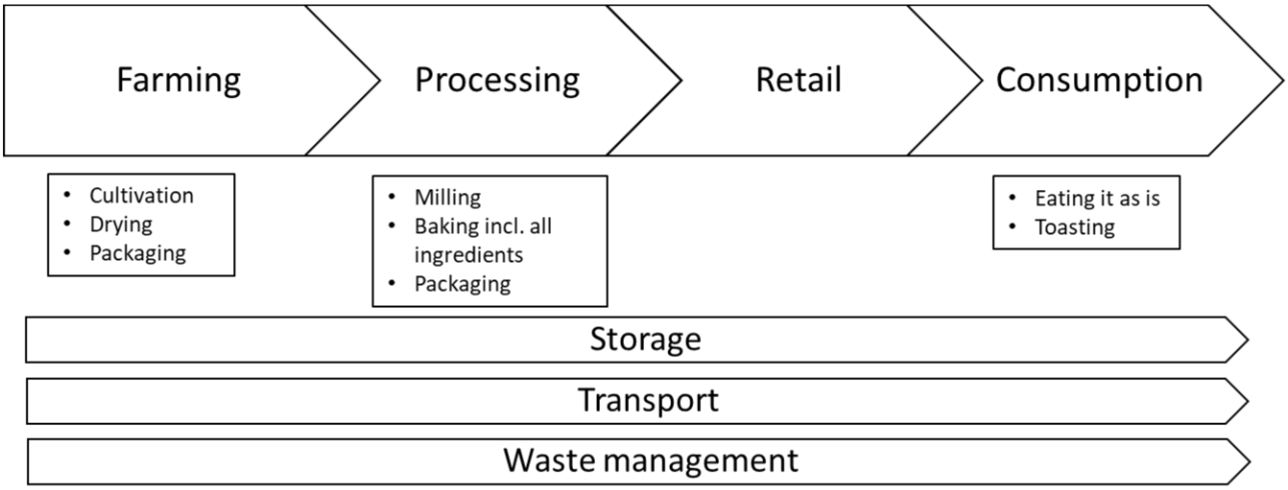

Figure 5.1 – Example of the system boundaries for consumption of bread. Inspired by Espinoza-Orias et al. (2011) [25].

With regard to climate impact, several studies conclude that the raw material phase (agricultural activities, including use of pesticides and fertiliser) is the most burdensome phase [25-28]. Processing and distribution are also hot spots [27,29]. Additionally, the ingredients used for bread making influence the environmental impact. Based on weight, a study found that breads made with simple ingredients such as flour, water, yeast and salt had the lowest impact, but based on energy as a functional unit bread made with animal fat had the lowest impact [28]. Depending on how the bread is treated at the consumer phase, consumption and waste disposal are also important stages [25,27].

Data on the environmental impact of foods are accessible in different databases. The databases can be very different with regard to both system boundaries and the parameters included. However, no matter which database is used, you can compare the different foods within the individual database. One example is the French LCI database AGRIBALYSE® for the agriculture and food sector. The latest version, published in 2020, comprises LCIs for 2.500 agricultural and food products produced and/or consumed in France, combining a production-based approach and a consumption-based approach [29]. Another example is the Cool Food Pledge Calculator from World Resources Institute (WRI), designed to help food providers set targets and track climate impacts over time [13]. It is based on climate impact data emissions from agricultural supply chains from Poore & Nemecek (2018) and with the option to add carbon opportunity costs from Searchinger et al. (2019) [15, 30]. Data often describe the environmental impact in overall food groups. E.g., bread and cereals may be divided into rye bread, wheat bread and pasta, or it may be in one group. Typically, oat/oatmeal are described separately. Rice is similarly described separately, but there is usually no distinction between white and brown rice. Furthermore, rice is often not presented as the ready to eat product as bread is.

5.3. ENVIRONMENTAL IMPACT OF DIFFERENT KINDS OF GRAINS AND GRAIN PRODUCTS

In general, plant foods have a relatively low climate impact compared to animal foods. Grains and cereals are, together with vegetables, fruits, legumes and pulses, among the food groups with the lowest climate impact (CO_2-eq/kg food) [30,31]. In the review by Poore & Nemecek (2018b), all stages from production up to and including retail, with waste, are included [30]. The climate impact from land use change is included, based on a model from Blonk Consultants [32,33]. The model is consistent with PAS2050-1, which is a publicly available specification (PAS) providing a method for assessing the life cycle greenhouse gas emissions of goods and services [34]. Clune et al. (2016) includes all stages up to and including the regional distribution centres, i.e. before retail. Land use change is not included [31].

Although rice and other grains used for breakfast cereals, bread and pasta have a lower content of protein than meat and other animal products, both the climate impact per weight and the climate impact per 100 g of protein are lower than for animal products. E.g., the climate impact per kg of wheat or rye bread is only about one tenth of the climate impact of pork and more than one twentieth of the climate impact of beef (dairy herd) [30]. The same pattern applies to land use.

Rice has a higher climate impact than wheat and rye (flour and bread) [30,31]. Oatmeal has a relatively high median value for both climate impact and land use compared to wheat and rye bread [30]. However, the value for oats is no higher than for rye and wheat in Clune et al. (2016), e.g. 0.38 kg CO_2-eq per kg product for oats and 0.52 kg CO_2-eq per kg product for wheat [31]. Figure 5.2 shows the variation of median values for climate impact and land use for starch rich products [30]. It also illustrates the large variation in data for each type of product and that not all products are comparable. E.g., one must be aware that comparing 1 kg uncooked rice with 1 kg bread might not be fair to the rice. For 1 kg of cooked rice, only about 400 g of raw rice must be included. If one disregards the energy, water and salt used for cooking the rice, then in theory one could divide the climate impact of the raw rice by 2.5, which largely offsets the difference. It is also worth noticing the relative low climate impact and land use from potatoes.

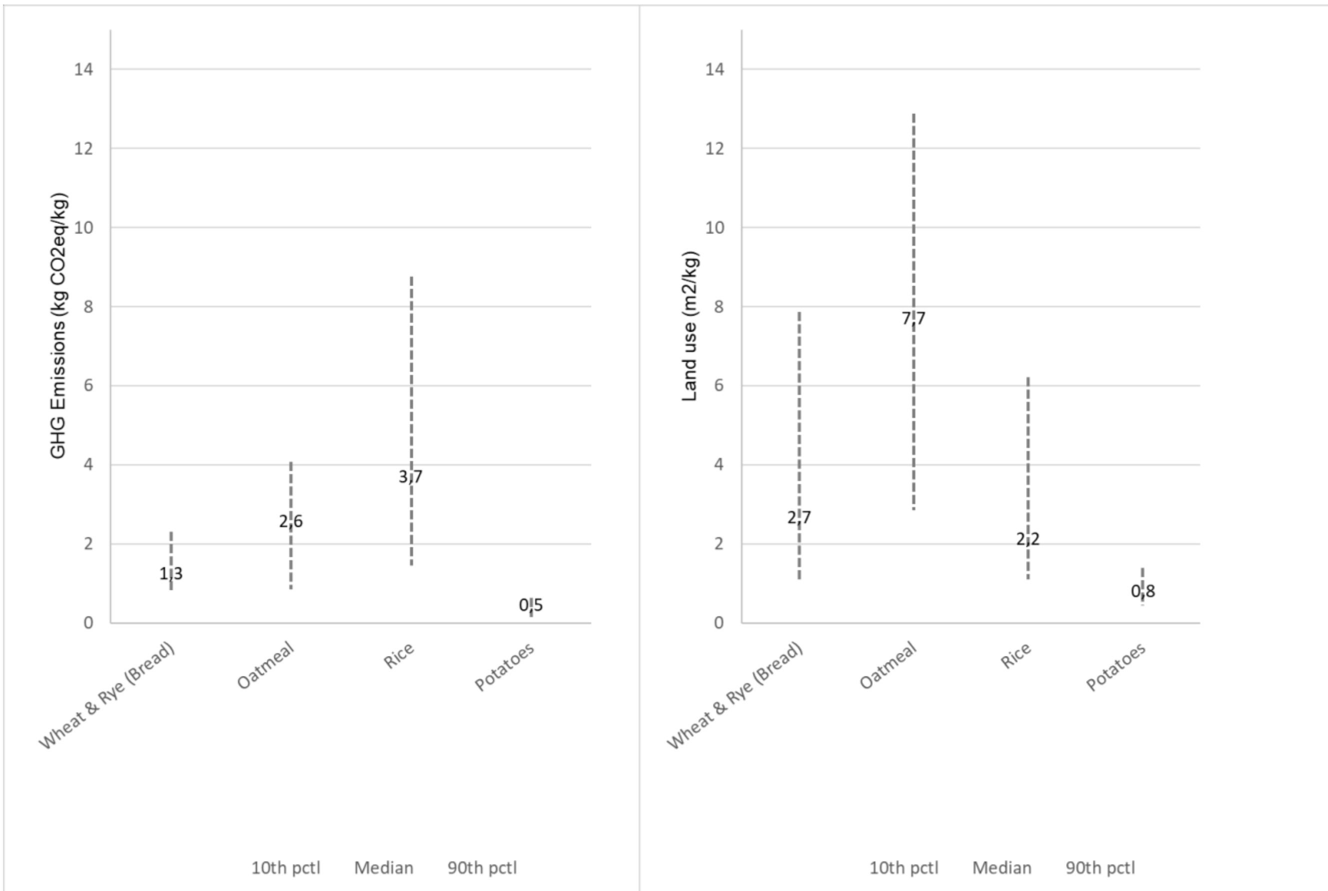

Figure 5.2 – Climate impact and land use from wheat, rye, oat, rice and potatoes. Modified by Lassen et al. (2020) from Poore & Nemecek (2018b) [10,30]. Left: climate impact as CO2-eq per kg retail weight (data based on: IPCC 2013); and right: land use as m2 per kg retail weight. The dotted lines illustrate the variation between the 10% percentile and the 90% percentile. The number is the median value.

Water used for irrigation and processing is also part of the environmental impact. Agricultural production is estimated to account for 86% of the water used globally [35,36]. Rice has the largest share in the total water volume used for global crop production. One estimate is that it consumes about 21% of the total volume of water used for crop production at field level [36]. The second largest water consumer is wheat (12%). Problems with water scarcity must be addressed both locally and globally due to the interconnected nature of the world economy [21]. E.g., Italian durum wheat is grown using modest amounts of irrigation, but with a moderate to high water scarcity. In contrast, the cultivation of basmati rice in India requires much larger amounts of irrigation water and it is grown in regions that are generally characterized by moderate to high water scarcity [35,37]. As a result of this, the blue water scarcity footprint of basmati rice has been found to be two orders of magnitude greater than pasta in the British diet [35].

Whole grains and refined grains

Few studies have examined the environmental impact of whole-grain products compared to products made with refined grains. A study on the carbon footprint of white and wholemeal bread in the United Kingdom found that wholemeal bread had the lowest carbon footprint, with the carbon footprint of wholemeal bread being 6-7% lower than that of white bread [25]. The flour used for the wholemeal bread was exclusively wholemeal flour made from the whole grain, while the white bread was made with white flour containing 75% of the grain. The wholemeal bread had a lower carbon footprint due to a more efficient utilisation of the wheat grain. Jensen & Arlbjørn (2014) refer to a study done by Kingsmill in 2012 in which wholemeal bread had an approximately 5% lower carbon footprint than white/mixed bread [27]. The content of wholemeal flour in the wholemeal bread is not specified.

The Whole Grains Council also argues for a more efficient yield of wheat grain and shows an example of one bushel of wheat resulting in 60 loaves of whole-grain bread and only 42 loaves of white bread [38].

It is not clear to what degree these calculations take into account possibly extra grinding to produce whole-grain flour and the use of the separated grain parts in other foods or animal feed.

Organic grains and grain products

Organic agriculture is a production system that relies on ecological processes, biodiversity and cycles adapted to local conditions, rather than use of chemical pesticides and fertilizers [39]. A meta-analysis found that on average, organic farming increased species' richness (as a measure of biodiversity) by about 30%, though with great variety. The average effect size and the response to agricultural intensification depends on taxonomic group, functional group and crop type. E.g., the crop types showed varying responses, with large positive effect sizes in cereals and mixed farming, and moderate positive effect sizes for all others [40].

With regard to other environmental parameters, a study found that organic systems require more land, cause more eutrophication, and use less energy, but have similar greenhouse gas emissions per unit of food as conventional systems [41]. In an Italian study comparing organic rice production to traditional production the greenhouse gas emission per hectare decreased but the emission per kg increased due to lower grain yield [42]. Similarly, a case study on wholemeal bread found a higher carbon footprint per unit of organic product compared to the conventional product due to lower yield per unit of area, and to the consequent attribution to a smaller amount of products of the greenhouse gas emissions generated in the field phase of the life cycle [43]. Finally, a life cycle assessment of eight scenarios of bread production found that combining organically grown wheat, industrial milling, and a large bread factory was the most advantageous way of producing bread. This was found with respect to e.g. greenhouse gas effects and eutrophication, but not with respect to land area required to produce grain for 1 kg of bread [44].

5.4. ENVIRONMENTAL IMPACT OF GRAINS AND WHOLE-GRAIN PRODUCTS IN THE DIET

When evaluating the environmental impact of specific foods, it is not enough to evaluate the foods separately. It is essential to consider how they are included in the overall diet because the foods are included in different quantities, contribute with different combinations and amounts of nutrients, and there are significant differences in intake between populations.

Despite differences in absolute values, results from the literature show that a typical western diet from Northern Europe and the United States has a high climate impact and high land use compared to e.g. Indian and Peruvian diets because of a higher content of ruminant meat and dairy products in a typical western diet [45]. The foods consumed in Europe with the highest environmental burden are meat and dairy products [46]. Notarnicola et al. (2017) found, that reducing the content of meat and dairy products in an average European diet by 25% and substituting the energy content with cereals could reduce the environmental impact with regard to e.g. climate change, land use and water resource depletion [46]. With this replacement the mean protein intake falls, but it is still higher than the dietary requirements set by WHO [47]. Whether the content of other nutrients was sufficient with this replacement was not calculated.

A study based on food availability per capita in 2003 in Europe, describes the European diet in several clusters [48]. In three Nordic countries and France 36.7% of the energy originated from animal products and 24.6% from cereals. In contrast, in South-East Europe the energy contribution was 24.6% from animal products and 34.8% from cereals. These differences in dietary composition are important to consider when evaluating the environmental impact of European diets.

In an average diet based on dietary survey data in four European countries (Denmark, Czech Republic, Italy, and France), grains contribute to about a third of the energy intake, but only about 10% of the greenhouse gas emission and 15% of the land use [49]. In contrast, meat products contribute to about 10% of the energy intake, more than a third of the greenhouse gas emissions, and about half of the land use.

Evidence based on reviewing dietary modelling studies indicates that eating diets with reduced intake of animal products – especially red meat – and increased intake of vegetables, fruit, legumes, seeds, nuts, and whole grains is both healthier and associated with a lower impact on the environment [50]. The magnitude of this effect depends on composition of the current diet and the magnitudes of changes. A review by Aleksandrowicz et al. (2016) reported a median reduction in greenhouse gas emissions of 12% (quartile 1 (Q1): 2%; Q3: 16%) for dietary patterns following healthy guidelines. Slightly greater effect was found in relation to reduction of land use (median 20%; Q1: 16%; Q3: 26%) [51].

In a study by Behrens et al. (2017) in 28 high-income countries including 21 European countries, a diet in accordance with the dietary guidelines led to reductions in climate impact of an average of 13%. The most significant changes to comply with the dietary guidelines were reducing sugars, oils, meat and dairy and increasing fruit, vegetables, and nuts. In addition, in 14 of the 21 high-income European countries the contribution of energy from grains was increased, while it was reduced in seven countries [52].

When sustainability aspects are included in dietary guidelines, the reduction may be different from not including sustainability. A study from the United Kingdom showed a reduction in climate impact of 31% for a diet in compliance with the Eatwell Guide with a similar energy intake as the average dietary intake [53]. In addition, they found that the savings on land use were 34%. This is the result of reducing the amount of dairy, meat, rice, pasta, pizza and sweet foods, and increasing potatoes, fish, wholemeal and white bread compared to the current UK diet.

When taking sustainability aspects into account, apart from reducing animal products and increasing plant products, one can choose the food with the smallest environmental impact within each food group, e.g. less ruminant meat and more poultry or less rice and more potatoes according to data from Poore & Nemecek (2018b) [30].

5.5. THE NUTRITIONAL SIGNIFICANCE OF GRAINS AND WHOLE-GRAIN PRODUCTS IN A PLANT-BASED DIET

A plant-based diet can be defined as a diet that consists mostly or entirely of plant-based foods [54]. When recommending a more plant-based diet with less animal-based products, it is important the diet contains foods that contribute the nutrients that might be scarce because of reducing meat, fish, eggs and dairy products. Depending on which and how much you reduce the content, the nutrients can be protein, n-3 fatty acids, vitamin A, vitamin B2, vitamin B12, vitamin D and calcium, iodine, iron, zinc and selenium. This includes a stronger emphasis on the intake of e.g. legumes, nuts and seeds, vegetables including dark green vegetables, whole-grain products, and vegetable oils [9,21].

Grains play a significant role in most diets and this is also the case in an example of a global healthy reference diet that could help limit environmental changes. Such a diet was developed by the EAT-Lancet Commission [4]. In this diet, whole grains included an amount of 232 g/day (dry weight). Based on the EAT-Lancet reference diet, a study developed an example of a Danish adapted healthy plant-based diet [9]. Compared to the average Danish diet, the content of bread, grains and cereals increased by almost 60% and the content of whole grain doubled, when modelling a diet with reduced content of animal products to a more sustainable level. The total amount of bread, pasta, rice, breakfast cereals and flour/grits were also used to maintain an isocaloric content and ended at around 390 g (240 g bread, 30 g pasta (cooked), 24 g rice (cooked), 10 g breakfast cereals, 35 g flour/grits (cooked)) per 10 MJ [9]. Around 75% of the bread, grains and breakfast cereals were whole-grain products and the dietary content of whole grain came just under 120 g per 10 MJ.

This level of whole-grain intake was necessary in this model to reach the recommended level of zinc and iron in particular. Grains (bread, pasta, rice, breakfast cereals and flour/grits) contribute e.g. 26% of protein, 41% vitamin B1, 33% iron and 36% zinc in the Danish adapted healthy plant-based diet (unpublished data). In this diet, the content of essential amino acids is adequate due to a combination of different plant protein sources (legumes, nuts and grains) and a small content of animal products.

An increase in dietary grain content was also found in a study on optimizing the current Italian observed diet with regard to both nutrition and greenhouse gas emissions. The diet optimization resulted in a nutritionally adequate pattern minimizing greenhouse gas emission values [55]. In this study the mean content of bread, flour, pasta, rice, biscuits and the like increased by almost 30% compared to the Italian observed diet for an adult population. Reducing the content of meat increased the contribution of cereals to the intake of protein by almost 20%, and iron by about 10% [55].

Some grains have a high content of minerals and whole grains, in particular, have a significant content of those minerals that must be taken into account in a plant-based diet. E.g., the whole-grain versions of millet, oat, rye and brown rice have a significant content of iron and zinc (Frida.fooddata.dk). A regulation from the European Union (EU) defines a significant content as more than 15% of the nutrient reference values supplied by 100 g or 100 ml in the case of products other than beverages [56].

Grains grown in areas with a high content of selenium in the soil also have a significant content of selenium, but the concentration of selenium in the soil in Europe is low compared to other parts of the world [57,58], making it difficult to get enough selenium from plant-based sources alone. In Finland, selenate is added to agricultural fertilizers resulting in an increased intake of organic selenium for both humans and animals [23].

When using grains as a source of iron and zinc, bioavailability becomes important. To increase the bioavailability of iron and zinc from grains, the presence of animal tissue such as meat and fish, as well as vitamin C in the diet enhances the iron absorption [59]. In addition, some food-processing practices (e.g. soaking, fermenting and longer rising time) can reduce the phytate content of grains, resulting in an increase in the bioavailability of iron and zinc from grains [60].

5.6. CONCLUSION

Grains and cereals are, together with vegetables, fruits, legumes and pulses, among the food groups with the lowest climate impact per kg of food. When comparing the different types of grains and cereals, rice tends to have a higher impact than wheat, rye and oats.

Few studies have compared whole-grain products with products made from refined grains, but whole-grain bread might have a slightly lower climate impact per kg than bread made from refined grains. Further, it is not clear to which degree the studies take possibly extra grinding and the use of the separated grain parts in other foods or animal feed into account.

When using estimates of the environmental impact of foods, one must be aware of any differences in e.g. the system boundaries, life cycle assessment methods and production conditions. Fortunately, reviews and databases with environmental data typically adjust for these differences.

When evaluating the environmental impact of specific foods, it is not enough to evaluate the foods separately. It is essential to consider how they are included in the overall diet because the foods are included in different quantities, contribute with different combinations and amounts of nutrients, and there are significant differences in intake between populations.

Although grains make up a relatively large proportion of the typical European diet, they still make up a smaller part of the climate impact from a total diet due to the high climate impact from most animal products.

No matter the diet, whole grains play a significant role and can help raise the nutritional content of a diet. When transforming the diet to a more healthy and sustainable plant-based diet with less animal products, whole-grain products become even more important. Together with legumes, grains contribute essential amino acids. Further, whole-grain products have a significant content of those minerals that may be limited in a more plant-based diet, e.g. iron and zinc.

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CHAPTER 6
Establishing a quantitative recommendation for whole-grain intake

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6.1. INTRODUCTION

This chapter aims to clarify relevant aspects regarding the establishment of a quantitative recommendation for whole-grain intake that other European countries can use for a national accepted recommendation.

Results from previous several prospective cohort studies and meta-analyses show inverse associations between whole-grain intake and incidence of non-communicable diseases and mortality [1-3] (see also Chapter 3 of this report). These results still need to be verified in randomised, controlled trials (RTC) but completing such RCTs might not be possible due to the necessary time course and risk of low compliance in long-time trials. However, since the results of the cohort studies are consistent, they have formed the basis for recommendations about whole-grain intake in many countries worldwide.

Recommendations for whole-grain intake can be based on health effects taking both endpoints of non-communicable diseases and effect size of risk of disease, mortality, and disability-adjusted life-years (DALYs) into account. This method is used in the estimate of recommendations for optimal level of intake of certain nutrients and food groups in the Global Burden of Disease Study [4]. The method requires complicated statistical modelling and does not take nutrient supply and other nutritional issues into account. Being a global model, neither does it consider local dietary habits. When the EAT-Lancet Commission introduced their planetary, healthy diet from sustainable food systems, associations between food intake and health outcomes formed the basis for recommendations of intake of several food groups, mainly the major protein sources (e.g. meat, fish, and dairy foods) [5]. However, for the carbohydrate sources (grains and tubers), the recommendations were adjusted to maintain target energy intake and not just to reduce disease risk. Since there is sound evidence for positive associations between whole-grain intake and health, the Commission suggested that all grains in the diet should be whole grains [5]. The EAT-Lancet commission quantified the healthiness of the suggested diet and confirmed the adequacy of most micronutrients, the only exception being vitamin B_{12}.

In most European countries, the official dietary guidelines include a recommendation for whole-grain intake [6] (see also Chapter 1 and Appendix A in this report). Most guidelines are qualitative: e.g. “Prefer whole grain” (e.g. Belgium, Malta, Poland, France); “Replace white-flour bakery products with whole-grain bakery products” (Czech Republic). However, some guidelines are quantitative: “Eat at least 125 g of whole-grain products every day and replace refined products with whole-grain products” (Belgium); “Eat at least 90 grams of brown bread, wholemeal bread or other wholemeal products/4-5 servings of whole-grain foods every day” (The Netherlands); “Eat 70 grams of whole grain per day if you are a woman and 90 grams per day if you are a man" (Norway, Sweden); "Eat whole-grain foods – at least 75 g of whole grains per day or more [a]" (Denmark). Some guidelines are semi-quantitative: "It is recommended to consume 5-8 servings of a variety of cereals per day, with the largest quantity being whole grain" (Greece); "Prefer wholemeal bread and other whole grain products. Replace at least half of the white bread with wholemeal" (Bulgaria); "Go for wholegrain varieties wherever possible; choose whole grains at least twice a day" (Ireland); "Swap refined grains with whole grains and consume at least one serving of whole grain food as bread, pastry or side dish a day" (Hungary).

Sustainability is becoming an integrated part of the dietary guidelines in several countries. Replacing meat and other animal-based foods with plant foods such as vegetables, legumes and whole grains is an essential step towards a more sustainable diet (for details about whole grains and sustainability see Chapter 5).

Considering sustainability, the EAT-Lancet Commission suggested that in a more sustainable diet all grain foods consumed should be whole grains and that the daily whole-grain intake should be 232 g/2500 kcal [5]. In a study adapting the EAT-Lancet diet to Danish conditions, Lassen and colleagues estimated that the optimal whole-grain level for supply of energy and nutrients, including micronutrients, in a healthier and more sustainable Danish diet was about 120 g/10 MJ [7]. This is similar to the 125 grams per day (100-150 g) suggested in the Global Burden of Disease Study, where it is concluded that the current low whole-grain intake is one of the main dietary risk factors for deaths and DALYs in many countries, including Central, Eastern and Western Europe [4].

In this chapter, we suggest a simple way to establish a whole-grain recommendation and the aspects to consider. In addition, it is discussed briefly how sustainability can be taken into account.
Please observe, it is important to distinguish between whole grains (the grains themselves) and whole-grain food products (foods containing whole grains and possibly other ingredients) (see Chapter 1).

6.2. DEVELOPING A QUANTITATIVE WHOLE-GRAIN INTAKE RECOMMENDATION

The US was the first Western country to introduce a recommendation for whole-grain intake. The dietary guidelines for Americans 2005 recommended that healthy adults with an average energy requirement of 8.4 MJ/day should eat at least six servings of grain products per day of which at least half should be whole grains [8]. The recommendation was communicated to Americans through the "MyPyramid Food Guidance System", from which it appeared that one serving of whole-grain food product might contain between 16 g and 28 g of whole grain, depending on the type of food.

The Danish dietary guidelines were updated to include advice about whole grains in 2009, following the outcome of an expert group evaluation and recommendation [9]. The current Danish dietary guideline does not include a recommendation for total cereal products, only for whole grains [10].

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[a] The recommendation is 75 g/10 MJ but it is communicated to the public as 75 g/day, because the Danish reference diet is per 10 MJ.

We recommend that dietary guidelines should be based on sound scientific evidence. A possible way to develop a whole-grain recommendation is shown in figure 6.1 and further described in the following sections.

Establishing the basis for the amount of whole-grain intake associated with health effects

A number of research questions must be defined, e.g. "What is the relationship between whole-grain intake and incidence of specified diseases and mortality risk?", the diseases mainly being non-communicable diseases (figure 6.1, step 1).

The evidence should be synthesised from systematic literature searches and the causal associations estimated and described. Preferably, the quality of the review and the meta-evidence should be evaluated using well-recognised tools such as AMSTAR 2 or NutriGrade [11,12]. For further description of this step, see Chapter 3.

We suggest the basis for a quantitative recommendation for whole-grain intake should be based on systematic reviews of prospective cohort studies in populations similar to the target population for the recommendation (figure 6.1, steps 2-4).

Step 1	Define research questions
Step 2	Perform a systematic literature search
Step 3	Identify relevant studies; select studies appropriate for the target population
Step 4	Extract and combine results on whole-grain intake associated with health benefits
Step 5	Express in a usable way for a national recommendation
Step 6	Take local dietary habits into consideration
Step 7	Take the nutrient contribution from grain foods to the total diet into consideration and adjust the recommendation accordingly
Step 8	Optionally, consider sustainability
Step 9	Decide how the recommendation should be communicated

Figure 6.1. Process for establishing a quantitative recommendation for whole-grain intake.

When dietary guidelines are communicated to the consumers, results of scientific evidence are often rewritten to a language that is easy to understand. Whether a whole-grain recommendation is communicated to the consumers in grams or servings/portions, and whether it is expressed per energy unit or per day, is for the responsible authority to decide based on local practice (figure 6.1, step 5).

As basis for the Danish whole-grain recommendation, the assessment carried out by a Danish expert group in 2007 was based on a review of the scientific evidence for health effects of whole grains, mainly based on cohort studies [13], supported by knowledge about the nutritional composition of whole grains. At that time, most available cohort studies were American, and it was concluded that results from these cohorts could not be transferred directly to the Danish population because of large differences in dietary patterns and whole-grain intake. However, few Norwegian, Swedish and Finnish cohort studies were also available, and they were considered suitable for Danish conditions.

The amount of whole grains (grams or servings/portions) associated with reduced disease incidence should be identified from the appropriate cohort studies. In the Norwegian, Swedish and Finnish studies, used as the basis for the current Danish recommendation, intake of at least four servings of whole-grain food products per day was associated with reduced disease risk [14-18]. The actual type of whole-grain food products consumed were not identified in the studies. Therefore, the conversion to Danish conditions was based on the distribution of cereal products in an average Danish diet and their whole-grain content.

In Denmark, recommendations for nutrients and food intake are expressed in relation to an energy intake of 10 MJ, corresponding to the average energy intake in adult Danes [19]. Recommendations for intake of food groups are expressed as grams per 10 MJ, which is also the designation used for evaluation of how well the population lives up to the recommendations. However, when the recommendations are communicated to consumers through the official Danish dietary guidelines, the amounts are expressed either as servings per day (e.g. fruit and vegetables) or as grams per days (e.g. whole grains). The current whole-grain recommendation is 75 g/10 MJ or more. Thus for population groups with an energy requirement different from 10 MJ, the whole-grain recommendation should be scaled up or down accordingly. Notice that since the health effects identified in systematic reviews of cohort studies are often presented as “an intake of X servings or more (X typically three or four) compared with one serving or less”, the recommendation should be perceived as a minimum amount, even though higher intake does not necessarily provide further health benefits.

At present, no studies are published on health effects of whole-grain intake in children that can be used as basis for an intake recommendation. However, in general, Danish children 2 years and older are recommended to eat a diet similar to the recommended diet for adults (this age may differ in other countries). The whole-grain recommendation is no exception. Thus in practice, the whole-grain recommendation for small children 2-10 years old and for larger children and adults with a low energy requirement should be downscaled according to their lower energy requirement.

Taking local dietary habits into account

As far as possible, dietary guidelines for population groups should be adjusted to comply with the groups’ normal dietary habits [20] (figure 6.1, step 6).

Since food intake in cohort studies is mostly collected via food frequency questionnaires (FFQ), the results are typically expressed as servings or portions per day (or per week). Thus, if such results are used for a quantitative whole-grain recommendation, the number of servings has to be converted to grams, and if possible, the serving sizes used in the FFQ for the different whole-grain food products should be identified. A conversion of servings to grams should be based on analyses of dietary patterns that will reveal which whole-grain foods contributed most to the intake in the cohort studies, taking the different serving sizes of different whole-grain foods into account.

In the US, one serving of a whole-grain food product contains from 16 grams (baked goods) to 28 grams (cereal grains like pasta and rice; and breakfast cereals) of whole grains [21]. In Denmark, the whole-grain content of one serving of a whole-grain food product varies from 10 grams in a 40 g-slice of wheat bread to 65 grams in one serving of rolled oats [22]. Using these serving sizes, a recommendation of four servings of whole-grain food products per 10 MJ corresponds to 40-260 grams of whole grains per 10 MJ, which is a very broad interval not suitable for a recommendation in itself. Whether a recommendation is expressed in servings or grams, it is important to take the large variety in serving size into account.

In systematic reviews it is often not specified which types of whole-grain products make up the majority of products eaten in the cohort studies included. Therefore, one should consider the local food culture and composition of a typical diet, including the proportions of different grain products and their whole-grain content for a local quantitative whole-grain recommendation. E.g. if the local cereal intake is mainly bread and breakfast cereals, the whole-grain content in bread and cereal products should be weighted higher in the conversion of servings to grams.

Taking nutrient contribution into account

Regardless if the focus is on a traditional diet with higher whole-grain content or on other dietary patterns, e.g. vegetarian diets, the diet should be evaluated in the context of the local nutrient recommendations, e.g. the Nordic Nutrition Recommendations in Denmark (figure 6.1, step 7).

The Nordic Nutrition Recommendations recommend a dietary fibre intake of 3 g/MJ (30 g/10 MJ), primarily from a variety of foods naturally rich in dietary fibres [23]. As a prerequisite to ensure variety, the diet modelling could be based on the assumption that approximately half of the fibres should originate from fruit and vegetables, and half from cereal products (bread, breakfast cereals, pasta and rice). In some countries, the dietary guidelines include a recommendation for total cereal intake. Thus, modelling dietary compositions, including the ratio between total grains and whole grains, should ensure that the recommended fibre intake is achieved.

It is relevant to consider other nutrients in a similar way, depending on which nutrients are limited in the dietary pattern being analysed. In a healthier and more sustainable Danish (Western) diet, vegetables, legumes, nuts and whole grains typically replace animal-based foods. Thus, the essential nutrients that are normally supplied by the animal-based foods must come from plant foods in the more sustainable diet. In an average Danish diet, animal-based foods account for a significant amount of the dietary content of protein, vitamin A, vitamin D, several B-vitamins, calcium, iron, zinc and selenium [19]. Whole grains contain some of the nutrients that become limited in a healthier and more sustainable Danish diet, and different types of whole grains contribute with different nutrients, accentuating the concept of variation.

If whole grains must contribute significantly to the intake of different nutrients, it may be necessary to increase the recommendation for whole grains further than indicated by the current results from cohort studies on health effects of whole grains.

Taking sustainability into account

Some countries may want to take sustainability into account (figure 6.1, step 8). For a detailed description about whole grains and sustainability, see Chapter 5.

In a healthier and more sustainable diet, the whole-grain content may exceed the level that has been shown to provide health benefits in a diet with a high content of animal-based foods. The recommended whole-grain content in a more sustainable diet may be so high that a toxicologically safety assessment would be recommended (see Chapter 4).

Communicate the recommendation to the public

Finally, the communication of the recommendation to the public should be considered (figure 6.1, step 9). This involves e.g. the local food and/or health authorities.

6.3. CONCLUSION

We suggest that setting a recommendation for whole-grain intake should be based on the scientific evidence for associations between whole-grain intake and incidence of diseases such as non-communicable diseases and mortality. The amount of whole grains (grams or servings/portions) associated with reduced disease incidence should be identified from the appropriate cohort studies.

The amount of whole grains that is shown to provide health benefits should be evaluated in the context of local dietary habits and nutrient recommendations. Adding a sustainable perspective is expected to increase the whole-grain recommendation at the expense of animal-based foods, since the contribution of essential nutrients from whole-grain food products in a healthier and more sustainable diet becomes highly relevant.

It should be emphasised that different types of whole grains should be consumed, since they contribute with different nutrients and other compounds.

Whether a whole-grain recommendation is communicated to the consumers in grams or servings, and whether it is expressed per energy unit or per day, is for the responsible authority to decide based on local practice.

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APPENDIX A
Whole-grain definitions in different countries and organisations

Several countries have defined whole grain and whole-grain food products, either in national legislation or as a code of conduct. To explore which of the European Union Member States have national whole-grain definitions, an enquiry was sent to all EU countries through the EFSA Focal Point Network[a], and the answers received are included below. Definitions reported through the EFSA Focal Point Network are labelled with *.

This overview also includes definitions used in non-EU countries and some private organisations.

Austria*

Austria does not have a legislated whole-grain definition but uses a guideline called "Codex Alimentarius Austriacus" (Österreichisches Lebensmittelbuch) [1]. The guideline is mainly made for producers and not for consumers.

Whole meal (wholemeal) is the term used to refer to ground grains that are identical to or have approximately the same composition as the unprocessed grains.
Whole-grain bread is made from whole grains, whole meal or wholemeal flour. Addition of other types of flour for up to 10% of the total weight of the grain products is allowed.
The three pseudo-cereals are considered as grains, and can thus be classified as whole grain.

Belgium*

No legal definition of whole grains exists in Belgium. However, the definitions suggested by the Healthgrain Forum for whole grains "Whole grains shall consist of the intact, ground, cracked or flaked kernel after the removal of inedible parts such as the hull and husk. The principal anatomical components - the starchy endosperm, germ and bran - are present in the same relative proportions as they exist in the intact kernel", and for whole-grain food products "A whole-grain food is one for which the product is made with ≥30 % whole-grain ingredients on a dry-weight basis and more whole-grain ingredients than refined-grain ingredients", are used [2,3].

Bulgaria*

There is no commonly accepted definition of whole grains in Bulgaria but since April 2011, national standards were approved by the Bulgarian Food Safety Agency for the production of flour and bread, including whole-grain versions. The standards are available in Bulgarian language only.

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[a] EFSA (European Food Safety Authority) is a European agency funded by the European Union that operates independently of the European legislative and executive institutions (Commission, Council, Parliament) and EU Member States. EFSA provides independent scientific advice to the decision makers who regulate food safety in Europe.
The Focal Point Network comprises representatives of the national food safety authorities of the EU Member States, Iceland and Norway. Observers from Switzerland and the EU Candidate Countries also attend Advisory Forum meetings. Through the Forum, EFSA and the Member States can join forces in addressing European risk assessment and risk communication issues.

Croatia*

Croatian legislation (in Croatian language only) defines whole grains as “whole grains containing husks”, and whole grain cereals as “cereals consisting of pericarp (bran), endosperm and/or germ”, i.e. the husk has been removed. Buckwheat is included as a cereal plant species [4].

The definitions are followed by special provisions where cereal products are defined considering, quality standards, the purpose, composition, properties, and types of technological process (for mill products from wheat, rye, corn, buckwheat; special purpose flour and semolina; finished cereal products; mixtures for bakery products; bakery products, pasta, dough and dough products). Whole-grain wheat bread must contain at least 80% of whole-grain wheat-mill products calculated on the total quantity of mill products. Whole-grain rye bread must contain at least 70% of rye flour or other whole-grain rye-mill products calculated on the total quantity of mill products. Whole-grain corn bread must contain at least 60% of whole-grain corn-mill products calculated on the total quantity of mill products. Mixed wholemeal bread must contain more than 50% of flour or other whole-grain mill products of different types calculated on the total quantity of mill product.

Cyprus*

Cyprus has no official definition for whole grains but the definition in Regulation (EU) No 1308/2013 is followed, i.e. “*grains from which only part of the end has been removed, irrespective of characteristics produced at each stage of milling*.” [5].

The regulation concerns market standards of agricultural products, including shape and quality of rice for which this definition applies. It is therefore not related to the concept “whole grains” as it is discussed in this chapter.

Czech Republic*

A definition is set by the Czech Decree No. 18/2020 Coll., on requirements on mill products, pasta, bakery products, confectionary products and doughs: “Whole-grain bread is a bakery product which is made of at least 80%[†] whole-grain flours or the equivalent volume of mill grain products so that all parts of a grain are included.” ([†]of total weight of mill products used) .

Denmark

In 2008, a Danish expert group suggested a definition of whole grains and whole-grain products [6]. The definition was strictly botanical, including only few genera from the grass family leaving out wild rice and teff. Subsequently, the whole-grain definition was used as basic criterion for the Danish Whole-Grain Logo administered by the Danish Whole-Grain Partnership, and later as one of the criteria for the Nordic Keyhole label. Since 2009, the definition has been part of the Danish legislation.

Whole grains are defined as complete cereal grains (endosperm, germ and bran). The grains may be cut, cracket, flaked or milled but the three fractions must be present in the same proportions as in the intact grain of the individual cereals. The species wheat, spelt, rye, oat, barley, maize, rice, millet, durra and other sorghum species are considered whole grains [7].

In a guidance document for use of the Nordic Keyhole label it is specified that endosperm, germ and bran may be separated during milling but in the final flour they must be present in the same proportions as in the intact grains of the individual cereals. A loss of up to 2% of the grain or 10% of the bran during cleaning of the grains is accepted, when the cleaning is performed for safety and quality reasons [8].

To avoid misleading consumers, whole-grain products must contain a minimum amount of whole grain. To carry the Danish Whole-Grain Logo, criteria are set for whole-grain content in ten different food groups. Foods must contain at least 50-100% whole grains on dry matter basis depending on food group [9]. Besides, it is a prerequisite that the products meet nutrient profiles on fat, fibres, salt and sugars, that are equal to the criteria for the Nordic Keyhole label.

Another set of slightly less strict criteria exists for the Nordic Keyhole label [10]. Food groups containing a cereal part such as cereal foods (e.g. bread and breakfast cereals) and ready-made meals (e.g. sandwiches and pizzas) must have a specified minimum whole-grain content that varies from food group to food group. Foods must contain at least 30-100% whole grains on dry matter basis depending on food group. In addition, the products must meet nutrient profiles on fat, dietary fibre, salt and sugars.

Estonia*

Estonian legislation does not have a grain/whole-grain product definition. However, there is a voluntary agreement (in Estonian) between the Ministry of Rural Affairs, the Veterinary and Food Board, the National Health Development Institute and different Estonian food industry organisations. The agreement also contains a definition of the grain/wholegrain [11].

France

France has no legal definition of whole grains or whole-grain food products.

To allow for communication about whole-grain content to consumers, the French biscuit industry has introduced guidance for its members [12]. To label foods “source of whole grain”, they must contain 15-39% of the recipe by weight as whole grains. If products are being labelled “rich in whole grain” they must contain more than 40% of the recipe by weight as whole grains.
For moist bread, 10% of the final weight must contain whole grains to use the claim “contains whole grains,” and 30% of the final weight must be whole grains to be “rich in whole grains.” For rusks, 15% of the final weight must be whole grains to claim “contain whole grain”, and 40% of the final weight must be whole grains to claim “rich in whole grain”. In whole-grain biscuits, at least 15% of the ingredients should be whole grains.
Besides this, the “biscuits et gateaux”-association has proposed that the products should contain at least 40% cereals, less than 35% energy from fat, less than 35% saturated fat, no trans fatty acids and less than 40% total sugars if they are labelled as whole grain.

Germany

In Germany, the law establishes different criteria for different types of whole-grain products but contains no definition of whole grains [13-15]. According to German law, use of the term whole-grain requires that at least 90% of the flour in bread and pastries must be whole grains. If oat is part of the whole-grain fraction, at least 20 of the 90% grains must be oat. In fine baked goods, at least 90% of the grains and starch ingredients must be whole grain flour.

For pasta, 100% of the grain component must be whole grains in order to use the designation whole grain.

German authorities do not allow the use of a whole-grain label on biscuits, because they are considered to contain too much sugar and fat.

Greece*

According to the Ministry of Health and the European Federation of Energy Traders, paragraph 12 of Article 106 of the National Food and Drink Code (in Greek) sets out the definition and specifications of 100% whole-grain flour from pure wheat for the manufacture of corresponding bread as well as the production of whole-wheat pasta flour. The specifications concern moisture, gluten, acidity in sulphuric acid and the residue in carbon tetrachloride [16].

Hungary*

In Hungary, the legislative definition of whole-grain based foods is: "cereal-based foods produced by using all parts of the cereal or pseudo-cereal grain kernel (containing germ and bran), and food made from at least 50% of such ingredients" [17]. Furthermore, whole-grain food products have to comply with other relevant regulations such as Decree No. 152 of 2009 (XI. 12.) on the binding provisions of the Codex Alimentarius Hungaricus [18,19].

In Codex Alimentarius Hungaricus, the following whole-grain food products are defined:

- Whole-wheat flour: contains all parts of the wheat kernel, including germ and bran, and therefore it is almost a fully wholemeal grist with wheat-like colour.
- Wholemeal rye flour: is a grist produced by all parts of the rye kernel (Secale cereale L.).
- Wholemeal spelt flour: grist made from the grains of spelt wheat for human consumption. It is almost a wholemeal product with the colour of spelt wheat. It contains wholemeal spelt flour in a wide range of particle sizes and bran with larger particle size.
- Wholemeal triticale flour: grist produced by all parts of triticale (x Triticosecale Wittm.).
- Wholemeal wheat bread: is usually a leaven based dough made of at least 60% of wholemeal flour (wheat, rye or spelt) and a maximum of 40% of other grists (mostly flour) such as wheat, rye or spelt. It is produced by preparing, shaping, leavening and baking the dough.

Iceland

The Nordic Keyhole label can be used on foods on a voluntary basis. Thus, the same legal definitions apply for whole grains and whole-grain food products as mentioned for Denmark.

Ireland*

There is no legal definition of a grain or whole grain, and there is no real distinction made between cereal grains and pseudo-cereals.

Italy

In Italy, the term "integrale" refers to whole-grain flour. The grains are milled, and the amount of bran in the flour is adjusted until the ash content is between 1.30 and 1.70 g/100 g dry matter. Protein must be at least 12.00 g/100 g dry matter [20]. It is not specified that the germ fraction must be present in the flour.

Pasta made entirely from “integrale” flour can be labelled “pasta de semola integrale di grano duro” [20].

Latvia*

There is no legislative definition of whole grain and/or whole-grain food products in Latvia.

Lithuania*

According to the national legal act (in Lithuanian language only) “Wholegrain products” refers to products made by processing (grinding, crushing, or thermally treating) whole cleaned grains. These products contain all the components characteristic of grain (endosperm, germ and bran) in proportions typically found in whole grains [21].

Since 2013 it has been possible to use the Nordic Keyhole label on foods in Lithuania. Thus, definitions of whole grains and whole-grain products similar to the one mentioned for Denmark also apply.

Malta*

There is no legally endorsed definition of whole grain or whole-grain food products in Malta.

Norway

The Nordic Keyhole label can be used on foods on a voluntary basis. Thus, the same legal definitions apply for whole grains and whole-grain food products as mentioned for Denmark.

Poland*

Whole grains and whole-grain food products have not been legally defined in Poland. However, some products that are either on the Polish market or found in marketing information bear a whole-grain description in accordance with a common understanding of this term, e.g. whole-grain flour means fully milled flour, i.e. produced from all the edible parts of the grain (endosperm, germ and bran) in the same proportion as they occur in the natural grain [22].

Portugal*

In Portugal, a national legislation (in Portuguese language only), Ordinance n.º 52/2015, of 26th February, sets the characteristics to which different types of bread and related products must comply. This legislation includes a definition of “whole-grain bread”, according to the type of wheat or rye flours that can be used in bread making [23].

Romania*

There is no definition of whole grain/whole-grain products in the national legislation.
There are private organisations in Romania using the definition: “Whole grains shall consist of the intact, ground, cracked or flaked kernel after the removal of inedible parts such as the hull and husk. The principal anatomical components - the starchy endosperm, germ and bran - are present in the same relative proportions as they exist in the intact kernel. Small losses of components - i.e. less than 2% of the grain/10% of the bran – that occur through processing methods consistent with safety and quality are allowed.”.

Slovak Republic*

National regulations define whole-grain food products and the requirements for them: "Wholemeal flour means a mill product with a higher proportion of packaging particles obtained by multi-stage milling of cereal grains after removal of the germ" [24]; and: "wholemeal pasta is pasta made from wholemeal flour" [25].

Slovenia*

In the rules on the quality of cereal and bakery products, whole grains are defined as: "Wheat wholemeal products (wheat wholemeal flour and wheat wholemeal groats) are made by grinding cleaned whole grains", and "unpolished rice (brown rice, cargo rice, natural rice, wholemeal rice) if only the outer husk has been removed" [25]. Wheat wholemeal bread shall be made from at least 80% wheat wholemeal flour or wholemeal wheat groats. Wholemeal mixed bread must contain at least 51% of different types of wholemeal flour or crumb, calculated on the total amount of flour [26].

Spain*

In Spanish legislation (in Spanish language only), there are quality standards for flours, meal and other cereal products plus bread that mention whole grain and whole-grain products [27].

Sweden*

The Nordic Keyhole label can be used on foods on a voluntary basis. Thus, the same legal definitions apply for whole grains and whole-grain food products as mentioned for Denmark.

Switzerland*

In Switzerland, whole-grain flour of wheat ("Vollkornmehl") is obtained from the whole grain of wheat, with or without outermost husk parts; the total yield must be at least 98 % by mass of the whole grain [28]. Whole-grain flour of cereals other than wheat ("Spezialvollkornmehl") is obtained from the whole-grain of cereals other than wheat or whole starchy cereals.

The Netherlands*

According to Dutch law, the term "whole grain" means the starch rich endosperm, germ and bran present in the natural proportion, also after processing [29].

Bread can only be labelled "100% whole grain" if all the flour in the recipe is 100% whole grain.
For biscuits, there is an old (1989) but still valid permission by the Food Inspection Agency for biscuits to be labelled as "whole grain" if at least 50% of the flour is whole grain .
In practice, the requirement of 100% whole grain flour is applicable for all types of bread, pasta and breakfast cereals, whereas biscuits and related bakery products apply the "at least 50%-option".

A new national legislation from July 2020 on whole grains is defined in the "Commodities Act Decree on Flour and Bread". The word whole grain (wholemeal) may be used in the designation of a product referred to in the Decree provided that the naturally occurring starchy kernel, germ and bran of the cereal in question are present in their natural proportions, whether or not after having undergone processing (Article 16); and the designation brown bread or wheat bread may be used only for bread in which (wholemeal) wheat flour, whether or not mixed with broken wheat and wheat flakes, is the main component and in which bran is visible to the naked eye (Article 9) [30].

Turkey*

In Turkey, there are legal definitions and technical features (in Turkish language only) for the definitions of whole-wheat flour. The flour obtained by grinding the wheat cleaned from foreign substances to include all the anatomical parts of the wheat grain [31] and for wholemeal bread, whole-wheat bread (bread type produced from whole-wheat flour), and whole-wheat flour bread (at least 60% of whole-wheat flour is added to wheat flour) [32].

United Kingdom

There is no legal definition of whole grain or whole-grain food products in the UK. However, the term "wholemeal" can be used about flour derived from wheat. The word wholemeal may only be used on bread products if all the flour used as an ingredient in the preparation of the bread is wholemeal [33].

The Institute of Grocery Distribution (IGD), a private industry organisation in the UK, defines whole grain as "the edible entire grain after removal of inedible parts such as the hull and glume. It must include the entire germ, endosperm and bran". Examples of whole grains are: amaranth, barley, buckwheat, maize, millet, oats, quinoa, rye, sorghum, teff, triticale, rice (including brown and wild rice), and wheat (including club, common wheat, durum wheat, einkorn, emmer, faro, Kamut®, spelt) (list is not exhaustive) [34].

The Institute of Grocery Distribution further states: "Whole grain also includes grains that have been subjected to processing (e.g. milling, cracking, crushing, rolling, flaking, extrusion, malting) but only if after processing the proportions of the germ, endosperm and bran are present in the same or virtually the same proportions as the original grain. Temporary separation of whole grain constituents during processing for later recombination is acceptable provided the proportions of the germ, endosperm and bran are the same or virtually the same as in the original grain. Simply adding together these three whole grain constituents as separate ingredients does not constitute a whole grain and making a claim that it does could be misleading to consumers. Different varieties of the same grain may be combined during processing and be called whole grain (e.g. different varieties of wheat) as long as the final product contains the component parts of the grain in line with their pre-processed proportions.". Malted grains may be included if the amount of whole grains stated for the product is computed on the dry weight, if the sprout does not exceed kernel length, and if the nutrient values have not diminished [34].

Australia and New Zealand

The authorities in Australia and New Zealand define whole-grain food products as any food which uses every part of the grain including the outer layers, bran and germ [35]. This definition applies even if these parts are separated during processing and regardless of whether the grain is in one piece or milled into smaller pieces.

The term wholegrain refers to:

- whole and intact grains as found in some bread and crisp breads
- puffed or flaked grains in some breakfast cereals
- coarsely milled or kibbled wheat found in breads such as pumpernickel
- ground grains such as whole-wheat flour used to make wholemeal bread.

The term wholemeal applies to foods in which the whole grains have been refined into finer particles. This gives manufacturers the option of describing their foods as either wholegrain or wholemeal to avoid misleading the customer.

Canada

On the Government of Canada's home page it is stated: "There are many types of grains, including cereal grains such as wheat, rice, oats, barley, corn, wild rice, and rye, as well as pseudo-cereals such as quinoa and buckwheat. These grains can be either whole or refined. (…) Whole grains contain all three parts of the kernel (the bran, the endosperm and the germ)" [36].
No Canadian regulation or guidance related to whole-grain content in whole-grain food products was found.

In Canada, when wheat is milled, parts of the kernel are separated and then recombined to make whole-wheat flour. Under the Food and Drug Regulations, up to 5% of the kernel can be removed to help reduce rancidity and prolong the shelf life of whole-wheat flour. The portion of the kernel that is removed for this purpose contains much of the germ and some of the bran. Thus, whole-wheat flour is not whole grain. Whole-wheat bread is made from whole-wheat flour. Therefore, 100% whole-wheat bread may not be whole grain. To be certain that they are getting whole grain, consumers in Canada must therefore look for the words "whole grain whole wheat" [36].

United States of America

In the US, there is no official definition of what is a whole grain or a whole-grain food product. However, the Food and Drug Administration has issued a draft guidance about what the agency considers "whole grain" to industry and to assist manufacturers in labelling their products. The American Food and Drug Administration (FDA) states: "Cereal grains that consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components – the starchy endosperm, germ and bran – are present in the same relative proportions as they exist in the intact caryopsis – should be considered a whole grain food." The FDA further states: "Cereal grains may include amaranth, barley, buckwheat, bulgur, corn (including popcorn), millet, quinoa, rice, rye, oats, sorghum, teff, triticale, wheat, and wild rice." [37].

A whole-grain food can be a complete food such as brown rice or it can be a food ingredient such as whole-wheat flour in bread. However, there is no criterion for minimum whole-grain content of a whole-grain food product in the US, but if a food producer wants to make an authorized health claim referring to whole grains the food must contain at least 51% whole grains (% of total weight) and meet other requirements, e.g. for dietary fibre content [38].

In 2012, the Food and Nutrition Services division of the U.S. Department of Agriculture defined "whole grain-rich" foods for use in national school-meals programs. A whole grain-rich food must have at least 50% of its grain as whole grain and meet one of three requirements: 1) Contain at least 8 g of whole grain per serving, or 2) Include a FDA-approved whole-grain health claim on its packaging, or 3) For non-mixed dishes (e.g. breads, cereals) whole grain must be the primary ingredient by weight; for mixed dishes (e.g. pizza, corn dogs) whole grain must be the primary *grain* ingredient by weight [39].

The Whole Grains Council, a US based non-profit consumer advocacy group of millers, manufacturers, scientists and chefs, has approved the definition "Whole grains or foods made from them contain all the essential parts and naturally-occurring nutrients of the entire grain seed in their original proportions. If the grain has been processed (e.g., cracked, crushed, rolled, extruded and/or cooked), the food product should deliver the same rich balance of nutrients that are found in the original grain seed." [40]. This means that 100% of the original kernel – all of the bran, germ, and endosperm – must be present to qualify as a whole grain. The Whole Grains Council lists grains most familiar to consumers as whole grains but mention that "other cereal grasses from the *Poaceae* family, such as canary seed, Job's tears, Montina, Timothy, fonio, etc. are also whole grains, when consumed with all of their bran, germ and endosperm. (…) Amaranth, quinoa, and buckwheat are not in the *Poaceae* botanical family, but these "pseudo-grains" are normally included with true cereal grains because their nutritional profile, preparation, and use are so similar. (…) Oilseeds and legumes (such as flax, chia, sunflower seeds, soy, chickpeas, etc.) are not considered whole grains by the WGC." [40].

The Whole Grains Council has issued a series of three Whole-grain Stamps that can help consumers identify foods with whole grains. In products with the 100%-Stamp, all grain ingredients are whole grain, in the 50%-Stamp, 50% of all grain ingredients are whole, and products with the Basic Stamp provide at least 8 grams of whole grains but may contain more refined grains than whole grains. Besides, each Stamp also shows how many grams of whole grains are in a serving of the product [41].

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APPENDIX B
WholEUGrain umbrella review: search protocol, search terms, inclusion and exclusion criteria

SEARCH STRATEGY

The structured literature search was restricted to searches in PubMed and the Cochrane Library, and both authors performed all searches independently. Both authors also searched the Cochrane Library for additional references, as well as through the reference lists of included studies/reports for additional references not found through the systematic searches.

SEARCH TERMS

We performed our search in the PubMed database using MeSH terms. The use of MeSH terms ensures that the searches conducted included all synonyms, spelling forms, singular and plural forms, etc. for the search terms of interest. Since MeSH terms are usually added to new articles 2-3 months after entry on the PubMed database, we also conducted classical searches (including all search words included under each MeSH term-category) for a limited time period of 4 months up to the final search date.

- Cardiovascular Diseases [MeSH] AND Whole grains [MeSH]
- Diabetes Mellitus, Type 2 [MeSH] AND Whole grains [MeSH]
- Cancer: Neoplasms [MeSH] AND Whole grains [MeSH]
- Mortality [MeSH] AND Whole grains [MeSH]
- Body Weight [MeSH] AND Whole grains [MeSH]

INCLUSION CRITERIA

Language

Studies/reports in English were included.

Time range

We included studies published between different restricted timespans, depending on the date for the latest systematic literature review (SLR) and/or meta-analysis of the disease or observation of interest conducted by an expert panel (see below for the specific timespans for each section). These SLRs and meta-analyses were also included in the summaries of results presented in Chapter 3.

<u>Cardiovascular diseases (CVDs)</u>

A SLR and dose-response meta-analyses of prospective studies by Aune et al. (2016) [1] conducted a search that ended on April 3rd 2016. Thus, the search period for the WholEUGrain umbrella review was April 4th 2016 – February 20th 2020.

Type-2 diabetes

The Cochrane Collaboration published a SLR in 2010 [2], and the literature search ended on May 2006. Thus, the search period for the WholEUGrain project review was May 1st 2006 – February 20th 2020.

Cancer

The latest SLR by WCRF [3] (with focus on colorectal cancer) conducted a search that ended on April 30th 2015. Thus, the search period for the WholEUGrain project review was May 1st 2015 – February 20th 2020.

Mortality

A systematic literature review and dose-response meta-analyses of prospective studies by Aune et al. (2016) [1] conducted a search that ended on April 3rd 2016. Thus, the search period for the WholEUGrain project review was April 4th 2016 – February 20th 2020.

Overweight

The latest WCRF CUP project literature review [4] reports on the latest evidence gathered on the subject, with a search that ended on August 21st 2016. Thus, the search period for the WholEUGrain project review was August 21st 2016 – December 31st 2020.

Types of studies

Systematic literature reviews and meta-analyses of prospective cohort studies were included for the sections on CVDs, cancer, type 2 diabetes, and mortality. Systematic literature reviews and meta-analyses of both prospective cohort studies and randomized controlled studies were included in the section on overweight.

Population

The literature searches were restricted to studies on adults, with the exception of the section on overweight, where both adults and children were included in the search. No exclusion criteria in relation to demographic or socioeconomic factors were applied.

Observations of interest

Studies researching the association between whole-grain intake and disease outcomes for cancer, type 2 diabetes, CVDs, overall mortality, and risk of overweight were included. Results reported as either relative risk (RR), hazard risk (HR) or odds ratio (OR) were accepted. For the section on overweight, the observations of interest also included changes in body weight, BMI, and other adiposity measures, like waist circumference, body fat percentage, fat mass, and fat-free mass.

Studies were eligible for inclusion if they reported a quantity of whole-grain intake expressed in either grams/ounces or number of portions, or an assessment of either low vs. high whole-grain intake (e.g. based on quartile/quintile distributions). Studies were eligible if they reported estimates of intake of whole grains or estimates of intake of whole-grain food products.

Outcome measures

Eligible studies had to include one or more of the following outcome diseases/conditions: cancer, type 2 diabetes, cardiovascular diseases (coronary heart disease, ischemic heart disease, coronary artery disease, ischemic stroke or heart failure), overall mortality, and overweight-relevant indicators (weight changes, BMI, waist circumference, body fat percentage, fat mass, fat-free mass).

EXCLUSION CRITERIA

Any studies whose data collection or data interpretation was funded by agencies with commercial interests in the results were excluded.

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APPENDIX C
WholEUGrain umbrella review: quality-assessment tools

As a part of the review process, two tools for evaluating the quality of the included studies were developed (see tables 4B1 and 4B2). Every study was evaluated independently by each author, and rated on the basis of several parameters regarding design and method-quality.

The tool used for quality-assessment of studies included in the sections on CVD, type 2 diabetes, cancer and mortality was developed by adapting the guidelines of the USA's National Institutes of Health [1]. With this tool, studies can score from 0 to a maximum of 18 points (see table 4B1).

Similarly, a tool for evaluating the quality of studies included in the overweight section was developed (see table 4B2). This tool was developed separately, since we included reviews and meta-analyses of both RCTs and cohort studies in the overweight section. Therefore, we adapted an approach similar to the one described by the World Cancer Research Fund International's Continuous Update Project review on the subject [2]. This tool was developed by adapting and adjusting the guidelines from the systematic review checklists of the National Institute for Health and Care Excellence (NICE) and the Critical Appraisal Skills Programme (CASP). With this tool, studies can score from [-] to a maximum of [++] points (see table 4B2).

Each study was graded according to its overall score, which reflects the quality of the study as well as the risk of potential bias arising from its design and execution:

- 0-6 points or [-] — Poor: Few or no checklist criteria have achieved the highest or the middle scores. The quality of the study is low and there is considerable risk of bias due to the study's design and execution.
- 7-16 points or [+] — Fair: Some of the checklist criteria have achieved the highest or middle scores. The criteria that have not been fulfilled or not adequately described are unlikely to alter the conclusions of the study. There is a low risk of bias due to the study's design and execution.
- 17-18 points or [++] — Good: All or most of the checklist criteria have been fulfilled with the highest scores. Where they did not meet the highest score, the conclusions are very unlikely to be altered. There is low to no risk of bias due to the study's design and execution.

Table 4B1 – Quality-assessment tool for the sections on CVD, type 2 diabetes, cancer and mortality.

Quality parameters			Points
Study information	Research question for the review	Clearly defined (e.g. with PICO – population, intervention, comparator, outcome)	1
		Not clearly defined	0
	Study type	SLR & meta-analysis	2
		SLR alone	1
		Non-systematic review	0
	Design	Prospective cohort studies	2
		Retrospective cohort studies	1
		Both cohort studies and case-control studies	1
		Case-control studies	0
	No. of studies included	Over 10	2
		5 - 9	1
		Under 5	0
Review methodology	Literature search & resources	Systematic & broad approach (e.g. databases & other resources e.g. grey literature AND manual search of reference lists), clearly described	2
		Systematic approach with only databases	1
		Non-systematic approach (e.g. no predefined eligibility / exclusion criteria)	0
	Screening and review of studies	Dual review (two independent authors)	1
		Non-dual review or not well described method for screening and review	0
	Quality assessment	Assess quality with quality tool(s)	1
		Does not assess quality of included studies	0
	Review presentation	Presentation of key characteristics for included studies (either narrative or table format)	1
		Non-systematic presentation of study characteristics	0
	Risk of publication bias assessment	Funnel plot or calculation	2
		Narrative description of risk bias	1
		No assessment	0
	Heterogeneity	Calculated/described	1
		Not calculated/described	0
Measurement types	Whole-grain intake	Both types	2
		Quantity (in grams or portions)	2
		Qualitative categories (e.g. high vs. low)	1
		Use of dietary fibre as proxy for whole-grain intake	0
	Outcome definition	Hard endpoints (no. of cases)	1
		Proxys (symptoms)	0

Table 4B2 – Quality-assessment tool for the overweight section.

Study identification (author, year, ref.ID)	
Factor:	Score
1. Does the review address an appropriate and clearly-focused question that is relevant to one or more of the guidance topic's key questions? Answer "yes" if: • the review aimed to look at intake of whole grain and its effect on anthropometric measures of body weigh/composition; • and if there are clearly stated inclusion/exclusion criteria (e.g. by using the PICO checklist).	
2. Does the review include the types of studies relevant to the key research question? Answer "yes" if: • it includes RCTs, or only cohorts/longitudinal observational studies, or both types • Answer "no" if other study types are included (e.g. cross-sectional or case-controls)	
3. Is the literature search sufficiently rigorous to identify all the relevant studies? Must meet following criteria for a "yes": • At least 2 electronic sources were searched (databases and/or grey literature) • Must include years and names of databases searched • Search terms must be available/traceable (either in text or suppl. materials) • Screening of studies for inclusion was performed by min. two independent authors	
4. Is the quality of included studies appropriately assessed and reported? Must meet following criteria for a "yes": • Methods of assessment provided • Quality of included studies reported or traceable in supp. materials • Quality of included studies considered in discussion/conclusions	
5. Is an adequate description of the analytical methodology used included, and are the methods used appropriate to the question? Must meet following criteria for a "yes": • E.g. if meta-analysis is used, is it appropriate and is heterogeneity assessed and taken into consideration if it exists? • Was publication bias assessed? • If mixed study types are included, are these analysed separately in the results section?	
6. Were the characteristics of the included studies provided? Must meet following criteria for a "yes": • Overall study characteristics presented in an aggregated form such as a table • data should be provided on the participants (age, sex, country of origin, health status) • interventions/exposures and outcomes • effect size of intervention/cohort	
7. Were potential conflicts of interest reported? Potential sources of support should be clearly acknowledged for the systematic review and considered for the included studies.	
8. Can the results be applied to a general population? Answer "yes" if majority of reviews include data for healthy populations, or representative of populations, where results can be generalised.	

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APPENDIX D
WholEUGrain umbrella review: Judging the evidence

Below is a summary of the adapted criteria for judging the evidence, as they are applied by the World Cancer Research Fund in their Continuous Update Project, as described in the Third Expert Report from 2018 [1].

STRONG – CONVINCING

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of NCDs. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

Requirements:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Presence of a plausible biological gradient (dose-response) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausible.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant outcomes.

STRONG – PROBABLE

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of NCDs.

Requirements:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- No substantial unexplained heterogeneity within or between study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of NCDs; any exceptions require special, explicit justification.

Requirements:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry levels and is intended to allow any exposure for which there are sufficient data to warrant consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded "limited – no conclusion" for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (e.g. lack of adjustment for known confounders) or by any combination of these factors.
With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of NCDs.

SPECIAL UPGRADING FACTORS

When present, such factors can upgrade the judgement reached. An exposure deemed a "limited – suggestive" causal factor in the absence, for example, of a biological gradient, might be upgraded to "probable" if one were present. The application of these factors requires judgement, and the way in which such judgements affect the final conclusion must be stated.

Factors to consider:

- Presence of a plausible biological gradient (dose-response) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (OR or RR of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomized trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant outcomes.

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Appendix E
WholEUGrain umbrella review: overview of included studies and data overlap

Table E.1 – Overview and characteristics of the included studies in the CVD section.

	Reference & Type	Studies	Exposure	Outcome	Analyses	Total no. cases	Quality
WholEUGrain umbrella review	Reynolds et al. 2019 [1] SLR & MA	N = 11 prospective cohorts USA (6), Finland (1), Sweden (2), Denmark (1), Spain (1)	Whole grains n=11	Risk of CVD, CHD & stroke	High vs. low; dose-response (linear & non-linear); sensitivity analyses when $I^2 > 50\%$ or $P_{het} < 0.10$; influence analyses for the effect of each individual study; analyses for high quality data	CVD: 4,357 CHD: up to 7,697 Stroke: 1,247	Good
WholEUGrain umbrella review	Bechthold et al. 2019 [2] SLR & MA	N = 16 prospective cohorts USA (8), China (1), Denmark (2), Sweden (4), Finland (1)	Whole grains n=12 WG products n=4	Risk of HF, stroke or CHD	High vs. low; dose-response (linear & non-linear); subgroup analyses with sex, length of follow-up, geographic location, no. of cases, dietary assessment validation; sensitivity analyses for studies with low risk of bias.	HF: up to 6,455 Stroke: up to 11,116 CHD: up to 8,652	Good
WholEUGrain umbrella review	Barret et al. 2019 [3] SLR	N = 3 prospective cohorts USA (3)	Whole grains n=1 WG products n=2	Risk of CHD and stroke	NAp	NAp	Fair
WholEUGrain umbrella review	Deng et al. 2017 [4] SLR	N = 1 meta-analysis (incl. 4 prospective cohorts)	Whole grains	Risk of stroke	High vs. low.	NA	Fair
	Aune et al. 2016 [5] SLR & MA	N = 16 prospective cohorts USA (9), Sweden (2), Norway, Sweden & Denmark (1), Finland (1), China (1), Spain (1), unknown (1)	Whole grains n=13 Both whole grains & WG products n=3	Risk of CVD, CHD & stroke	High vs. low; dose-response (linear & non-linear); subgroup and meta-analyses stratified by study characteristics (duration of follow-up, sex, geographical location, number of cases, validated dietary assessment, study quality, and adjustment for confounding factors); influence analyses for the effect of each individual study	CVD: up to 26,243 CHD: up to 7,068 Stroke: up to 2,337	Good

SLR: systematic literature review; MA: meta-analysis; CVD: cardiovascular diseases; CHD: coronary heart disease; HF: heart failure; WG: whole grain; I^2: heterogeneity; P_{het}: significance value for heterogeneity; NA: not available; NAp: not applicable.

Table E.2 – Overview and characteristics of the included studies in the type 2 diabetes section.

	Reference & Type	Studies	Exposure	Outcome	Analyses	Total no. cases	Quality
WholEUGrain umbrella review	Reynolds et al. 2019 [1] SLR & MA	N = 8 prospective cohorts USA (6), Finland (1), Sweden (1)	Whole grains n=8	Risk of type 2 diabetes	High vs. low, dose-response (linear and non-linear); sensitivity analyses when $I^2 > 50\%$ or $P_{het} < 0.10$; influence analyses for the effect of each individual study; analyses for high quality data.	14,686	Good
WholEUGrain umbrella review	Schwingshackl et al. 2017 [6] SLR & MA	N = 13 prospective cohorts USA (7), Finland (1), Sweden (2), Australia (1), Denmark (1), Germany (1)	Whole grains n=8 WG products n=5	Risk of type 2 diabetes	High vs. low, dose-response (linear and non-linear); stratified dose-response analyses by subgroup (sex, age, length of follow-up, geographic location, no. of cases, outcome assessment, and dietary assessment methods); sensitivity analysis for studies with low risk of bias.	29,633	Good
WholEUGrain umbrella review	Aune et al. 2013 [7] SLR & MA	N = 12 prospective cohorts USA (8), Finland (1), Sweden (2), Germany (1)	Whole grains n=8 WG products n=1 Both n=3	Risk of type 2 diabetes	High vs. low; dose-response (linear & non-linear); sensitivity analyses excluding one study at a time (for a min. of 5 studies in analysis); subgroup analyses for gender, duration of follow-up, geography, no. of cases, and adjustment for confounders.	19,829	Fair
WholEUGrain umbrella review	Cho et al. 2013 [8] SLR	N = 6 prospective cohorts USA (5), Finland (1)	WG products n=6	Risk of type 2 diabetes	NAp	NAp	Fair
WholEUGrain umbrella review	Ye et al. 2012 [9] SLR & MA	N = 6 prospective cohorts USA (5), Finland (1)	WG products n=6	Risk of type 2 diabetes	High vs. low; subgroup analyses (sex, study quality, health status, study duration, level of dietary intake, and method of outcome measurement).	NA	Fair
WholEUGrain umbrella review	de Munter et al. 2007 [10] SLR & MA	N = 5 prospective cohorts USA (4, Finland (1)	WG products n=5	Risk of type 2 diabetes	Dose-response (linear); sensitivity analyses for the effect of each individual study.	10,944	Fair
	Priebe et al. 2008 [11] Cochrane SLR	N = 5 prospective cohorts USA (4), Finland (1)	WG products n=5	Risk of type 2 diabetes	NAp	NAp	--

SLR: systematic literature review; MA: meta-analysis; WG: whole grain; I^2: heterogeneity; P_{het} value: significance value for heterogeneity; NA: not available; NAp: not applicable.

Table E.3 – Overlap of datasets from prospective cohort studies included in the systematic literature reviews and meta-analyses of whole grains and diabetes reviewed.

Prospective cohorts	Priebe et al. 2008 (Cochrane)	WholEUGrain umbrella review					
		de Munter et al. 2007	Ye et al. 2012	Cho et al. 2013	Aune et al. 2013	Schwingshackl et al. 2017	Reynolds et al. 2019
Liu et al. 2000 – NHS (USA)	√		√	√			
Meyer et al. 2000 – IWHS (USA)	√	√	√	√	√	√	√
Fung et al. 2002 – HPFS (USA)	√	√	√	√	√		√
Montonen et al. 2003 – FMCHES (FIN)	√	√	√	√	√	√	√
van Dam et al. 2006 – BWHS (USA)	√	√	√	√	√	√	√
de Munter et al. 2007 – NHS I & NHS II (USA)		√	√		√		√
Kochar et al. 2007 – PHS (USA)				√		√	
Ericson et al. 2013 – MDC (SWE)					√	√	
Hodge et al. 2004 – MCCS (AUS)						√	
Lacoppidan et al. 2015 – DCH (DNK)						√	
Parker et al. 2013 – WHI (USA)					√	√	√
von Ruesten et al. 2013 – EPIC-Postdam (GER)						√	
Sun et al. 2010 – HPFS (USA)					√	√	
Sun et al. 2010 – NHS I (USA)					√	√	
Sun et al. 2010 – NHS II (USA)					√	√	
Wirström et al. 2013 – NA (SWE)					√	√	√
Fisher et al. 2009 - EPIC-Postdam (GER)					√		

IWHS: Iowa Women's Health Study; HPFS: Health Professionals Follow-up Study; FMCHES: Finnish Mobile Clinic Health Examination Survey; BWHS: Black Women's Health Study; NHS: Nurse's Health Study; PHS: Physicians Health Study; MDC: Malmö Diet Cancer study; MCCS: The Melbourne Collaborative Cohort Study; DCH: Diet, Cancer and Health cohort; WHI: Women's Health Initiative; EPIC: European Prospective Investigation into Cancer and Nutrition; NA: non-available. Country codes: AUS: Australia, DNK: Denmark, FIN: Finland, GER: Germany, SWE: Sweden, USA: United States of America.

Table E.4 – Overview and characteristics of the studies retrieved through the WholEUGrain umbrella review and included in the cancer section.

Reference & Type	Studies	Exposure	Outcome	Analyses	Total no. cases	Quality
Reynolds et al. 2019 [1] SLR & MA	N = 7 prospective cohorts USA (3), Finland (1), Sweden (1), Denmark (1), Scandinavian countries (1; Norway, Sweden & Denmark)	Whole grains n=6 WG products n=1	Risk of colorectal cancer Risk of prostate cancer	High vs. low; dose-response (linear & non-linear); sensitivity analyses when $I^2 > 50\%$ or $p_{het} < 0.10$; influence analyses for the effect of each individual study; analyses for high quality data	8,803 colorectal cancer 7,010 prostate cancer	Good
Xiao et al. 2018 [12] SLR & MA	N = 4 prospective cohorts + 7 case-control studies USA (2), Italy (2), Greece (1), Switzerland (1), Denmark (1), Sweden (1), Germany (1), Iran (1), Korea (1)	Whole grains n=1 WG products n=11	Risk of breast cancer	High vs. low; dose-response (linear); influence analyses for the effect of each individual study; sensitivity & stratified analyses for sources of heterogeneity; subgroup analyses by study design, sample size, publication year, numbers of adjusted variables, and quality scores of studies.	11,589	Fair
Schwingshackl et al. 2017 [13] SLR & MA	N = 7 prospective cohorts + 2 case-control studies USA (5), Sweden (1), Netherlands (1), Iran (1), China (1)	Whole grains n=8 WG products n=1	Risk of total cancer	High vs. low.	NA	Fair
Lei et al. 2016 [14] SLR & MA	N = 1 prospective cohort + 7 case-control studies (only 5 studies incl. in MA) USA (5), Netherlands (1), Italy (1), Finland (1)	Whole grains n=2 WG products n=6	Risk of pancreatic cancer	High vs. low; subgroup analyses by study design, geographic area, type of whole grains, gender, control type, study quality, and adjustments factors; sensitivity analyses, omitting 1 study at a time.	2,548	Fair
Makarem et al. 2016 [15] SLR	N = 20 longitudinal studies USA (14), Denmark (4), Sweden (2)	Whole grains n=16 WG products n=3 Both n=1	Risk of breast cancer; endometrial cancer; kidney cancer; prostate cancer; oesophagus and stomach cancer; small intestine cancer; colorectal cancer; head and neck cancers; non-Hodgkin's lymphoma	NAp	NAp	Fair

SLR: systematic literature review; MA: meta-analysis; NA: not available; NAp: not applicable.

Table E.5 – Overview and characteristics of the included studies in the mortality section.

Reference & Type		Studies	Exposure	Outcome	Analyses	No. cases	Quality
WholEUGrain umbrella review	Zong et al. 2016 [16] SLR & MA	N = 12 prospective cohorts USA (8), Scandinavia (NO, SE, DK) (1), Sweden (1), Norway (1), UK (1)	Whole grains n=6 WG products n=6	Risk of all-cause mortality	High vs. low; dose-response (linear & non-linear); subgroup analyses by study location, WG assessment (foods vs. ingredients), type of dietary questionnaire, WG as main exposure (yes/no), sample size, median follow-up duration, adjustments for dietary factors, Newcastle-Ottawa Scale score, means age at baseline.	97,867	Good
	Chen et al. 2016 [17] SLR & MA	N = 12 prospective cohorts USA (n=6), Scandinavia (NO, SE, DK) (n=1), Sweden (n=1), Norway (n=1), Netherlands (n=1), UK (n=1), Spain (n=1)	Whole grains n=3 WG products n=9	Risk of all-cause mortality	High vs. low; dose-response (linear & non-linear); sensitivity analyses for the effect of each individual study; stratified analyses by geographic region, sex, duration of follow-up, methods for exposure assessment, types of intake (WG or GW products), quality scores, exclusion of prevalent disorders at baseline, and adjustment for potential confounders.	100,653	Good
	Wei et al. 2016 [18] SLR & MA	N = 11 prospective cohorts USA (n=8), Norway (n=1), Scandinavian countries (n=1; Norway, Sweden & Denmark), Spain (n=1)	NA	Risk of all-cause mortality	High vs. low; dose-response (linear & non-linear); subgroup and meta-regression analyses were performed according to age, baseline mean age, duration of follow-up and methods of dietary assessment; adj. for confounding factors, including histories of hypertension, dyslipidaemia and type 2 DM; sensitivity analyses for the effect of each individual study.	94,638	Good
	Li et al. 2016 [19] SLR & MA	N = 10 prospective cohorts USA (n=8), Sapin (n=1), Scandinavian countries (n=1; Norway, Sweden & Denmark)	NA	Risk of all-cause mortality	High vs. low; dose-response (linear & non-linear); subgroup analyses (sex, continent, furation of follow-up, degree of adjustment for confounding incl. history of hypertension, dyslipidaemia, type 2 diabetes, and dietary fiber intake); sensitivity analyses for the effect of each individual study.	92,647	Good
	Ma et al. 2016 [20] SLR & MA	N = 11 prospective cohorts USA (n=7), Spain (n=1), Netherlands (n=1), Norway (n=1), Scandinavian countries (n=1; Norway, Sweden & Denmark)	Whole grains n=3 WG products n=8	Risk of all-cause mortality	High vs. low; dose-response (linear); sensitivity analyses for the effect of each individual study; subgroup analyses by gender, study location, follow-up period, cohort size, adjustment for confounders (total energy intake, BMI, smoking status, alcohol consumption, physical activity level) or intermediate variables (diabetes, blood pressure & serum cholesterol).	101,282	Good
	Benisi-Kohansal et al. 2016 [21] SLR & MA	N = 11 prospective cohorts USA (n=6), Spain (n=1), UK (1), Sweden (n=1), Denmark (n=1), Norway (n=1)	Whole grains n=6 WG products n=5	Risk of all-cause mortality	High vs. low, dose-response (linear and non-linear); sensitivity analyses for the effect of each individual study; subgroup analyses for type of WG (total or products), study quality, duration of follow-up, sex, dietary assessment tools, and location.	101,979	Good
	Schwingshackl et al. 2017 [22] SLR & MA	N = 19 prospective cohorts USA (9), Spain (1), UK (1), Netherlands (1), Switzerland (1), Norway (1), Sweden (3), Scandinavian countries (Norway, Sweden & Denmark) (1), China (1)	Whole grains n=14 WG products n=5	Risk of all-cause mortality	High vs. low, dose-response (linear and non-linear); subgroup analyses by sex, duration of follow-up, location, number of cases, validation of dietary assessment; sensitivity analyses for studies with low risk of bias.	121,217	Good

	Zhang et al. 2018 [23] SLR & MA	N = 9 prospective cohorts USA (7), Spain (1), Norway (1)	Whole grains n=4 WG products n=5	Risk of all-cause mortality	High vs. low, dose-response (linear and non-linear); sensitivity analyses for the effect of each individual study; subgroup analyses for publication year, study duration, area, sex, mean age, number of deaths.	84,464	Fair
	Reynolds et al. 2019 [1] SLR & MA	N = 10 prospective cohorts USA (n=7), Spain (n=1), Netherlands (n=1), Scandinavian countries (n=1; Norway, Sweden & Denmark)	Whole grains n=9 WG products n=1	Risk of all-cause mortality	High vs. low, dose-response (linear and non-linear); sensitivity analyses for the effect of each individual study; analyses for high quality data	99,224	Good
	Aune et al. 2016 [5] SLR & MA	N = 11 prospective cohorts USA (7), Scandinavia (NO, SE, DK) (1), China (1), Spain (1), Netherlands (1)	Whole grains n=10 Whole grains & WG products n=1	Risk of all-cause mortality	High vs. low; dose-response (linear & non-linear); subgroup analyses stratified by study characteristics (duration of follow-up, sex, geographical location, number of cases, validated dietary assessment, study quality, and adjustment for confounding factors); sensitivity analyses for the effect of each individual study.	100,726	Good

SLR: systematic literature review; MA: meta-analysis; WG: whole grain; NA: not available; NAp: not applicable.

Table E.6 – Overview of coincident prospective cohort studies included in meta-analyses of whole grains and overall mortality.

Prospective cohorts	Aune et al. 2016	WholEUGrain project review								
		Zong et al. 2016	Chen et al. 2016	Wei et al. 2016	Li et al. 2016	Ma et al. 2016	Benisi-Kohansal et al. 2016	Schwingschackl et al. 2017	Zhang et al. 2018	Reynolds et al. 2019
Wang et al. 2016 – LNITC (CHN)	√							√		
Zhong et al. 2016 – NHANES III (USA)		√								
Zhong et al. 2016 – NHANES 1999-2004 (USA)		√								
Boggs et al. 2015 – BWHS (USA)	√			√	√	√		√	√	√
Johnsen et al. 2015 – HELGA (NOR, SWE, DNK)	√	√	√	√	√	√		√		√
Huang et al. 2015 – NIH-AARP DHS (USA)	√	√	√	√	√	√	√	√	√	√
Roswall et al. 2015 – SWLHC (SWE)		√	√					√		
Vormund et al. 2015 – Swiss MONICA (CHE)								√		
Wu et al. 2015 – NHS-I (USA)	√	√	√	√	√	√	√	√	√	√
Wu et al. 2015 – HPFS (USA)	√	√	√	√	√	√	√	√	√	√
Yu et al. 2015 – SCCS (USA)								√		
Buil-Cosiales et al. 2014 - PREDIMED (ESP)	√		√	√	√	√	√	√	√	√
Tognon et al. 2012 – VIP (SWE)								√		
Olsen et al. 2011 – DCH (DNK)							√			
Tognon et al. 2011 – GGPSG (SWE)		√					√	√		
van den Brandt et al. 2011 – NldCS (NLD)			√			√		√		√
Jacobs et al. 2007 – IWHS (USA)	√	√	√	√	√	√	√	√		√
Sahyoun et al. 2006 – NA (USA)	√		√	√	√	√	√	√		√
Liu et al. 2003 – PHS (USA)			√	√	√		√	√	√	
Steffen et al. 2003 – ARCS (USA)	√	√	√	√	√	√	√	√	√	√
Appleby et al. 2002 – HFS (GBR)							√			
Jacobs et al. 2001 – NoCS (NOR)		√	√	√		√	√	√	√	
Jacobs et al. 1999 – IWHS (USA)									√	
Key et al. 1996 – CBVHC (GBR)		√	√					√		

ARCS: Atherosclerosis Risk in Communities Study; BWHS: Black Women's Health Study; CBVHC: Cohort of British vegetarians and health-conscious people; DCH: Diet, Cancer and Health cohort; GGPSG: Gerontological and Geriatric Population Studies in Gothenburg; HELGA: 3 sub-cohorts from Norway, Sweden, and Denmark; HFS: Health Food Shoppers Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; LNITC: Linxian Nutrition Intervention Trial Cohort; MONICA: Multinational MONItoring of trends and determinants in CArdiovascular disease; NHS-I: Nurse's Health Study I; NHANES: National Health and Nutrition Examination Survey; NIH-AARP DHS: NldCS: Netherlands Cohort Study; NoCS: Norwegian County Study; National Institute of Health-American Association of Retired Persons Diet and Health Study; PREDIMED: Primary Prevention of CVD with a Mediterranean Diet; PHS: Physicians Health Study; SCCS: Southern Community Cohort Study; SWLHC: Swedish Women's Lifestyle and Health cohort; VIP: Vasterbotten Intervention Program; NA: not available. Country codes: CHE: Switzerland, CHN: China, DNK: Denmark, ESP: Spain, GBR: United Kingdom, NLD: Netherlands, NOR: Norway, SWE: Sweden, USA: United States of America.

Table E.7 – Overview and characteristics of the included studies in the WholEUGrain umbrella review for the overweight section.

Reference & Type	Studies	Exposure	Outcomes	Analyses	Total no. participants	Quality
Reynolds et al. 2020 [24] SLR	N = 2 cohort studies GBR (1), Netherlands (1)	NA	Body weight & weight gain	NAp	5,019	Good
Wang et al. 2020 [25] SLR & MA	N = 20 RCTs USA (5), DK (4), Finland (2), Sweden (1), UK (2), Iran (1), Australia (1), New Zealand (1), Netherlands (1), Germany (1), China (1)	WG products =20	Body weight, BMI & waist circumference	Average reduction in body weight or waist circumference; BMI collected but no results reported; subgroup analysis for positive vs. negative results.	App. 1,800 (incl. controls)	Fair
Sadeghi et al. 2020 [26] SLR & MA	N = 21 RCTs USA (8), UK (3), Denmark (3), Italy (2), Finland/Italy (1), Finland (1), Sweden (1), Australia (1), Switzerland (1)	WG products =21	Body weight BMI Fat mass Fat-free mass Waist circumference	Mean differences in changes; subgroup analyses based on sex, BMI, health status, duration of intervention, study design, use of hypo- vs. isocaloric diets, WG-diet vs. WG-products, anthropometric measures as primary vs. secondary outcomes; sensitivity analyses to assess influence of single studies.	1,798	Good
Maki et al. 2019 [27] SLR & MA	N = 6 prospective cohorts USA (4), Spain (1), Sweden (1) N = 8 RCTs USA (4), Denmark (2), GBR (1), TWN (1)	WG products =6	BMI Body weight	For RCTs Secondary and sensitivity analyses to assess the relationship of higher WG versus a control on: (1) change in waist circumference (cm), (2) change in body fat percentage, (3) weight change (kg) in a subset of studies that included subjects of both sexes, and (4) weight change (kg) in hypocaloric intervention studies.	Observational studies = 136,834 RCTs = 973	Fair
Schlesinger et al. 2019 [28] SLR & MA	N = 6 prospective cohorts USA (3), Spain (2), Australia (1)	Whole grains =2 WG products =4	Risk of overweight/obesity, abdominal obesity, and weight gain	High vs. low; dose-response (linear & non-linear); sensitivity analyses excluding studies not adjusting for energy intake	> 185,000	Good
Reynolds et al. 2019 [1] SLR & MA	N = 11 RCTs UK (2), Vietnam (1),Taiwan (1), USA (2), Italy/Finland (1), China (1) Finland (2), Canada (1),	Whole grains =1 WG products =10	Changes in body weight, BMI, waist circumference and fat mass	High vs. low, sensitivity analyses due to high heterogeneity	919	Good
McRae 2017 [29] Umbrella review of MAs	N = 2 MAs of RCTs Harland & Garton 2008 n=15 RCTs Pol et al. 2013, n=26 RCTs	Harland & Garton 2008 Whole grains =15 Pol et al. 2013 Whole grains =18 NA n=8	Changes in body weight, BMI, and waist circumference	High vs. low	121,889	Fair

SLR: systematic literature review; MA: meta-analysis; RCTs: randomised controlled trials; WG: whole grains; NA: not available; NAp: not applicable; GBR: Great Britain.

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