WHOLE GRAIN INTAKE AND CARDIOVASCULAR DISEASE AND WHOLE GRAIN INTAKE AND DIABETES A REVIEW

November 2008

Fabiana F. De Moura, Ph.D.
Editor

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Battle Creek, MI 49016

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FOREWORD

The Life Sciences Research Office, Inc., (LSRO) provides scientific assessments of topics in the biomedical sciences. Reports published by LSRO are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of science and medicine.

This report was developed under a contract between the Kellogg Company and LSRO. The findings, conclusions, and recommendations contained in this report were developed independently of the Kellogg Company and are not intended to represent the views of the Kellogg Company or any of its employees.

An Expert Panel provided scientific oversight and direction for this study. LSRO independently appointed members of the Expert Panel on the basis of their qualifications, experience, judgment, and freedom from conflict of interest, with due considerations for balance and breadth in the appropriate professional disciplines. Panel members were selected with the concurrence of the LSRO Board of Directors. Biographical and professional information on members of the Expert Panel is provided in Appendix I.

Fabiana DeMoura, Ph.D. drafted this report on the basis of available information and the deliberations and recommendations of the Expert Panel. The Kellogg Company provided a limited review of the report to assure factual accuracy and contractual conformance. The LSRO Board of Directors reviewed and approved the final report. Upon approval, LSRO published the report with no additional input or review.

Participation in the preparation of this report or membership on the Expert Panel, or the LSRO Board of Directors, does not imply endorsement of all statements in the report. LSRO accepts full responsibility for the study conclusions and accuracy of the report.

Michael Falk, Ph.D.
Executive Director
Life Sciences Research Office, Inc.
November 5, 2008

WHOLE GRAIN INTAKE AND CARDIOVASCULAR DISEASE AND WHOLE GRAIN INTAKE AND DIABETES A REVIEW

TABLE OF CONTENTS

TABLES

EXECUTIVE SUMMARY

Cardiovascular disease (CVD) and diabetes are significant causes of morbidity and mortality. Heart disease and stroke are the first and third leading causes of death, respectively, accounting for approximately 40% of deaths in the US annually (American Heart Association & American Stroke Association, 2008). In addition, approximately 21 million children and adults, 8% of the US population, have diabetes (American Diabetes Association, 2008). In the last decade, epidemiological studies have reported a reduction in the risk of CVD and Type 2 diabetes among habitual consumers of whole grains compared to those who rarely eat whole grains (Jacobs, Jr. et al., 1998; Meyer et al., 2000).

However, it wasn't until 1999 that a standard definition of whole grains was recommended on the basis of a consensus among an ad hoc committee of experts from the former American Association for Cereal Chemists (AACC). In 2006, the AACC whole grains definition was adopted by the US Food and Drug Administration (FDA) in the document "Whole Grain Label Statements" to provide guidance to the industry about what the agency considers to be whole grain and to assist manufacturers in labeling their products. In that document whole grains are defined as consisting of the intact, ground, cracked or flaked fruit of the grains whose principal components—the starchy endosperm, germ and bran—are present in the same relative proportions as they exist in the intact grain (U.S. Food and Drug Administration, 2006). Throughout this review, the whole grains definition was referred to as the FDA's definition of whole grains.

In this context, the Kellogg Company requested that the Life Sciences Research Office, Inc. (LSRO) conduct an independent review of the scientific literature to evaluate the effect of applying the FDA definition of whole grains on the strength of scientific evidence in support of whole-grains health claims for risk reduction of CVD and diabetes. This report was undertaken in consultation with an independent Expert Panel that was composed of scientific experts in the fields of cereal chemistry, nutrition, epidemiology and food regulation (Appendix I).

Health Claim Regulations in the United States

Health claims for food labels are authorized in the United States by two amendments to the Federal Food, Drug and Cosmetic Act: the Nutrition Labeling and Education Act of 1990 (NLEA) and the Food and Drug Administration Modernization Act of 1997 (FDAMA). Under the NLEA, a health claim is a food label statement that characterizes a relationship between a food substance or specific food and a disease. These health claims must be authorized and published as regulations by the FDA to be used in food labels (U.S. Congress, 1990). FDAMA health claims are based on an authoritative statement from an appropriate federal agency or the National Academy of Sciences (NAS) (U.S. Congress, 1997). Manufacturers may submit to FDA a notification of a FDAMA health claim and if FDA does not prohibit or modify it within 120 days of receipt of the notification, the claim may be used. Therefore, the health claim provisions in

FDAMA were intended to expedite the process by which the use of food label health claims are authorized (U.S. Food and Drug Administration, 1998a).

Currently, three NLEA health claims have been approved for grain products (not whole grains), one related to cancer and two related to coronary heart disease (CHD). All health claims for grain products refer to a specific substance – one to total dietary fiber, the others to soluble dietary fiber – and a disease component. The FDAMA health claim addressing whole grains is based on the following authoritative statement "diets high in plant foods—i.e., fruits, vegetables, legumes, and *whole grain cereals*—are associated with lower occurrence of CHD and cancers of the lung, colon, esophagus, and stomach" extracted from the NAS report. At present there are no health claims that relate grain products to diabetes.

Whole Grains Composition

A whole cereal grain is the fruit (also known as the seed, caryopsis, or kernel) of plants belonging to the *Poaceae* (or *Gramineae*) family also known as grasses. Some examples of cereal grains are wheat, rice, barley, corn, rye, oats, millets, sorghum, teff, triticale, canary seed, Job's tears, fonio, and wild rice. The seed is composed of three parts: the endosperm which comprises approximately 80-90% of the grain, the bran which is the outer layers of the whole grain and the germ or embryo that is located at the base of the grain. Although all grains contain the three anatomical parts there is a great variability among the various whole grains in their content of macronutrients, micronutrients and bioactive components, including components thought to have a role in disease prevention, such as, fiber, folate, phenolic compounds, lignan, and sterols. For example, the total fiber content of bulgur and barley is approximately 5-fold higher than that of brown rice. Rye contains the highest amount of lignan and sterols (other than phenolic acids and phenolic lipids) compared to wheat, oats, and barley. Furthermore, some nutrients are absent in some grains, but present in high amounts in other grains as in the case of vitamin A, ß-carotene, lutein and zeaxanthin that are present in high levels in corn but absent in brown rice, oats, and sorghum.

LSRO Study Approach

LSRO conducted a comprehensive search of the literature by searching MEDLINE for articles published through February, 2008. The following search strategy was used to identify relevant articles: (whole grain OR whole grains) AND (cardiovascular disease OR heart OR coronary heart disease OR stroke OR blood pressure OR myocardial infarction OR health OR diabetes). LSRO considered only human intervention and observational studies, because according to FDA, these studies can provide evidence from which scientific conclusions can be drawn about substance and disease relationships in humans (U.S. Food and Drug Administration, 2007). In addition, only studies that measured a validated endpoint or a surrogate endpoint for CVD and/or diabetes in a healthy US population and population's representative of the US were considered.

In order to evaluate the effect of applying the FDA definition of whole grains on the strength of scientific evidence, LSRO first analyzed only studies that explicitly described or defined whole grains according to the FDA definition of whole grains. Later LSRO expanded the analysis, to include studies with a broader definition of whole grains, studies that considered added bran and germ as whole grains or studies that did not explicitly use the term "whole grains" but were, in fact, conducted with individual whole grains (*e.g.* studies with oats or barley). Five studies were included in the analysis when considering only studies that met the FDA definition. The expanded approach included additional human studies for a total of 29 (15 intervention and 14 observational) studies for the association between whole grains and CVD, and 21 (10 intervention and 11 observational) studies for the association between whole grains and diabetes. Thirty-eight studies were excluded that evaluated the association between whole grains and CVD or whole grains and diabetes but did not meet one or more of our inclusion criteria.

Conclusions

A consistent definition of whole grains has not been applied in existing research that investigates the health benefits of consuming whole grains. As such, drawing specific conclusions on benefits of "whole grains" in general from the body of scientific evidence is confounded, typically with bran/dietary fiber. Using the FDA definition for whole grains as a selection criterion is limiting because the vast majority of existing studies often use a broader meaning to categorize a grain product as whole grain. Applying the FDA definition of whole grains excludes the majority of observational studies, because they include the intake of bran and germ to evaluate the health effect of whole grains, and a great number of intervention studies that use individual grains, because they do not explicitly state that the endosperm, bran and germ are present in the same proportion.

LSRO concluded that the scientific evidence on the relationship of whole grain consumption and CVD can be evaluated two ways. First, there is no consistent scientific evidence to support a whole grain and CVD risk health claim if only whole grain studies that conform to the FDA whole grain definition are considered. In contrast, a whole grain and CVD health claim is supported using a broader concept of whole grain, typically used in the literature that includes whole-grain foods containing principal components such as bran. A health claim for the relationship between soluble fiber from oats and barley and risk of CHD has been approved by the FDA (U.S. Food and Drug Administration, 2008a).

LSRO concluded that the scientific evidence on the relationship of whole grain consumption and diabetes is suggestive but inconclusive whether the analysis was restricted to studies that defined whole grain according to the FDA definition, or included studies using a wider classification of whole grains.

Finally, LSRO concluded that the health benefits observed from consumption of one whole grain do not necessarily reflect the same type or the same magnitude of benefit from other whole grains. This is because of the diversity among whole grains in terms of macronutrient, micronutrient, and bioactive components.

INTRODUCTION

Health claims referring to the health benefit of dietary intake of whole grains have been approved for use on food labels by the US Food and Drug Administration (FDA) since 1999 (U.S. Food and Drug Administration, 1999). Recently, the FDA defined the term whole grains within the context of food labeling (U.S. Food and Drug Administration, 2006). This report evaluates the effect of applying the FDA definition of whole grains upon the evidence in support of whole grains health claims in food labels, in particular, the relationship between whole-grains consumption and the risks of CVD and diabetes. The project was developed under a contract between Kellogg Company and the LSRO. An expert advisory panel provided oversight for the development of this report (**Appendix I**).

Whole Grains Definition

In 2006, FDA issued the *Whole Grain Label Statements* to "provide guidance to the industry about what FDA considers to be whole grains and to assist manufacturers in labeling their products" (U.S. Food and Drug Administration, 2006). In that document FDA specified that, "***whole grains 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"***[1]. Though this definition was originally put forth by the former American Association for Cereal Chemists (AACC) in 1999 (AACC International, 2008), the definition will be referred to as the FDA's definition of whole grains.

Health Claim Regulations in the United States

Health claims for food labels are authorized in the United States by two amendments to the Federal Food, Drug and Cosmetic Act: the Nutrition Labeling and Education Act of 1990 (NLEA) and the Food and Drug Administration Modernization Act of 1997 (FDAMA). Health claims are to be displayed on the labels of food packaging to educate consumers about the health benefits of foods that qualify for the respective health claim. Under the NLEA, a health claim is a food label statement that characterizes a relationship between a food substance or specific food and a disease. These health claims must be authorized and published as regulations by the FDA to be used in food labels (U.S. Congress, 1990). FDAMA health claims are based on an authoritative statement from an appropriate federal agency or the National Academy of Sciences (NAS) (U.S. Congress, 1997). Manufacturers may submit to FDA a notification of a FDAMA health claim and if FDA does not prohibit or modify it within 120 days of receipt of the notification, the claim may be used. Therefore, the health claim provisions in FDAMA were intended to expedite the process by which the use of food label health claims are authorized (U.S. Food and Drug Administration, 1998a).

[1] Examples of whole grains listed in the guidance document are barley, buckwheat, bulgur, corn, millet, rice, rye, oats, sorghum, wheat, and wild rice.

Nutrition Labeling and Education Act of 1990 Health Claims

The FDA may authorize a health claim if the agency determines, based on the totality of publicly available scientific evidence, that there is "significant scientific agreement" among qualified scientific experts experienced in evaluating such claims, and that the claim is supported by such evidence (U.S. Food and Drug Administration, 2007). To date, the FDA has authorized 12 NLEA health claims that are based on significant scientific agreement. For grain products (not whole grains) three NLEA health claims have been approved, one related to cancer and two related to coronary heart disease (CHD). All health claims for grain products refer to a specific substance – one to total dietary fiber, the others to soluble dietary fiber – and a disease component. Examples of health claims approved for the relationship between grain products and the risk of CHD and between soluble fiber and risk of CHD are presented below.

(1) Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and the risk of CHD.

> Diets low in saturated fat and cholesterol and rich in fruits, vegetables, and grain products that contain some types of dietary fiber, particularly *soluble fiber*, may reduce the risk of *heart disease*, a disease associated with many factors. [21 CFR §101.77(e)] (U.S. Code of Federal Regulations, 2001b).

(2) Soluble fiber from certain foods and risk of CHD.

> *Soluble fiber* from foods such as [*oat bran, rolled oats, whole oat flour, oatrim, whole grain barley and dry milled barley, psyllium husk from the dried seed coat*, and, if desired, the name of the food product], as part of a diet low in saturated fat and cholesterol, may reduce the risk of *heart disease*. A serving of [name of food] supplies ___ grams of the [grams of soluble fiber specified in paragraph (c) (2) (i) (G) of this section] soluble fiber from [name of the soluble fiber source from paragraph (c) (2) (ii) of this section] necessary per day to have this effect. [21 CFR §101.81(e)] (U.S. Code of Federal Regulations, 2001a).

The health daim for *soluble fiber* and reduced risk of CHD [21 CFR §101.81] was first approved by the FDA in 1997 for foods containing whole-oat sources of soluble fiber (*rolled oats, oat bran*[2]*, and whole oat flour*) in response to a petition submitted by the Quaker Oats Company (U.S. Code of Federal Regulations, 2001a). In 1998, the FDA amended 21 CFR § 101.81 to add a health claim for psyllium seed husk soluble fiber and CHD in response to petition submitted by the Kellogg Company (U.S. Food and Drug Administration, 1998b). The soluble fiber health claim was further amended in 2002 to add a hydrolyzed oat flour product (*oatrim*) in response to a petition submitted by Quaker Oats Company and Rhodia (U.S. Food and Drug Administration, 2002). In 2005, FDA amended the soluble fiber health claim to include *barley and barley products* as an additional source of beta-glucan soluble fiber in response to a petition submitted by the National Barley Foods Council (U.S. Food and Drug Administration, 2005). In

[2] Oat bran is a component of whole grain.

2008, a hydrolyzed barley flour product (*barley betafiber*) was also added as a substance eligible for the claim in response to a petition submitted by Cargill (U.S. Food and Drug Administration, 2008b). Hydrolyzed flour products from oats and barley are clearly not whole grain, nor is psyllium fiber, since the psyllium product used as a food or dietary supplement ingredient is the husk -- not the caryopsis. Therefore, Sec 101.81 is not a whole grain health claim but a soluble fiber claim.

Food and Drug Administration Modernization Act of 1997 (FDAMA) Health Claims

Of the five health claims based on authoritative statements, only one addresses whole grains. The health claim notification on whole grain foods and cancer/heart disease submitted by General Mills became available for use on July 8, 1999 (U.S. Food and Drug Administration, 1998a). The notification cited the following statement from the executive summary of the NAS report "Diet and Health: Implications for Reducing Chronic Disease Risk" (National Research Council, 1989) as an authoritative statement:

"Diets high in plant foods—i.e., fruits, vegetables, legumes, and *whole grain cereals*—are associated with lower occurrence of CHD and cancers of the lung, colon, esophagus, and stomach."

Furthermore, the FDA has also adopted a *de facto* definition of *whole grain foods* by not objecting to the definition found in the 1999 General Mills whole grain health claim notification to the FDA (U.S. Food and Drug Administration, 1999). It states that a whole grain food shall be one in which at least 51% of the food is whole grain ingredients by weight per reference amount customarily consumed (RACC). The notification further stated that to assess compliance the dietary fiber content could be compared to that of whole wheat (11g/100g), the predominant grain consumed in the US. However, this "*whole grain food*" definition (1) fails to define what is a whole grain ingredient, (2) fails to state whether the 51% refers to a dry weight or wet weight basis, and (3) excludes many predominantly whole grain foods that are not made from whole wheat because most whole grains have less than the 11% dietary fiber content of whole wheat. In this report, the whole grain definition as stated in the FDA Guidance (2006) and not the whole grain food definition as stated in the General Mills notification will be used to evaluate the scientific relationship of whole grain intake and risk of CVD and diabetes. The whole grain food definition may be more appropriately applied to determine which foods labels are eligible to bear the health claim.

The second Health Claim Notification for Whole Grain Foods with Moderate Fat Content was submitted by Kraft Foods and became available on December 9, 2003 (U.S. Food and Drug Administration, 2003). Although essentially the same whole grain health claim as that in the 1999 General Mills notification, the Kraft Foods notification modified the maximum total fat criterion and added a *trans* fat criterion to the claim. The statements referred to the association between low saturated fat and cholesterol intake and a reduction in the risk of CHD and other chronic diseases.

At present, there are no health claims that relate grain products to diabetes.

Whole Grains and Fiber

The 2005 Dietary Guidelines for Americans states that "consuming at least 3 ounce-equivalents[3] of whole grains *per* day can reduce the risk of CHD, may help with weight maintenance, and may lower risk for other chronic diseases." (U.S. Department of Health and Human Services, 2005). The guidelines further state that "consuming at least half of the recommended grain servings as whole grain is important, for all ages, at each calorie level, to meet the fiber recommendation".

For many years the terms "whole grains" and "fiber" have been used interchangeably. As a result, the assessment of whole grain intake may include a combination of high fiber foods and whole grain foods. The inclusion of fiber in the whole grains category is clearly demonstrated in assessment of dietary intake of whole grains in the US by the Continuing Survey of Food Intakes by Individuals 1994–1996. It states "some grain ingredients, including oat bran and wheat bran, which are not strictly whole grain, were classified as such if they had a high fiber content because a major objective of whole-grain recommendations has focused on promoting adequate fiber consumption" (Cleveland et al., 2000). However, besides fiber, whole grains contain many other compounds that may protect against chronic disease (Slavin, 2003).

Whole Grains Composition

Whole grains contain diverse macronutrients, micronutrients and bioactive components, including components thought to have a role in disease prevention, such as, fiber, folate, phenolic compounds, lignan, and sterols. Moreover, there is considerable variability in these components among the various grains. This section describes whole grains in further detail and presents a brief comparison of the composition of some grains.

A whole cereal grain is the fruit (also known as the seed, caryopsis, or kernel) of plants belonging to the *Poaceae* (or *Gramineae*) family also known as grasses. The term "cereal grain" has also been used for seeds of plants in non-*Gramineae* families, which are known as pseudo-cereals. A list of true and pseudo-cereals is presented in **Table I**.

The seed is composed of three parts: the bran, endosperm and germ. The bran is the outer layers of the whole grain. It contains high amounts of insoluble fibers in the form of arabinoxylan, cellulose, and lignin; and also smaller amounts of minerals, vitamins, lipids, pigments and enzymes (Frølich & Nyman, 1988; Fulcher et al., 1981; Hoseney, 1994; Nilsson et al., 1997). The germ or embryo is located at the base of the grain and

[3] One ounce is about 1 slice of bread, 1 cup of breakfast cereal or ½ cup of cooked rice or pasta.

Table I. True and Pseudo Cereals

True Cereals	**Scientific name**
Wheat including spelt, emmer, faro, eikorn, kamut, durums	*Triticum* spp.
Rice, African rice	*Oryza* spp.
Barley	*Hordeum* spp.
Corn (Maize, Popcorn)	*Zea mays*
Rye	*Secale cereale* spp.
Oats	*Avena* spp.
Millets	*Brachiaria* spp., *Pennisetum* spp., *Panicum* spp., *Setaria* spp., *Paspalum* spp., *Eleusine* spp., *Echinochloa* spp.
Sorghum	*Sorghum* spp.
Teff (tef)	*Eragrostis* spp.
Triticale	*Triticale*
Canary Seed	*Phalaris arundinacea*
Job's Tears	*Coix lachrymal-job*
Fonio, Black Fonio, Asian Millet	*Digitaria* spp.
Wild rice	*Zizania aquatica*
Pseudo Cereals	**Scientific name**
Amaranth	*Amaranthus caudatus*
Buckwheat, Tartar Buckwheat	*Fagopryum* spp.
Quinoa	*Chenopodium quinoa Wild*

Source: AACC International Whole Grains Task Force (2008).

contains proteins, sugars, minerals, enzymes, lipids such as linolenic, linoleic, oleic, and palmitic acids (Ashworth & Christiansen, 1981; Barnes, 1982), tocopherols and tocotrienols (Panfili et al., 2003), and phenolic compounds (Sen et al., 1994). The endosperm contains mainly starch but also protein in significant amounts. The endosperm cell wall is composed of carbohydrate polymers (primarily arabinoxylan and ß-D-glucan), smaller amounts of protein, phenolic acids and other constituents (Fincher & Stone, 1986). In the grain-refining process, the bran is removed, resulting in loss of dietary fiber, vitamins, minerals, phytoestrogens, phenolic compounds and phytic acid (Slavin, 2003).

Tables II & **III** present a comparison of some nutrients in a variety of cereal grains and brans. Among whole grains there is a great variability in content of certain nutrients (**Table II**). For example, the total fiber content of bulgur (18.3 g/100 g) and barley (17.3 g/100 g) is ~5-fold higher than that of brown rice (3.4 g/100 g). In addition, the amount of ß-glucan (soluble fiber) in barley and oats is 2- to 4-fold higher than that in rye and wheat, as a consequence 70–80% of neutral sugar content from soluble fiber of oats

and barley is glucose that originates from the ß-glucan (**Table V**). The difference in potassium and sodium content is even greater, ~75- and 17-fold, respectively, when comparing the grains with the lowest to the highest amount of those minerals (**Table II**). Furthermore, some nutrients are absent in some grains, but present in high amounts in other grains. For example, vitamin A, ß-carotene, lutein and zeaxanthin are present in high levels in corn but absent in brown rice, oats, and sorghum.

The phytochemical distribution of whole grains and brans also differs. The phytochemical composition of barley, oat, rye and wheat grains and brans is compiled in **Table IV**. While oats and barley are known for their high levels of soluble fiber, they are lower in phenolic lipids such as alkylresorcinols and phenolic acids than wheat and rye. Rye also contains the highest amount of lignan and sterols (other than phenolic acids and phenolic lipids) compared to wheat, oats, and barley. Because of the rich and variable content of potential bioactive components and the importance of grains in the western diet, grains have been thought to have an important role in the maintenance of human health. However, the diversity of the type and amount of components among the various types of grains and the fact that many grain types are often eaten by individuals with different backgrounds and in the context of other food components, complicates the ability to evaluate the health benefits of individual grains in observational studies and the ability to extrapolate the effects of clinical trials of individual grains to predict their impact in the context of varied diets over long time periods.

Table II. Nutrient Content (*per* 100g) of a Variety of Grains[1,2]

Nutrient	Barley (hulled)	Brown Rice	Bulgur	Corn (yellow)	Oats	Rye	Sorghum	Wheat	Wild Rice
Proximates									
Energy, Kcal	354	362	342	365	389	335	339	327	357
Protein, g	12.48	7.50	12.29	9.42	16.89	14.76	11.30	12.61	14.73
Total lipid, g	2.30	2.68	1.33	4.74	6.90	2.50	3.30	1.54	1.08
Carbohydrate[5], g	73.48	76.17	75.87	74.26	66.27	69.76	74.63	71.18	74.90
Fiber, total dietary, g	17.3	3.4	18.3	7.3	10.6	14.6	6.3	12.2	6.2
Minerals									
Calcium, mg	33	33	35	7	54	33	28	29	21
Iron, mg	3.60	1.80	2.46	2.71	4.72	2.67	4.40	3.19	1.96
Magnesium, mg	133	143	164	127	177	121	-	126	177
Phosphorus, mg	264	264	300	210	523	374	287	288	433
Potassium, mg	452	268	410	287	429	264	350	363	427
Sodium, mg	12	4	17	35	2	6	6	2	7
Zinc, mg	2.77	2.02	1.93	2.21	3.97	3.73	-	2.65	5.96
Copper, mg	0.498	0.277	0.335	0.314	0.626	0.450	-	0.434	0.524
Manganese, mg	1.943	3.743	3.048	0.485	4.916	2.680	-	3.985	1.329
Selenium, µg	37.7	-	2.3	15.5	-	35.3	-	70.7	2.8
Vitamins[3]									
Thiamin, mg	0.646	0.413	0.232	0.385	0.763	0.316	0.237	0.383	0.115
Riboflavin, mg	0.285	0.043	0.115	0.201	0.139	0.251	0.142	0.115	0.262
Niacin, mg	4.604	4.308	5.114	3.627	0.961	4.270	2.927	5.464	6.733
Pantothenic acid, mg	0.282	1.493	1.045	0.424	1.349	1.456	-	0.954	1.074
Vitamin B6, mg	0.318	0.509	0.342	0.622	0.119	0.294	-	0.300	0.391
Folate, µg	19	20	27	19	56	60	-	38	95
Choline, total, mg	-	-	28.1	-	-	30.4	-	31.2	35.0
Vitamin A, IU	22	0	9	214	0	11	0	9	19
Vitamin E [4], mg	0.57	-	0.06	0.49	-	1.28	-	1.01	0.82
Vitamin K, µg	2.2	-	1.9	0.3	-	5.9	-	1.9	1.9
Other									
Beta-carotene, µg	13	-	5	97	-	7	-	5	11
Lutein + Zeaxanthin, µg	160	-	220	1355	-	210	-	220	220

Data source: USDA National Nutrient Database for Standard Reference, Release 20 (U.S. Department of Agriculture, 2008).
[1]Nutrient values and weights are for edible portion.
[2]Scientific names and specifications of grains (top row, from left to right): Barley hulled (*Hordeum vulgare L.*), Rice (*Oryza sativa L.*), brown and medium-grain raw; Bulgur (*Triticum*) dry; Corn, yellow (*Zea mays mays L.*); Oats (*Avena sativa L.*); Rye (*Secale cereale L.*); Sorghum (*Sorghum spp.*); Wheat (*Triticum aestivum L.*), hard red winter; Wild rice, raw (*Zizani spp*.).
[3]The values for vitamin C and vitamin B_{12} for all the grains listed above were (0.0 mg/100 g).
[4]Vitamin E values are for a-tocopherol. Dash (-) represents the nutrients not listed in the USDA database for the respective grains.
[5]The sum of available and non-available carbohydrate.

Table III. Nutrient Content (*per* 100g) of Cereal Bran[1,2]

Nutrient	Corn Bran	Oat Bran	Rice Bran	Wheat Bran
Proximates				
Energy, Kcal	224	246	316	216
Protein, g	8.36	17.30	13.35	15.55
Total lipid, g	0.92	7.03	20.85	4.25
Carbohydrate[4], g	85.64	66.22	49.69	64.51
Fiber, total dietary, g	79.0	15.4	21.0	42.8
Minerals				
Calcium, mg	42	58	57	73
Iron, mg	2.79	5.41	18.54	10.57
Magnesium, mg	64	235	781	611
Phosphorus, mg	72	734	1677	1013
Potassium, mg	44	566	1485	1182
Sodium, mg	7	4	5	2
Zinc, mg	1.56	3.11	6.04	7.27
Copper, mg	0.248	0.403	0.728	0.998
Manganese, mg	0.140	5.630	14.210	11.500
Selenium, µg	16.5	45.2	15.6	77.6
Vitamins				
Thiamin, mg	0.010	1.170	2.753	0.523
Riboflavin, mg	0.100	0.220	0.284	0.577
Niacin, mg	2.735	0.934	33.995	13.578
Pantothenic acid, mg	0.636	1.494	7.390	2.181
Vitamin B6, mg	0.152	0.165	4.070	1.303
Folate, µg	4	52	63	79
Choline, total, mg	18.1	32.2	32.2	74.4
Betaine, mg	4.6	19.6	-	1293.3[*]
Vitamin A, IU	71	0	0	9
Vitamin E, mg	0.42	1.01	4.92	1.49
Vitamin K, µg	0.3	3.2	1.9	1.9
Other				
Beta-carotene, µg	32	0	0	6
Lutein + Zeaxanthin, µg	1355	180	220	240

[1]Data source: USDA National Nutrient Database for Standard Reference, Release 20 (U.S. Department of Agriculture, 2008). Nutrient values and weights are for edible portion.
[2]Scientific names and specifications of grains (top row, from left to right): Corn (*Zea mays mays L.*); Oats (*Avena sativa L.*); Rice (*Oryza sativa L.*); Wheat (*Triticum aestivum L.*).
[3]Vitamin E values are for a-tocopherol.
[4]The sum of available and non-available carbohydrate.
[*]Value obtained from Likes et al. 2007 (unit=mg/100 g of flour). Dash (-) represents the nutrient not listed in the USDA database for the respective grain.

Table IV. Phytochemical Content of Cereal Grains and Brans[a]

Phytochemicals	Whole Cereal Grain				Bran			
	Barley	Oat	Rye	Wheat	Barley	Oat	Rye	Wheat
Lignan[2,3] (µg/100g)								
Total	58	13.7	112	35.5	63	179	299	110
Matairesinol	0	0.3	65	2.6	0	155	167	0
Secoisolariciresinol	58	13.4	47	32.9	63	24	132	110
Isoflavonoids[2] (µg/100g)								
Total	21.7	0	0	0	22.7	0	0	10.4
Daidzein	14	0	0	0	6.4	0	0	3.5
Genistein	7.7	0	0	0	16.3	0	0	6.9
Phenolic acids[4-8] **(**µg/g,dw)								
Total	478	9.4	1210	640	-	360	3360	5655
Ferulic	478	2.1	1035[b]	640	-	360	2780	5410
Sinapic	-	-	120[b]	-	-	-	390	75
p-coumaric	-	7.3	55[b]	-	-	-	190[b]	170
Phenolic lipids[9-10] (µg/g)								
Akylresorcinols	45	-	734	583	-	ND	2758	2211
Sterols[11] (mg/100g,wb)								
Total sterols	67.8	33.5	88.7	66.4	-	-	-	-
Campesterol	17	4	17	12	-	-	-	-
Campestanol	0.8	trace	8.3	6.5	-	-	-	-
Stigmasterol	3	1.6	3.4	1.9	-	-	-	-
Sitosterol	46	27	48	36	-	-	-	-
Sitostanol	1	0.9	12	10	-	-	-	-

[a]This is an illustrative table comparing the dietary fiber and phytochemical content of four cereal grains and their respective brans. It is not meant to be representative. The references used to compile the table are listed below: (1) (Henry, 1985); (2) (Adlercreutz & Mazur, 1997); (3) (Nilsson et al., 1997); (4) (Adom & Liu, 2002); (5) (Andreasen et al., 2000); (6) (Andreasen et al., 2001); (7) (Zupfer et al., 1998); (8) (Bryngelsson et al., 2002); (9) (Ross et al., 2003); (10) (Chen et al., 2004); (11) (Piironen et al., 2002).

[b]Average values of different cultivars; dw: dry weight; wb: wet base; ND: not detected. Dash (-) represents data not found; it does not necessarily mean that data are unavailable.

Table V. Dietary Fiber Content of Cereal Grains and Brans[a]

	Dietary Fiber (% dry weight)										
	Neutral sugars[b]								ß-glucan	Uronic acids	Klason lignin
	Soluble fraction				*Insoluble fraction*						
	Glc	Xyl	Ara	Man	Glc	Xyl	Ara	Man			
Whole grain											
Barley [1,2,3]	69	15	12	2	39	37	19	4	4.4	0.3	1.7
Oat [1,2,4,5,6]	87	4	5	2	44	34	18	2	3.4	0.3	nd
Rye [1,2]	27	41	24	3	29	40	23	4	1.9	0.5	1.9
Wheat [1,5]	11	48	30	4	28	42	29	tr	0.7	0.2	nd
Bran											
Barley [2]	58	21	14	3	44	40	13	2	nd	0.9	5.5
Oat [2,4,6,7]	78	7	7	2	46	35	14	2	7.3	0.3	nd
Rye [2]	11	54	29	2	31	42	21	3	nd	0.7	2.9
Wheat [5,8]	14	55	30	tr	30	46	23	tr	nd	1.4	5.9

[a] Adapted from Marlett 1991. The reported values are an average of different cultivars. (1) (Henry, 1985); (2) (Salomonsson et al., 1984); (3) (Marlett, 1991); (4) (Shinnick et al., 1988); (5) (Cummings & Englyst, 1987); (6) (Frølich & Nyman, 1988); (7) (Wood et al., 1991); (8) (Neilson & Marlett, 1983).
[b] Ara: arabinose; Glc: glucose; Man: mannose; nd: no data; tr: trace amount; Xyl: xylose

Project Purpose

The purpose of the present report is to evaluate the effect of applying the FDA definition of whole grains to the evidence in support of whole-grains health claims, in particular the scientific relationship between whole grains consumption and the risk of CVD and diabetes. In the last decade, epidemiological studies have demonstrated a reduction in the risk of CVD and Type 2 diabetes among habitual consumers of whole grains compared to those who rarely eat whole grains (Jacobs, Jr. et al., 1998; Meyer et al., 2000). Currently, heart disease and stroke are the first and third leading causes of death, respectively, accounting for approximately 40% of all deaths in the US (American Heart Association & American Stroke Association, 2008). In addition, approximately 21 million children and adults, 8% of the US population, have diabetes (American Diabetes Association, 2008).

METHODOLOGY

A comprehensive search of the scientific literature was conducted by searching MEDLINE for articles published through February, 2008. The following search strategy was used to identify relevant articles:

- Whole grain OR Whole grains; AND
- Cardiovascular disease; OR
- Heart; OR
- Coronary heart disease; OR
- Stroke; OR
- Blood pressure; OR
- Myocardial infarction; OR
- Health; OR
- Diabetes.

The MEDLINE searches returned 634 potentially relevant articles. Reviews, editorials and meta-analysis studies (n = 200) were excluded, as were studies not written in English (n = 28). Animal and *in vitro* studies were also excluded (n = 79). A total of 327 articles remained. After reading titles and abstracts, 204 articles were evaluated further. An additional 8 articles were identified from a Web of Science database search using the same keywords used for the MEDLINE search. Other studies were identified from relevant reviews and articles.

Inclusion Criteria

The inclusion criteria were derived from the specifications of the FDA guidelines for studies eligible to establish a health claim (U.S. Food and Drug Administration, 2007). Only studies that fall into the following categories were included in this report:

- Study design: human intervention and observational studies only.
- Studies that measured a validated endpoint or a *surrogate* endpoint for CVD and/or diabetes:
    - **Cardiovascular disease**: validated endpoints (CHD, myocardial infarction (MI), ischemic heart disease (IHD) and stroke), surrogate endpoints (blood pressure (BP), total serum cholesterol concentration (TC), and serum low-density lipoprotein cholesterol (LDL-C) concentration).
    - **Diabetes:** validated endpoint (Type 2 diabetes), surrogate endpoints (elevated blood sugar concentrations and insulin resistance).
- Study population:
    - US population and populations representative of the US.
    - Healthy population or a high risk for diabetes or CVD, *e.g.*, hypercholesterolemic, obese, hyperinsulemic, but absent of CVD or diabetes.
- Studies were evaluated into two categories according to whole grain definition:

- **FDA definition**: includes studies that explicitly describe or define whole grains according to the FDA definition of whole grains.

- **Expanded definition**: also includes studies that explicitly describe or define whole grain but do not meet FDA definition of whole grains by including bran and germ, and studies that do not explicitly use the term "whole grains" but were in fact conducted with individual whole grains (*e.g.* studies with oats or barley).

In this LSRO report, only human studies were used as primary evidence. FDA may use animal and *in vitro* studies as background information, but scientific conclusions from those studies can not be drawn regarding the relationship between the substance and disease in humans (U.S. Food and Drug Administration, 2007). This is because the physiology of animals is different than that of humans, and the artificial environment of *in vitro* studies cannot account for the multitude of normal human physiological processes.

RESULTS

Included Studies

Five studies (Andersson et al., 2007; de Munter et al., 2007; Jensen et al., 2006; Jensen et al., 2004; Rave et al., 2007) were included in the FDA definition. The expanded definition included additional human studies that defined whole grains but did not necessarily conform to the FDA definition for the association between whole grain intake and CVD and diabetes. Also included were studies that did not use the term "whole grains" although they in fact evaluated the effect of a specific whole cereal grain (*i.e.*, oats, barley) on CVD and diabetes. These studies were mostly published in the late 1980's when the term whole grain was not often used. The expanded definition included 29 (15 intervention and 14 observational) studies for the association between whole grains and CVD, and 21 (10 intervention and 11 observational) studies for the association between whole grains and diabetes.

Excluded Studies

Thirty-eight studies were excluded that evaluated the association between whole grains and CVD or whole grains and diabetes but did not meet one or more of our inclusion criteria for either the FDA or expanded definition. A list of the excluded studies and reasons for exclusion are presented in **Appendix II**.

Intervention Studies on Cardiovascular Disease

A brief description of the intervention studies included in the report for the association between whole grains and CVD is presented here. The study designs and results are summarized in **Table VI**.

FDA Definition

The association between whole grain intake and BP was investigated in a randomized, non-blinded crossover study (Andersson et al., 2007). Participants were 22 postmenopausal women and 8 men, who were healthy, although moderately overweight [body mass index (BMI): 26–35], with a mean age of 59 ± 5 y. Subjects were advised to continue their usual diet and to add a specific amount (total amount of whole grains consumed was 112 g/day) of either refined grain or whole grain products. The products (bread, crisp bread, muesli, and pasta) were provided to the subjects and they were consumed for 6 weeks, with a 6- to 8-week washout period. The whole grain products contained a minimum of 50% whole grain/dry substance, including the starchy endosperm, germ, and bran, in mainly milled form. Whole grain rice was examined by light microscopy and included as a whole-grain product because the bran was intact and >80% of the germ was present. Wheat, rye, oats, and rice were all included, but wheat dominated. At the end of 6-week treatment period, whole grain consumption did not affect BP or serum lipid concentrations.

Thirty one obese (BMI: 27–36) German men (n = 13) and women (n = 18), aged 25–56 y, who had an elevated fasting blood glucose (6.3 ± 0.8 mmol/L) participated in a crossover study to investigate the effects of a hypo-energetic diet, including whole grains, on plasma lipid profile (Rave et al., 2007). Subjects were randomly assigned to replace at least two daily meals (200 g/day) with a starch-reduced whole grain (WG) derived from double-fermented wheat (Balantose™, Cargill GmbH, Freising, Germany) or a nutrient-dense meal replacement (MR) product (Slim Fast™, Unilever, Toronto, Ontario, Canada) for a 4-week treatment period with a 2-week washout period. The starch-reduced whole grain derived from double-fermented wheat contains all parts of the whole grain, *i.e*., germ, bran and endosperm. No statistically significant changes in TC, LDL-C, and BP were observed between the two treatments.

Expanded Definition

Judd & Truswell (1981) investigated the effect of oat consumption (does not explicitly use the term “whole grains”) on plasma lipid profile. Ten subjects, 4 women and 6 men aged 24–37 y, within 10% ideal body weight participated in a 3-week intervention study. Subjects consumed a control diet (no oats) during the first and third week of the study, and a diet containing oats in the second week. For the oats diet, rolled oats (125 g/day) were substituted for breakfast cereals which were cooked as porridge and were also substituted for wheat flour in bread, cakes, and biscuits. For the two control diets, fat and energy intakes were adjusted by adding oil with a similar fatty acid composition as the oat diet. Plasma TC was not significantly different between the oats diet and the control diet.

Two hundred eight healthy men (n = 108) and women (n = 100), aged 30–65 y, participated in a 12-week intervention study to investigate the effect of a modified fat diet including oat bran and oatmeal (the term “whole grains” is not explicitly used) on serum lipid profile (Van Horn et al., 1986). All participants followed the American Heart

Association (AHA) fat-modified diet for 6 weeks. Oat products were consumed as hot oat cereal (recommended form of consumption) in addition to the AHA diet for another 6 weeks. Subjects were randomly assigned to consume either 60 g/day of oat bran (Group 1), 60 g/day of oatmeal (Group 2), or no oat products (Group 3). At week 6 (AHA diet only), the mean serum TC levels of all subjects decreased by 0.28 ± 0.57 mmol/L (5.2%) ($p < 0.001$) from those at baseline levels. At week 12, only subjects in Group 2 exhibited an additional reduction of 0.16 mmol/L (standard deviation not reported) or 3.3% in their serum TC levels ($p = 0.038$). No other significant changes were observed.

Van Horn and colleagues (1988) continued their investigation of the effect of oatmeal consumption (the term "whole grains" is not explicitly used) on serum lipid profile. Two hundred thirty-six healthy men (n = 86) and women (n = 150) aged 30–65 y participated in a 12-week intervention study. Subjects consumed the AHA diet for 4 weeks and were then randomly assigned to either the AHA diet *plus* 60 g/day of oatmeal or the AHA diet only, for another 8 weeks. At week 4, similar reductions in serum TC levels were observed among all subjects. At week 8, the mean serum TC of subjects who consumed the AHA diet *plus* oatmeal further decreased by 0.18 ± 0.43 mmol/L (3.3%), a greater reduction than the 0.05 ± 0.35 mmol/L (1%) decrease exhibited by those who consumed the AHA diet only ($p = 0.008$). However, the significant difference in TC between the two diets disappeared by week 12 ($p = 0.074$). Similar results were obtained when the investigators applied the same study design to investigate the effect of instant oats (56 g/day) on lipid profile in men and women with hypercholesterolemia instead of healthy adults (Van Horn et al., 1991).

Davidson et al. (1991) evaluated the effect of consumption of oat products (does not explicitly use the term "whole grains") on serum lipid profile. One hundred forty hypercholesterolemic men (n = 80) and women (n = 60) aged 30–65 y with LDL-C levels above 3.37 mmol/L participated in this 12-week intervention study. Subjects were randomly assigned to one of the six treatment groups: oatmeal or oat bran at doses of 28, 56, or 84 g/day, or to the control group (ß-glucan control, 28 g of farina). At the end of week 6, significant decreases in serum TC levels were observed among the following treatment groups compared to the control group: -0.55 mmol/L or 7% ($p = 0.003$) for oatmeal (84 g/day), -0.69 mmol/L or 10% ($p = 0.02$) for oat bran (56 g/day), and -0.5 mmol/L or 7% ($p = 0.003$) for oat bran (84 g/day). LDL-C levels had also decreased by -0.56 mmol/L or 10% ($p = 0.02$), -0.80 mmol/L or 16% ($p = 0.0009$), and -0.56 mmol/L or 12% ($p = 0.02$), respectively. However, no significant differences were observed in the lipid profiles of subjects at the end of the 12-week treatment period.

Forty-three men and women with a mean BMI of 26.4 ± 3.3 with ages ranging from 18–30 y and 60–75 y participated in an 8-week intervention study to evaluate the effect of a hypo-caloric diet containing oats (the term "whole grains" not explicitly used) on BP and lipid profile (Saltzman et al., 2001). All subjects consumed a control diet for two weeks and were randomly assigned to a hypo-caloric diet or a hypo-caloric diet containing oats for 6 weeks. All foods and drinks were provided to the subjects who ate at the research facility at least 4 days a week, for the remaining days the food was carried out to be eaten somewhere else. Oats were consumed in the form of hot cereal (Quick Oats,

Quaker Oats Company, Barrington, IL) or were incorporated into other food items (breads and casseroles). The oat diet contained oats in all meals and snacks.

Compared to the hypo-caloric diet alone, the hypo-caloric diet containing oats resulted in greater reductions in systolic blood pressure (SBP) (oats: -6 ± 7 mmHg (5%), control: -1 ± 10 mmHg (0.8%), $p = 0.026$), TC (oats: -0.87 ± 0.47 mmol/L (18%), control: -0.34 ± 0.5 mmol/L (8%), $p = 0.003$) and LDL-C (oats: -0.60 ± 0.41 mmol/L (19%), control: -0.20 ± 0.41 mmol/L (7%), $p = 0.008$) at the end of the 6-week treatment period. No significant differences were observed in the reduction of diastolic blood pressure (DBP) between the two diets.

Keenan and colleagues (2002) investigated the effect of consuming oat cereal (the term "whole grains" not explicitly used) on BP and lipid profile of 18 hypertensive (SBP: 130 to 160 mmHg; DBP: 85 to 100 mmHg) and hyperinsulinemic (≥ 10 µU/mL) men and women aged 27–59 y. In this randomized, controlled pilot study subjects were assigned to the oat cereal (5.52 g/day ß-glucan) or control (1 g/day total fiber) groups for 6 weeks. Participants were allowed to prepare and consume their cereal as they wished. Subjects who consumed oat cereal showed significant reductions in SBP (from 143 ± 3.7 to 135 ± 2.6 mmHg (6%), $p < 0.01$) and DBP (from 93 ± 1.9 to 87 ± 2.2 mmHg (7%), $p = 0.02$). The levels of TC and LDL-C were also reduced by 16.2 ± 6.3 mg/dL (8%) ($p = 0.030$) and 15.8 ± 5.9 mg/dL (12%) ($p = 0.025$), respectively, in the oat cereal group. No significant changes in these variables were observed in the control group.

Davy (2002b) investigated the effect of oat consumption on the arterial BP of individuals with elevated arterial BP. Thirty-six men aged 50–75 y having BMI of 25–35 and elevated BP (SBP: 130–159 mmHg and/or DBP: 85–99 mmHg) were randomly assigned to consume an additional 14 g/day of dietary fiber in the form of oat or wheat cereal for 12 weeks. Whole grains were whole grain oat (60 g Quaker Oatmeal and 76 g Quaker Oat Bran ready-to-eat cold cereal, Quaker Oats Company, Barrington, IL) or whole wheat cereal (60 g Mother's Whole Wheat Hot Natural cereal, Quaker Oats Company, and 81 g Frosted Mini-Wheats, Kellogg, Battle Creek, MI) that were consumed daily at breakfast and as a snack. Blood pressure was measured at baseline, 4, 8, and 12 weeks. The casual resting arterial BP and 24-hour ambulatory arterial BP were measured at baseline and after 12 weeks of intervention. No significant changes were observed in the casual SBP as a result of the 12-week intervention in the oat (138.2 ± 2.4 *vs* 134.6 ± 3.1 mmHg) or wheat (142.3 ± 2.4 *vs* 140.3 ± 2.5 mmHg) groups, respectively (all $p > 0.05$), nor were changes observed in the casual DBP in the oat (88.5 ± 1.6 *vs* 87.6 ± 2.0 mmHg) or wheat (90.4 ± 1.5 *vs* 90.9 ± 2.0 mmHg) group during this period, respectively (all $p > 0.05$).

Another research group investigated the effect of barley intake on BP and lipid profile in hypercholesterolemic men (Behall et al., 2004b; Hallfrisch et al., 2003) and hypercholesterolemic men and women (Behall et al., 2006). All three studies followed the same protocol. Subjects consumed the AHA Step I diet for 2 weeks. After the two week adaptation period, they were assigned to 3 treatment diets for 5 weeks, the experiment followed a Latin square design. The test food (wheat diet) was composed of

pancakes, spice cookie bar, no-bake cookies, hot cereal, granola, steamed grain, tabbouleh, and muffins made with whole wheat flour, wheat flakes, and brown rice. The barley diet replaced the wheat and brown rice in the wheat diet for barley flakes, barley flour, or pearled barley that were donated by the Barley Foods Council. The wheat and barley diet was made with half barley and half whole wheat or brown rice in the test food. Breakfast and dinner were consumed in the Human Study Facility on weekdays.

Among the 16 non-hypertensive mildly hypercholesterolemic men aged 28–62 y there was no change in SBP after the 2-week treatment with the Step I AHA control diet. However, SBP was reduced by approximately 5% (112–114 *versus* 120 mmHg, p = 0.0004) after a 5-week treatment with all three whole grain diets (Hallfrisch et al., 2003). Compared to the control diet, all three whole grain diets significantly reduced DBP (p = 0.015) and mean arterial blood pressures (MABP) (p = 0.0009), but not when compared to baseline values. Compared to the Step I diet, plasma concentrations after the wheat diet, wheat and barley diet, and barley diet, were lower ($p < 0.0001$) for TC (-0.55 mmol/L or 14%, -0.6 mmol/L or 17%, and -1.01 mmol/L or 20%) and for LDL-C (-0.57 mmol/L or 17%, -0.58 mmol/L or 17%, and -0.94 mmol/L or 24%), respectively (Behall et al., 2004b).

The effect of barley on the lipid profile and BP of hypercholesterolemic men (n = 7), post- (n = 9), and pre- (n = 9) menopausal women was also reported (Behall et al., 2004a; Behall et al., 2006). Compared with pre-study concentrations, the plasma levels were significantly lower for the entire study population ($p < 0.001$) after the wheat, wheat and barley, and barley diets for TC (-0.21 mmol/L or 4%, -0.48 mmol/L or 9%, and -0.53 mmol/L or 10%) and LDL-C (-0.11 mmol/L or 8%, -0.36 mmol/L or 14%, and -0.43 mmol/L or 17%), respectively. The reductions observed in plasma levels were not significantly different among gender (men, pre-, and post-menopausal women).

Li (2003) investigated the effects of high barley intake on lipid metabolism of healthy Japanese women. In a randomized, crossover study design, 10 healthy women with a mean age of 20.4 ± 1.3 y and BMI 19.2 ± 2.0 were assigned to a control diet (standard Japanese food) or a barley diet (30% of carbohydrate in the control diet was replaced with barley; mean barley intake was 1.8 g/kg). The barley used in the study was whole grain that maintained 45% of bran. Both diets were consumed for 4 weeks (treatment period) with a 4-week washout period. Compared with the standard diet, the barley diet resulted in a reduction in fasting plasma TC (14.5%, $p < 0.05$) and LDL-C (21.5%, $p < 0.05$) at the end of the treatment period.

Table VI. Intervention Studies on the Association of **Whole Grain Intake** and Incidence of **Cardiovascular Disease**

Reference	Population	Study Design	Treatment	Duration	Subjects				Surrogate Endpoints			
					Sex	No. #	Age years	BMI kg/m^2	TC mmol/L	LDL-C mmol/L	SBP mmHg	DBP mmHg
FDA Definition												
Andersson et al., 2007	Sweden	Randomized Crossover	Control	6 weeks	F/M	22/8	59 ± 5	28.3 ± 2.0	5.5 ± 0.7	3.6 ± 0.7	130 ± 15	81 ± 9
			Whole Grains	6 weeks					5.5 ± 0.7	3.7 ± .07	129 ± 15	80 ± 10
Rave et al., 2007	Germany	Randomized Crossover	Control – Weight Loss	4 weeks	F/M	18/13	51 ± 13	33.9 ± 2.7	-0.7 ± 0.15†	-0.7 ± 0.14†	-1 ± 11†	-1 ± 8†
			Whole Wheat - Weight Loss	4 weeks					0.002 ± 0.09*†	-0.1 ± 0.1*†	-5 ± 10†	-3 ± 7†
Expanded Definition												
Judd et al.,1981	England	Crossover	Control	2 weeks	F/M	4/6	24-37		5.26			
			Rolled Oats	3 weeks					4.84			
			Control	2 weeks					5.21			
Van Horn et al. 1986	US	Randomized Parallel	Control	6 weeks	F/M	30/40	46 ± 10	25.7 ± 4.2	5.16 ± 1.09			
			Oat bran	6 weeks		37/32	42 ± 9	25.2 ± 4.1	4.94 ± 1.08			
			Oatmeal	6 weeks		32/37	44 ± 11	24.7 ± 5.3	4.88 ± 1.05*			
Van Horn et al. 1988	US	Randomized Parallel	Control	8-weeks	F/M	78/45			4.96 ± 1.12			
			Oatmeal	8-weeks		72/41			4.85 ±1.00			
Van Horn et al., 1991	US	Randomized Parallel	Control	8-weeks	F/M	19/19	42 ± 12	26.2 ± 3.8	6.30 ± 0.82	4.44 ± 0.77	124 ± 13	77 ± 11
			Oatmeal	8-weeks		21/21	43 ± 14	26.2 ± 3.4	6.15 ± 0.86	4.16 ± 0.83	124 ± 14	77 ± 9
Davidson et al., 1991	US	Single Blind Randomized Parallel	Control	6-weeks	F/M	5/10	53	25.8	6.79 ± 0.83	4.79 ± 0.73		
			Oatmeal-28	6-weeks		13/7	51	26.2	6.54 ± 0.68	4.47 ± 0.61		
			Oatbran-28	6-weeks		10/12	52	24.8	6.72 ± 0.89	4.61 ± 0.79		
			Oatmeal-56	6-weeks		7/15	55	26.1	6.63 ± 0.81	4.67 ± 0.75		
			Oatbran-56	6-weeks		5/14	53	24.8	6.20 ± 0.76*	4.09 ± 0.76*		
			Oatmeal-84	6-weeks		11/9	51	25.2	6.56 ± 0.92*	4.56 ± 1.00*		
			Oatbran-84	6-weeks		9/13	55	25.0	6.34 ± 0.78*	4.16 ± 0.70*		
Saltzman et al,. 2001	US	Randomized Parallel	Control-weight loss	8-weeks	F/M	12/9	44 ± 21	26.7 ± 3.2	-0.34 ± 0.50†	-0.20 ± 0.41†	-1 ± 10†	-3 ± 5†
			Oats-weight loss	8-weeks		11/11	45 ± 23	26.1 ± 3.4	-0.87 ± 0.47*†	-0.60 ± 0.41*†	-6 ± 7*†	-4 ± 6†
Keenan et al., 2002	US	Randomized Parallel	Control	6-weeks	F/M	4/4	46 ± 19	30.0 ± 4.7	5.11± 0.17	3.36 ± 0.16	135.8 ± 5.7	89.0 ± 1.6
			Oat Cereal	6-weeks		5/5	44 ± 17	28.8 ± 4.1	4.72 ± 0.15*	2.94 ± 0.20*	135.0 ± 2.6*	87.0 ± 2.2*

Table VI. Intervention Studies on the Association of **Whole Grain Intake** and Incidence of **Cardiovascular Disease** (*continued*)

Reference	Population	Study Design	Treatment	Duration	Subjects				Surrogate Endpoints			
					Sex	No. #	Age years	BMI kg/m^2	TC mmol/L	LDL-C mmol/L	SBP mmHg	DBP mmHg
Expanded Definition												
Davy et al., 2002	US	Randomized Parallel	Control	12-weeks	M	18	61 ± 2	29.2 ± 0.8			140.3 ± 2.5	90.9 ± 2.0
			Oat Cereal	12-weeks		18	57 ± 2	29.6 ± 0.8			134.6 ± 3.1	87.6 ± 2.0
Hallfrisch et al., 2003	US	Randomized Crossover (Latin Square)	Control	2-weeks	M	16	47 ± 10	26.7 ± 2.8			120[a]	76[a]
			Brown Rice/ Wheat	5-weeks		16					112[b]	71[b]
			Barley:Wheat/ Brown Rice (1:1)	5-weeks		16					114[b]	72[b]
			Barley	5-weeks		16					114[b]	72[b]
Behall et al., 2004b	US	Randomized Crossover (Latin Square)	Control	2-weeks	M	16	47 ± 10	26.7 ± 2.8	5.83 ± 0.22[a]	3.94 ± 0.21[a]		
			Brown Rice/ Wheat	5-weeks		16			5.28 ± 0.22[b]	3.37 ± 0.22[b]		
			Barley:Wheat and Brown Rice (1:1)	5-weeks		16			5.23± 0.22[b]	3.36 ± 0.21[b]		
			Barley	5-weeks		16			4.82 ± 0.21[c]	3.00 ± 0.21[c]		
Behall et al,. 2004a	US	Randomized Crossover (Latin Square)	Control	2-weeks	F/M	18/7	47	30.3	5.65 ± 0.13[a]	3.93 ± 0.13[a]		
			Brown Rice/ Wheat	5-weeks		18/7			5.44 ± 0.13[a]	3.82 ± 0.13[a]		
			Barley:Wheat and Brown Rice (1:1)	5-weeks		18/7			5.17 ± 0.13[b]	3.57 ± 0.13[b]		
			Barley	5-weeks		18/7			5.12 ± 0.33[b]	3.50 ± 0.13[b]		
Behall et al., 2006	US	Randomized Crossover (Latin Square)	Control	2-weeks	F/M	18/7	47	30.3				
			Brown Rice/Wheat	5-weeks		18/7					110.2 ± 2.4*	65.3 ± 1.7*
			Barley:Wheat and Brown Rice (1:1)	5-weeks		18/7					108.7 ± 2.4*	65.8 ± 1.7*
			Barley	5-weeks		18/7					114.0 ± 2.4	66.1 ± 1.7*
Li et al., 2003	Japan	Randomized Crossover	Control	4-weeks	F	10	20 ± 1	19.2 ± 2.0	3.57 ± 0.59	1.37 ± 0.24		
			Barley (1.8g/kg)	4-weeks		10			3.05 ± 0.54*	1.08 ± 0.22*		

BMI: body mass index; **TC:** total cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure
For Behall et al., 2004a and 2004b: values in a column with different superscript letters are significantly different, $p < 0.0001$
For Hallfrisch et al., 2003: values in a column with different superscript letters are significantly different. Diastolic, $p = 0.015$; Systolic, $p = 0.0004$
*p<0.05; † Difference between baseline and end of treatment period.

Observational Studies on Cardiovascular Disease

A brief description of the observational studies included in the report for the association between whole grains and CVD is presented here. The study designs and results are summarized in **Table VII**.

FDA Definition

The Health Professionals Follow-up Study (HPFS) was initiated in 1986 with 51,529 male health professionals aged 40–74 y. After excluding men diagnosed with CVD, diabetes, or cancer at baseline, data from 42,850 men remained for the investigation of whole grain intake and the incidence of CHD (Jensen et al., 2004). During the 14-year follow-up period (1986–2000) 1,818 incident cases of CHD (1,261 nonfatal MI and 557 fatal) occurred. Whole grain intake was assessed using a semi-quantitative food frequency questionnaire (SFFQ), which included open-ended questions regarding the usual serving size and frequency of consumption of foods not listed on the food frequency questionnaire (FFQ). Whole grains were considered in their intact and pulverized forms, and each whole grain ingredient was required to satisfy the content of an individual type of grain; *i.e.*, whole grain wheat must have the proper content of bran, endosperm, and germ. The whole grain designation was assigned to the following items in the database: whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal, and corn flour, brown rice, and brown rice flour, whole barley, whole rye and rye flour, bulgur, buckwheat, popcorn, amaranth, and psyllium. Wheat bran, corn bran, oat bran, rice bran, and wheat germ that were added to foods to increase the fiber content were further considered as added bran and germ, respectively. The whole-grain percentage for each food was then multiplied by the gram weight *per* serving to obtain the grams of whole grain content per RACC. Total whole-grain consumption (in g/day) was then calculated by summing the whole-grain intakes from 1) high-whole grain foods with = 51% whole-grain content by weight in accordance with the FDA whole-grain claim; 2) moderate whole-grain foods with = 25% whole-grain or bran content by weight according to the classification of Jacobs, Jr. et al. (1998); and 3) all foods consumed. Median whole grain intakes, from the lowest to the highest quintile, were 3.5, 9.6, 16, 24.7 and 42.4 g/day. The risk of CHD was reduced by approximately 15% when whole grain intake was greater than 25 g/day, which means that only the highest quintile of whole grain intake showed a significant positive association. Furthermore, the risk reduction for CHD was particularly strong when expressed on the basis of level of “added” bran (wheat bran, corn bran, oat bran, and rice bran added during processing or cooking) intake.

Data from 938 healthy men aged 40–75 y from the HPFS cohort study and women aged 25–42 y from the NHS cohort study was analyzed to investigate the relationship between whole grain intake and serum lipid profile in a cross-sectional study (Jensen et al., 2006). Whole grains were defined in a previous report by Jensen (2004) and the intake was assessed using a 131-item SFFQ. The median whole grain intake, from the lowest to the highest quintile, was 8.2, 15.9, 22.3, 29.6 and 43.8 g/day, respectively

which corresponded to TC levels of 5.74 ± 0.08, 5.87 ± 0.08, 5.80 ± 0.07, 5.66 ± 0.06, and 5.58 ± 0.07 mmol/L, respectively (*P* for trend = 0.02).

Expanded Definition

Prospective Cohort Studies

In the Adventist Healthy Study (AHS), associations between consumption of various foods and food groups including whole grains, and risk of incident fatal and nonfatal CHD events was investigated (Fraser et al., 1992). Non-Hispanic white California Seventh-Day Adventists aged 25 or older (n = 26,473) participated in this prospective cohort investigation. Subjects with heart disease and diabetes at baseline were excluded. The first event of CVD (fatal or nonfatal MI) was recorded during the 6-year follow-up period (1977–1982). Each participant's health status was queried annually, and medical records were reviewed for the diagnosis of CVD (nonfatal or fatal MI) according to the International Classification of Diseases codes. Bread was considered whole grain if made of 100% whole wheat or whole grain, sprouted wheat, wheat berry, or other (rye, cracked, wheat, pumpernickel, and soy). Whole grain intake was assessed using a 65-item SFFQ. During the follow-up period, there were 134 cases of incident definite nonfatal MI, 260 cases of incident definite fatal MI, and a total of 463 cases of incident coronary deaths. Subjects who usually consumed whole wheat bread had lower rates of definite nonfatal MI with a relative risk (RR) of 0.56 (95% CI: 0.45, 0.89; $p < 0.01$), than those who usually ate white bread.

In the Iowa Women's Healthy Study (IWHS), a prospective cohort study of post-menopausal women, Jacobs, Jr. et al. (1998) evaluated the relationship between whole grain and refined grain intakes in relation to risk of IHD. Participants were 31,284 post-menopausal women, aged 55–69 y, with no history of IHD at baseline in 1986. Over a 9-year follow-up period, 438 women died of IHD. Whole grain foods included dark bread, whole grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran and other grains (*e.g.*, bulgur, kasha, and couscous). Breakfast cereals were considered to be whole grain if the product contained = 25% whole grain or bran by weight, as determined either from the package label or from records shared by General Mills, Minneapolis, MN. Bran cereals were included in the whole grain category because findings were similar for bran cereals and whole grain cereals that did not contain added bran. Whole grain intake was assessed using a 127-item FFQ. Of 30,020 women who reported eating breakfast cereal, 18,721 reported typically consuming a product that was = 25% whole grain or bran. Ischemic heart disease was inversely associated with whole grain intake, with adjusted RR of 1.0, 0.96, 0.71, 0.64, and 0.70 for eating 0.2, 0.9, 1.2, 1.9, and 3.2 median servings/day of whole grains, respectively, (*P* for trend = 0.02).

The association between whole grain intake and CVD mortality (overall and by CHD and stroke, separately) was later evaluated in the IWHS 9-year prospective study (Jacobs, Jr. et al., 1999). Whole grains are described in a previous report by Jacobs, Jr. et al. (1998). Whole grain intake was assessed using a 127-item FFQ. Median whole

grain intakes were 0.2, 0.9, 1.2, 1.9, and 3.2 servings/day (lowest to highest quintiles), respectively. After adjustment for potential confounders, the hazard rate ratio (HR) for the highest *versus* the lowest quintile of whole grain intake was 0.82 (95% CI: 0.66, 1.01; *P* for trend = 0.02) for deaths caused by all CVD events. A similar HR of 0.82 (95% CI: 0.63, 1.06; *P* for trend = 0.03) was reported by deaths caused by CHD; and a insignificant HR of 0.87 (95% CI: 0.52, 1.48; *P* for trend = 0.38) was reported for deaths caused by stroke.

The Nurses' Health Study (NHS) is a cohort study initiated in 1976 with 121,700 female registered nurses aged 30–55. The associations between whole grain intake and incidence of CHD (Liu et al., 1999) and whole grain intake and incidence of stroke (Liu et al., 2000b) were investigated in the NHS. In both studies, whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake was assessed using the 126-item SFFQ.

Liu (1999) studied 75,521 women, aged 38–63, without previous diagnosis of diabetes or CVD at baseline, for the association of whole grain intake and the incidence of CHD. During the 10-year follow-up period (1984–1994), 761 cases of CHD (208 fatal and 553 nonfatal) were identified. The median whole grain intake, from lowest to highest quintiles, was 0.13, 0.43, 0.85, 1.31, and 2.7 servings/day (respectively). An inverse relationship between whole grain intake and CHD risk was observed when comparing the lowest and the highest quintiles of whole grain intake (RR= 0.67; 95% CI: 0.54, 0.84; *P* for trend < 0.001).

Liu et al. (2000b) investigated the association between whole grain intake and risk of ischemic stroke during a 12-year followed-up period. During that period, 352 incident cases of ischemic stroke occurred. The median whole grain intake, from the lowest to the highest quintiles was 0.13, 0.43, 0.85, 1.31, and 2.70 servings/day, respectively, with a corresponding age-adjusted RRs for ischemic stroke of 1.00 (reference), 0.71 (95% CI: 0.52, 0.98), 0.78 (95% CI: 0.57, 1.06), 0.56 (95% CI: 0.40, 0.79), and 0.64 (95% CI: 0.47, 0.89), respectively (all *P* for trend = 0.04).

The Atherosclerosis Risk in Communities Study (ARIC) is a multi-center, population-based investigation of the etiology and natural history of atherosclerotic disease in middle-aged adults. In the ARIC cohort study, Steffen and colleagues (2003) investigated the associations between whole grain intake and risk of incidence of coronary artery disease (CAD) and whole grain intake and risk of ischemic stroke. Participants were 15,792 men and women, aged 45–64 y, followed for an 11-year period. Whole grains were defined as described by Jacobs, Jr. (1998) and the intake was assessed using a 66-item SFFQ. The median whole grain intake, from the lowest to the highest quintile, was 0.1, 0.5, 1.0, 1.5, 3.0 servings/day, respectively, corresponding to the following age-adjusted HRs: for incident CAD, 1.00, 0.71 (95% CI: 0.55, 0.91), 0.80 (95% CI: 0.63, 1.02), 0.56 (95% CI: 0.43, 0.73), and 0.52 (95% CI: 0.39, 0.69), respectively (*P* for trend = 0.001); for incident ischemic stroke, 1.00, 1.09 (95% CI: 0.74, 1.60), 0.73 (95% CI: 0.47, 1.11), 0.78 (95% CI: 0.51, 1.19), and 0.62 (95% CI: 0.39, 0.99), respectively (*P* for trend = 0.016); and for all-cause mortality, 1.00, 0.84 (95% CI:

0.69, 1.01), 0.66 (95% CI: 0.54, 0.81), 0.63 (95% CI: 0.51, 0.78), and 0.52 (95% CI: 0.41, 0.65), respectively (*P* for trend = 0.001).

In the Physicians' Health Study (PHS), the risk of mortality from CVD was compared between individuals who ate whole grain breakfast cereal with those who consumed refined grain breakfast cereal (Liu et al., 2003a). Participants were 86,190 male physicians, aged 40–84, without CVD and cancer at baseline. There were 1,381 deaths from CVD (488 MI and 146 strokes) during the average 6-year follow-up period. Whole grains were defined as described by Jacobs, Jr. (1998) and the intake was assessed using a SFFQ. Compared with men who rarely or never consumed whole grain cereal, men in the highest category of whole grain intake (1 ≥ serving/day) had multivariate-estimated RR of CVD mortality of 0.80 (0.66, 0.97; *P* for trend = 0.008).

In the Women's Healthy Study (WHS), a prospective cohort study of US health professional women, Wang and collaborators (2007) evaluated the effect of whole grain and refined grain intakes on the development of hypertension. Participants were 28,926 women aged 45 years and older, who were not diagnosed with CVD, cancer, or hypertension at baseline in 1992. Over a 10-year follow-up period, there were 8,722 cases of hypertension. Whole grains were defined as described by Jacobs, Jr. (1998) and the intake was assessed using a 131-item SFFQ. The RRs for hypertension, for women who consumed less than 0.5 servings/day compared to those who consumed 0.5 to <1, 1 to <2, 2 to <4, and 4 ≥ servings/day, were 0.93 (95% CI: 0.87, 1.00), 0.93 (95% CI: 0.87, 0.99), 0.92 (95% CI: 0.85, 0.99), and 0.77 (95% CI: 0.66, 0.89), respectively (*P* for trend = 0.007). Furthermore, when modeled as a continuous variable, each 1 serving/day increase in whole grain intake was associated with a 4% (95% CI: 1, 6%, *p*-value not reported) reduction in hypertension risk after multivariate adjustment.

Cross-Sectional Studies

He et al. (1995) studied the relationship between oats intake to CVD risk factors in 850 ethnic minorities from southwest China aged 15–77 y. The study did not explicitly use the term "whole grains". Comparing an oats intake greater than 90 g/day with no intake of oats (0 g/day) a significant decrease is observed in the following CVD risk factors, SBP (-9.3 mmHg or 8%), DBP (-5.7 mmHg or 8%), TC (-0.44 mmol/L or 11%), and LDL-C (-0.09 mmol/L or 5%) all $p < 0.05$. Furthermore, in a multiple regression analysis, oats intake (100 g/day) was associated with lower BMI (-0.25, $p < 0.05$), SBP (-3.1 mmHg, $p < 0.001$), and DBP (-1.3 mmHg, $p < 0.001$).

The Framingham Offspring Study (FOS) is a longitudinal community-based study of CVD among offspring of the original participants of the Framingham Heart Study cohort and their spouses. Data from 2,941 offspring aged 26–82 y were evaluated in a cross-sectional study for the associations between whole grains and refined grains with serum lipid profile (McKeown et al., 2002). Whole grains were defined as described by Jacobs, Jr. (1998) and the intake was assessed using a 126-item SFFQ. Whole grain intakes, from the lowest to the highest quintile, were 0.1, 0.5, 0.9, 1.4, and 2.9 servings/day, and were associated with TC levels of 5.20, 5.15, 5.24, 5.19, and 5.09 mmol/L, respectively

(*P* for trend = 0.02); and LDL-C levels of 3.17, 3.14, 3.21, 3.17, and 3.04 mmol/L, respectively (*P* for trend = 0.006). In this study, the statistical significance of trends across categories of grain consumption was assessed with linear or logistic regression models by using grain consumption (in servings/week) as an ordinal variable and the median grain intake value in each category assigned as score.
Associations between whole grain or refined grain intake in relation to several risk factors for CVD was evaluated in another cross-sectional study with data from 827 (357 men and 470 women) healthy Iranians aged 18–74 y (Esmaillzadeh et al., 2005). Whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake was assessed using a FFQ. The median whole grain intake, from the lowest to the highest quartile, was 6, 40, 105, and 229 g/day, respectively, corresponding to the following odds ratios (OR): for hypertension, 1.00, 0.99 (95% CI: 0.95, 1.43), 0.93 (95% CI: 0.88, 1.24), 0.84 (95% CI: 0.73, 0.99), respectively (*P* for trend = 0.03).

The Baltimore Longitudinal Study of Aging (BLSA) is a prospective cohort study that began in 1958 with the objective of studying the physical, mental, and emotional effects of aging among healthy and active persons. In a cross-sectional analysis, data from 1,516 men and women aged 27–88 y, were analyzed for the associations of whole grains, refined grains, and cereal fiber with risk factors for chronic disease (Newby et al., 2007). Whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake was assessed with a 7-day dietary record. In this study, quintiles were developed separately for each outcome because of differences in sample size. Whole grain intakes were, for the lowest and highest quintiles respectively, 0.63 and 45.6 g/day for TC (n = 1,444), 3.9 and 54.8 g/day for LDL-C (n = 1,025), and 0.62 and 45.4 g/day for SBP and DBP (n= 1,464). Whole grain consumption was inversely associated with TC (*P* for trend = 0.02) and LDL-C (*P* for trend = 0.04), but not with SBP (*P* for trend = 0.79) and DBP (*P* for trend = 0.42).

Table VII. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Cardiovascular Disease**

Reference	Population	Study Design	Enrollment Dates / Follow-up	Assessment Instrument	Subjects: Sex	Subjects: Age (years)	Subjects: No. (#)	Whole Grain Intake	CHD/Stroke/Hypertension: RR	CHD/Stroke/Hypertension: 95% CI	Surrogate Endpoints: TC (mmol/l)	Surrogate Endpoints: LDL-C (mmol/l)	Surrogate Endpoints: SBP (mmHg)	Surrogate Endpoints: DBP (mmHg)	Controlled Factors
FDA Definition															
Jensen et al., 2004	US	Cohort	1986; 1988, 1990, 1992, 1994, 1996, 1998, 2000	131-item SFFQ	M	40–74	42,850	g/d 3.5 9.6 16 24.7 42.4	*P* for trend = 0.01 1 0.97 0.94 0.86 0.82	 0.84 – 1.11 0.82 – 1.09 0.74 – 1.01 0.70 – 0.96					Added bran intake, added germ intake, age, energy intake, smoking, alcohol, physical activity, family history, vitamin E supplements, fats, fruit, vegetables, fish
Jensen et al., 2006	US	Cross-Sectional	Female: 1996–1998 Male: 1993–1995	131-item SFFQ	F/M	F: 25–42 M: 40–74	938	g/d 8.2 15.9 22.3 29.6 43.8			*P* for trend = 0.02 5.74 ± 0.08 5.87 ± 0.08 5.80 ± 0.07 5.66 ± 0.06 5.58 ± 0.07	*P* for trend = 0.10 1.70 ± 0.03 1.68 ± 0.03 1.64 ± 0.03 1.69 ± 0.03 1.61 ± 0.03			Alcohol, smoking, BMI, physical activity, hypercholesterolemia, fat, fruit, vegetables
Expanded Definition															
Fraser et al., 1992	US Seventh-Day Adventists	Cohort	1974–1976; 1982	65-item SFFQ	F/M	25–older	26,473	*Types of Breads* White Mixed Wheat *	 1 0.51 0.45	 p < 0.01‡ 0.27–0.96 0.26–0.71					Non-fatal MI, age, sex, smoking, exercise, relative weight, blood pressure
								White Mixed Wheat *	1 0.87 0.82	Non-significant 0.53–1.41 0.50–0.21					Fatal MI, age, sex, smoking, exercise, relative weight, blood pressure
Jacobs, Jr. et al., 1998	US	Cohort	1986; 9 y	127-item FFQ	F postmenopausal	55–69	31,284	servings per day 0.2 0.9 1.2 1.9 3.2	*P* for trend = 0.02 1 0.96 0.71 0.64 0.7	 0.71–1.28 0.51–0.98 0.45–0.90 0.50–0.98					Age, energy intake, education, marital status, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, alcohol, vitamin supplement use, estrogen replacement therapy, fruit, vegetables, meat, fish

Table VII. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Cardiovascular Disease** (*continued*)

Reference	Population	Study Design	Enrollment Dates Follow-up	Assessment Instrument	Subjects			Whole Grain Intake	CHD/Stroke/ Hypertension		Surrogate Endpoints				Controlled Factors
					Sex	Age	No.		RR	95% CI	TC	LDL-C	SBP	DBP	
						years	#				mmol/l	mmol/l	mmHg	mmHg	
Expanded Definition															
Jacobs, Jr. et al., 1999	US	Cohort	1986; 9 y	127-item FFQ	F post-meno-pausal	55–69	31,284	servings per day		*P* for trend = 0.03					Age, energy intake, education, marital status, blood pressure, diabetes, heart disease, cancer, BMI, waist-to-hip ratio, age at first childbirth, physical activity, smoking, alcohol, vitamin supplement use, estrogen replacement therapy, fat, fruit, vegetables, meat, fish
								0.2	1						
								0.9	1.03	0.81–1.30					
								1.2	0.86	0.67–1.11					
								1.9	0.7	0.53–0.93					
								3.2	0.72	0.63–1.06					
Liu et al., 1999	US	Cohort	1984; 10 y	126-item SFFQ	F	38–63	75,521	servings per day		*P* for trend < 0.01					Age, smoking
								0.13	1						
								0.43	0.87	0.70–1.07					
								0.85	0.82	0.67–1.02					
								1.31	0.72	0.58– 0.90					
								2.70	0.67	0.54– 0.84					
Liu et al., 2000b	US	Cohort	1984; 10 y	126-item SFFQ	F	38–63	75,521	servings per day		*P* for trend = 0.04					Age, smoking
								0.13	1						
								0.43	0.71	0.52– 0.98					
								0.85	0.78	0.57–1.06					
								1.31	0.56	0.40–0.79					
								2.70	0.64	0.47–0.89					

Table VII. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Cardiovascular Disease (*continued*)**

Reference	Population	Study Design	Enrollment Dates / Follow-up	Assessment Instrument	Subjects: Sex	Subjects: Age (years)	Subjects: No. (#)	Whole Grain Intake	CHD/Stroke/ Hypertension: RR	CHD/Stroke/ Hypertension: 95% CI	Surrogate Endpoints: TC (mmol/l)	Surrogate Endpoints: LDL-C (mmol/l)	Surrogate Endpoints: SBP (mmHg)	Surrogate Endpoints: DBP (mmHg)	Controlled Factors
Expanded Definition															
Steffen et al., 2003	US	Cohort	1989 – 1991; 11 y	66-item FFQ	F/M	45–64	15,792	servings per day		*P* for trend = 0.001					Age, race, sex, energy intake
								0.1	1						
								0.5	0.71	0.55 – 0.91					
								1.0	0.8	0.63 – 1.02					
								1.5	0.56	0.43 – 073					
								3.0	0.52	0.39 – 0.69					
Liu et al., 2003	US	Cohort	1982; 6.6 y	Abbreviated SFFQ for whole grain cereal	M	40–84	75,521	servings per day		*P* for trend = 0.08					Age, smoking, alcohol, physical activity, BMI, diabetes, cholesterol, hypertension, multivitamins
								rarely	1						
								0.14	0.93	0.75 – 1.17					
								0.57	0.82	0.68 – 0.98					
								1	0.8	0.66 – 0.97					
Wang et al. 2007	US	Cohort	1992 – 1995; 10 y	131-item SFFQ	F	≥ 45	28,926	servings per day		*P* for trend = 0.007					Age, race, energy intake, smoking, alcohol, physical activity, family history CVD, menopause, estrogen, multivitamin use, diabetes, hypercholesterolemia
								< 0.5	1						
								< 1	0.93	0.87 – 1.00					
								< 2	0.93	0.87 – 0.99					
								< 4	0.92	0.85 – 0.99					
								> 4	0.77	0.66 – 0.89					

Table VII. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Cardiovascular Disease (*continued*)**

Reference	Population	Study Design	Enrollment Dates / Follow-up	Assessment Instrument	Subjects: Sex	Subjects: Age (years)	Subjects: No. (#)	Whole Grain Intake	CHD/Stroke/ Hypertension: RR	CHD/Stroke/ Hypertension: 95% CI	Surrogate Endpoints: TC (mmol/l)	Surrogate Endpoints: LDL-C (mmol/l)	Surrogate Endpoints: SBP (mmHg)	Surrogate Endpoints: DBP (mmHg)	Controlled Factors
Expanded Definition															
He et al. 1995	China, Yi People	Cross-Sectional	1989	FFQ, 24-h recall	F/M	15–77	850	*Oats* (g) 0 < 25 < 90 > 90			*p* < 0.05 ‡ 4.03 ± 0.99 3.99 ± 1.04 3.45 ± 0.91 3.59 ± 0.86	*p* < 0.05 ‡ 1.85 ± 0.94 1.78 ± 0.86 1.54 ± 0.85 1.76 ± 0.84	*p* < 0.05 ‡ 109.7± 12.4 108.5 ± 13.0 103.9 ± 10.6 100.4 ± 9.9	*p* < 0.05 ‡ 68.3 ± 10.3 67.2 ± 10.1 65.9 ± 9.1 62.6 ± 8.9	
McKeown et al., 2002	US	Cross-Sectional	1991 – 1995	126-item FFQ	F/M	26–82	2,941	servings per day 0.12 0.50 0.91 1.34 2.91			*P* for trend = 0.02 5.2 5.15 5.24 5.19 5.09	*P* for trend = 0.006 3.17 3.14 3.21 3.17 3.04	*P* for trend = 0.38 124.4 123.2 123.3 122.5 123.1	*P* for trend = 0.19 75.6 74.4 74.6 74.7 73.8	Age, sex, energy intake, hypertension, smoking, multivitamin, estrogen use, physical activity, BMI
Esmaillzadeh et al., 2005	Iran	Cross-Sectional	2000	FFQ	F/M	18–74	827	g/d 6 40 105 229	 1 0.99 0.93 0.84	*P* for trend = 0.03 0.95 – 1.43 0.88 – 1.24 0.73 – 0.99	 5.17 ± 0.05 5.15 ± 0.08 5.12 ± 0.08 4.99 ± 0.08	 3.31 ± 0.05 3.28 ± 0.08 3.21 ± 0.08 3.10 ± 0.08	 115 ± 1 115 ± 1 114± 1 115 ± 1	*p* < 0.05‡ 81 ± 1 79 ± 1 78 ± 1 77 ± 1	Age, sex, smoking, alcohol, physical activity, BMI, waist-hip ratio, total energy intake, percent of energy from fat, consumption of meats and fish, fruit s and vegetables, use of blood pressure medication and use of estrogen.
Newby et al., 2007	US	Cross-Sectional	1978	7-d diet record	F/M	27–88	1,516	g/d 0.63 45.6			*P* for trend = 0.02 5.71 ± 0.06 5.49 ± 0.06	*P* for trend = 0.04 3.16 ± 0.06 2.96 ± 0.06	*P* for trend = 0.79 129.2 ± 1.0 128.3 ± 1.0	*P* for trend = 0.42 79.8 ± 0.6 79.2 ± 0.7	Age, sex, energy

BMI: body mass index; **TC:** total cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure

‡ Compares the lowest to the highest quintile or quartile of whole grain intake.* Whole Wheat.

Intervention Studies on Diabetes

A brief description of the intervention studies included in the report for the association between whole grains and diabetes is presented here. The study designs and results are summarized at the end of this section in **Table VIII**.

FDA Definition

In another randomized, non-blinded crossover study, 30 Swedish women (n = 22) and men (n = 8) with mean age of 59 ± 3 y who were healthy and moderately overweight (BMI: 26–35) were advised to add refined grain or whole grain products to their diet (Andersson et al., 2007). The whole grain products contained a minimum of 50% whole grain/dry substance, including the starchy endosperm, germ, and bran, in mainly milled form. Whole grain rice was examined by light microscopy and included as a whole-grain product because the bran was intact and >80% of the germ was present. All the cereals in the study were provided by the investigators. The total amount of whole grain consumed was 112 g/day. Wheat, rye, oats, and rice were all included, but wheat dominated. The whole grain products were mostly based on milled flour with small particle size in the form of bread and pasta. Both intervention periods lasted for 6 weeks with a 6- to 8-week washout period. Peripheral insulin sensitivity did not improve when subjects consumed whole grain products or refined products and there were no differences between the two treatment periods.

Thirty one obese (BMI: 27–36) German men (n = 13) and women (n = 18), aged 25–56 y, who had an elevated fasting blood glucose (6.3 ± 0.8 mmol/L) participated in a crossover study to investigate the effects of a hypo-energetic diet including whole grains on fasting blood glucose, fasting serum insulin, and insulin resistance (Rave et al., 2007). Subjects were randomly assigned to replace at least two daily meals (200 g/day) with a starch-reduced whole grain derived from double-fermented wheat (WG) or a nutrient-dense meal replacement (MR) product for a 4-week treatment period with a 2-week washout period. The starch-reduced whole grain derived from double-fermented wheat (Balantose, Cargill, Germany) contains all parts of the whole grain, *i.e.*, germ, bran and endosperm. In both treatment groups (WG *versus* MR) there was an improvement ($p < 0.05$) in the fasting blood glucose (-0.4 ± 0.3 mmol/L *vs* -0.5 ± 0.5 mmol/L) and in the homeostasis model assessment of insulin resistance (HOMA-IR) (-0.7 ± 0.8 µU/ml x mmol/L *vs* -1.1 ± 1.7 µU/ml x mmol/L) with no significant difference between the two treatment groups. However, after adjustment of weight loss, the HOMA-IR score improved better with the WG product (-1.0 ± 0.2 µU/ml x mmol/L) than with the MR product (-0.1 ± 0.5 µU/ml x mmol/L) ($p = 0.049$). Furthermore, the fasting serum insulin decreased after diet with WG, but not with MR ($p = 0.031$).

Expanded Definition

Long Term Studies

Forty-three men and women with a mean age of 45 ± 23 y and BMI of 26.4 ± 3.3 participated in an 8-week intervention study to evaluate the effect of a hypo-caloric diet containing oats (does not explicitly use the term "whole grains") on insulin response (Saltzman et al., 2001). All subjects consumed a control diet for 2 weeks and were randomly assigned to a hypo-caloric diet or a hypo-caloric diet containing oats for 6 weeks. All foods and drinks were provided to the subjects who ate at the research facility at least 4 days a week, for the remaining days the food was carried out to be eaten somewhere else. Oats were consumed in the form of hot cereal (Quick Oats, Quaker Oats Company, Barrington, IL) or were incorporated into other food items (breads and casseroles). The oat diet contained oats in all meals and snacks. No significant differences (*P* for trend = 0.09) were observed in fasting insulin and insulin sensitivity between the two diets.

Davy and colleagues (2002b) investigated the effect of oat consumption on fasting blood glucose, insulin concentration, and insulin sensitivity. Thirty six men aged 50–75 y with BMI of 25–35 and elevated BP (SBP: 130–159 mmHg and/or DBP: 85–99 mmHg) were randomly assigned to consume an additional 14 g/day of dietary fiber in the form of oat or wheat cereal for 12 weeks. Whole grains were whole grain oat (60 g Quaker Oatmeal and 76 g Quaker Oat Bran ready-to-eat cold cereal, Quaker Oats Company, Barrington, IL) or whole wheat cereal (60 g Mother's Whole Wheat Hot Natural cereal, Quaker Oats Company, and 81 g Frosted Mini-Wheats, Kellogg, Battle Creek, MI). At the end of the 12-week intervention period, no significant changes were noted over time or across groups in fasting blood glucose, insulin concentration, or insulin sensitivity. The investigators observed a small but significant increase in body weight (~0.8 kg) in both groups over time.

In a randomized, non-blinded, crossover controlled trial, 11 overweight and obese (BMI: 27–36) hyper-insulinemic adults aged 25–56 y were assigned to treatment diets containing whole grains or refined grain (Pereira et al., 2002). Whole grains contained bran, germ and considerable fiber, but were mostly ground to flour. Approximately 80% of whole grain products were wheat and the remainder oats, rice, corn, barley, and rye. A sample of 1-day menu for whole-grain diet contained whole-oat-flour cereal, blueberry muffin with whole-wheat flour, whole-wheat bread, whole-grain chips, whole-wheat spaghetti, chocolate chip cookie made with whole-wheat flour. There was a 6-week treatment period with a 6- to 9-week washout period. After the 6-week treatment period, fasting insulin was 10% lower (-15 ± 5.5 pmol/L, $p = 0.03$) for individuals on the whole grain diet (141 ± 3.9 pmol/L) than those on the refined grain (156 ± 3.9 pmol/L) diet. Furthermore, there was a higher rate of glucose infusion and therefore, higher insulin sensitivity with the whole grain diet (mean difference: 0.07 x 10^{-4} mmol · kg^{-1} · min^{-1}/pmol/L; 95% CI: 0.003 x 10^{-4}, 0.144 x 10^{-4}; $p < 0.05$) as measured with the insulin clamp test.

Twenty post-menopausal women, healthy (n = 17) and with impaired glucose tolerance (n = 3), with a mean age of 59 ± 6 y and a mean BMI of 27.5 ± 2.9 participated in a crossover randomized trial to determine the effect of consumption of rye bread compared to that of white wheat bread on glucose and insulin responses (Juntunen et al., 2003). For the high-fiber rye bread approximately 17% of dietary fiber as rye bran was added in the bread. Rye and white wheat bread, in amounts equivalent to 23% and 27%, respectively, of the total energy intake were consumed for an 8-week treatment period with an 8-week washout period. The acute insulin response increased significantly (p = 0.047) after the treatment period with rye bread (9.9 ± 24.2%) compared to that of white wheat bread (2.8 ± 36.3%). No other significant change occurred.

Acute Studies

Healthy Swedish men (n = 3) and women (n = 6), aged 24–46 y with a mean BMI of 20.9 ± 1.5 participated in an intervention study to compare the effect of consumption of oat and barley porridge to that of bread on postprandial glucose and insulin levels (Liljeberg et al., 1996). Whole-meal porridges were made of oats, common barley or high fiber barley (defined as high β-glucan content) mixed with common barley, 50:50 (wet weight basis) and whole-meal bread products were prepared from whole-meal high fiber barley and common barley, mixed in ratios of 50:50 or 80:20, respectively. The subjects were served test products (bread and porridge) in random order as a breakfast after an overnight fast. The tests were performed one week apart. Common oat and barley porridges produced postprandial glucose and insulin responses similar to the white wheat bread reference, suggesting that the naturally occurring dietary fiber in these whole-meal flours has no impact on the glucose tolerance.

Behall and colleagues (1999) evaluated the effect of ultra-fine-ground whole grain wheat flour on plasma glycemic response. The investigators studied 26 healthy men (n = 13) and women (n = 13), 31–55 y and BMI 19.6–38.9. The four test carbohydrates [glucose (control), white bread, whole wheat bread, and ultra-fine whole wheat bread] were given to subjects in a Latin square design. Blood samples were collected at 0.5, 1, 2, and 3 hours after consumption of the test food. Glucose, but not insulin, AUCs were significantly higher after the glucose load than after the three breads.

Ten healthy men (n = 3) and women (n = 7), aged 24–50 y, participated in a randomized crossover study (Panlasigui & Thompson, 2006). Subjects were assigned to consume breakfast containing 50 g of carbohydrate as freshly cooked brown rice or as milled rice. Blood was drawn at several intervals until 180 minutes after breakfast. The incremental blood glucose area was 19.8% lower (-1.5 mmol/L, p < 0.05), with brown rice intake than with milled rice intake, respectively.

Nilsson and colleagues (2008) investigated the glycemia levels of 12 healthy Swedish men (n = 7) and women (n = 5), aged 21–41 y with a mean BMI of 22 ± 2 after they consumed meals with a variety of indigestible carbohydrates (wheat kernels, rye kernels, oat kernels, barley kernels, whole-grain barley flour porridge (made from flour

of the same barley kernels), and white-wheat bread enriched with barley dietary fiber. Oat and barley kernels were provided by Finax, Helsingborg, Sweden, and the wheat and rye kernels by Nord Mills, Malmo, Sweden. The wheat, rye, and barley kernels were boiled in water for 30, 35, and 23 minutes, respectively. The whole-grain barley flour porridge was cooked in a microwave for 5 minutes. The white-wheat bread was baked according to a standardized procedure (Liljeberg & Bjorck, 1994) in a home baking machine.

Subjects were randomly assigned to the 7 test meals (6 + control). Tests were conducted in two series. In series 1, the test meal was given at breakfast with blood taken throughout a 12-hour period. In series 2, the test meal was given at dinnertime; otherwise the design remained the same as series 1. The lowest postprandial blood glucose increments were achieved after barley or rye kernel breakfast. The barley or rye kernel breakfasts resulted in significantly lower blood glucose peaks (1.5 ± 0.2 and 1.6 ± 0.2 mmol/L, respectively) and AUCs (486 ± 40 and 557 ± 58 mmol·min/L, respectively, $p < 0.05$) than did breakfasts with white wheat bread (3.2 ± 0.4 mmol/L and AUC 699 ± 70 mmol·min/L, $p < 0.0001$). For whole grains consumed in the evening with a 12-hour blood glucose measurement only barley kernel intake had a lower blood glucose ($p < 0.05$) when compared to the white wheat bread.

Table VIII. Intervention Studies on the Association of **Whole Grain Intake** and Incidence of **Diabetes**

Reference	Population	Study Design	Treatment	Duration	Subjects				Surrogate Endpoints		
					Sex	No. #	Age years	BMI kg/m^2	Fasting Blood Glucose mmol/l	Insulin Resistance µU/ml X mmol/l	Fasting Plasma Insulin µU/ml
FDA Definition											
Andersson et al., 2007	Sweden	Randomized Crossover	Control	6 weeks	F/M	22/8	59 ± 5	28.3 ± 2.0	5.2 ± 0.8	**2.22**	9.6 ± 4.3
			Whole Grains	6 weeks					5.3 ± 0.8	**2.26**	9.6 ± 4.1
Rave et al., 2007	Germany	Randomized Crossover	Control - weight loss	4 weeks	F/M	18/13	51 ± 13	33.9 ± 2.7	-0.5 ± 0.5†	-0.1 ± 0.5†	-2.8 ± 4.8*†
			Whole Wheat-weight loss	4 weeks					-0.4 ± 0.08†	-1.0 ± 0.2*†	-1.8 ± 2.8*†
Expanded Definition											
Saltzman et al., 2001	US	Randomized Parallel	Control-weight loss	8 weeks	F/M	12/9	44 ± 21	26.7 ± 3.2	-0.005 ± 0.9†	-0.5 ± 2.1†	-1.6 ± 7.8†
			Oats-weight loss	8 weeks		11/11	45 ± 23	26.1 ± 3.4	-0.21 ± 0.29†	-1.1 ± 1.2†	-4.8 ± 4.4†
Davy et al., 2002	US	Randomized Parallel	Control	12 weeks	M	18	61 ± 2	29.2 ± 0.8	5.3 ± 0.1	**2.31**	9.8 ± 2.1
			Oat Cereal	12 weeks		18	57 ± 2	29.6 ± 0.8	5.6 ± 0.1	**3.66**	14.7 ± 2.1
Pereira et al., 2002	US	Randomized Crossover	Control	6 weeks	F/M	6/5	42 ± 3	30.2 ± 1.0	5.3 ± 0.1	6.2 ± 0.2	26.0 ± 0.7
			Whole Grain	6 weeks					5.2 ± 0.1	5.4 ± 0.2*	23.5 ± 0.7*

Table VIII. Intervention Studies on the Association of **Whole Grain Intake** and Incidence of **Diabetes (*continued*)**

Reference	Population	Study Design	Treatment	Duration	Subjects				Surrogate Endpoints		
					Sex	No. #	Age years	BMI kg/m^2	Fasting Blood Glucose mmol/l	Insulin Resistance µU/ml X mmol/l	Fasting Plasma Insulin µU/ml
Expanded Definition											
Juntunen et al., 2003	Finland	Randomized Crossover	Control Rye Bread	8 weeks 8 weeks	F	20	59 ± 6	27.5 ± 2.9	5.41 ± 1.09 5.43 ± 1.08	**1.97** **2.1**	8.2 ± 3.4 8.7 ± 5.0
Liljeberg et al., 1996	Sweden	Acute study	White bread (reference)	3 hours	F/M	6/3	24–46	20.9 ± 1.5	-0.12 ± 0.11[a,b,c]		
			White wheat flatbread	3 hours					-0.14 ± 0.07[b,c,d]		
			High-fiber flatbread (50:50)	3 hours					0.00 ± 0.07[a,b]		
			High-fiber flatbread (80:20)	3 hours					0.03 ± 0.09[a]		
			High-fiber porridge (80:20)	3 hours					0.09 ± 0.09[a,d]		
			Barley porridge	3 hours					-0.23 ± 0.08[c]		
			Oat porridge	3 hours					-0.19 ± 0.07[c]		
Behall et al., 1999	US	Acute study	Glucose (control)	3 hours	F/M	13/13	31–55	26.8 ± 1.5	162.9 ± 18.3[a]§		10.32 ± 0.72[a]§
			White bread	3 hours					94.8 ± 18.3[b]		9.08 ± 0.72[a]
			Whole wheat bread	3 hours					80.8 ± 18.3[b]		9.80 ± 0.72[a]
			Ultra fine whole wheat bread	3 hours					75.2 ± 18.3[b]		9.03 ± 0.72[a]

Table VIII. Intervention Studies on the Association of **Whole Grain Intake** and Incidence of **Diabetes (*continued*)**

Reference	Population	Study Design	Treatment	Duration	Subjects				Surrogate Endpoints		
					Sex	No. #	Age years	BMI kg/m^2	Fasting Blood Glucose mmol/l	Insulin Resistance µU/ml X mmol/l	Fasting Plasma Insulin µU/ml
Expanded Definition											
Panlasigui & Thompson 2006	Canada	Acute study	Milled rice	1 hour	F/M	7/3	33 ± 3	100 ± 10% ideal body weight	2.5		
			Brown rice	1 hour					1.0*		
Nilsson et al., 2008	Sweden	Acute study	White wheat bread	2 hours	F/M	5/7	28.3 ± 5	22.1 ± 2.0	698.5 ± 70.0 [a]§		
			Barley porridge	2 hours					658.5 ± 41.8[a,b]		
			Wheat kernels	2 hours					588.8 ± 40.5[a,b,c]		
			Rye kernels	2 hours					557.1 ± 58.2[b,c]		
			Oat kernels	2 hours					614.7 ± 49.3[a,b,c]		
			Barley kernels	2 hours					485.5 ± 40.1[c]		
			White wheat bread plus barley dietary fiber	2 hours					651.9 ± 42.0[a,b]		

BMI: body mass index; **TC:** total cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure
*p<0.05; † difference between baseline and end of treatment period; ¥ Insulin sensitivity expressed in units of: 1/min 1/mU 1/L; § AUC values expressed in mmol × min/L
Insulin resistance calculated as [fasting plasma glucose x fasting plasma insulin/22.5]
For Liljeberg et al., 1996, Behall et al., 1999 and Nilsson et al., 2008 means within a column not containing the same superscript are significantly different ($p < 0.05$)

Observational Studies on Diabetes

A brief description of the observational studies included in the report for the association between whole grains and diabetes is presented here. The study designs and results are summarized at the end of this section in **Table IX**.

FDA Definition

A total of 161,737 women in the Nurses' Health Study aged 37–65 y (NHS I) and 26–46 y (NHS II) participated in this cohort study (de Munter et al., 2007). During a 12 to 18-year follow-up period, 6,486 cases of Type 2 diabetes were identified. Whole grain included both intact and pulverized forms containing the expected proportion of bran, germ, and endosperm for the specific grain types. The following ingredients in the database were considered whole grains: whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal and whole corn flour, brown rice and brown rice flour, whole rye and whole rye flour, whole barley, bulgur, buckwheat, popcorn, amaranth, and psyllium. Bran and germ in this study refer to total bran and total germ respectively including both the amount naturally contained in whole grains and the amount eaten separately or added during industrial processing or during cooking by the participant. Whole grain intake from all sources was assessed using a FFQ. The median whole grain intake in the lowest and highest quintile of intake was 3.7 and 31.2 g/day for NHSI and 6.2 and 39.9 g/day for NHSII, respectively. After adjustment for potential confounders, the RR for the highest compared to the lowest quintile of whole grain intake was 0.63 (95% CI: 0.57, 0.69) for NHSI and 0.68 (95% CI: 0.57, 0.81) for NHSII (both: *P* for trend < 0.001). After adjustment for BMI, the RR was 0.75 (95% CI: 0.68, 0.83, *P* for trend < 0.001) for NHSI and 0.86 (95% CI: 0.72, 1.02; *P* for trend = 0.03) for NHSII. De Munter et al. (2007) also conducted a systematic review based on pooled data from six cohort studies in which they reported that 2 servings/day increment in whole grain consumption was associated with a 21% (95% CI: 13, 28) decrease in Type 2 diabetes, after adjustment for potential confounders and BMI.

Expanded Definition

Prospective Cohort Studies

In the IWHS, Meyer and colleagues (2000) evaluated the associations of carbohydrates, dietary fiber, dietary magnesium, and whole grains with the incidence of diabetes. Participants were 35,988 women aged 55–69 y who were not diagnosed with diabetes at baseline. During a 6-year follow-up period, 1,141 cases of diabetes occurred. Whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake was assessed using a 127-item FFQ. The median whole grain intake, from the lowest to the highest quintile, was 0.1, 0.6, 1, 1.5, and 2.9 servings/day, respectively. The multivariate-adjusted RR of diabetes were 1.0, 0.99, 0.98, 0.92, and 0.79 (*P* for trend = 0.0089) across quintiles of whole grain intake; 1.0, 1.09, 1.00, 0.94, and 0.78 (*P* for trend = 0.005) across quintiles of total dietary fiber intake; and 1.0, 0.81, 0.82, 0.81, and 0.67 (*P* for trend = 0.0003) across quintiles of dietary magnesium intake.

In the NHS prospective cohort, 75,521 women 38–63 y of age who were not diagnosed with diabetes or CVD at baseline participated in the study to investigate the relationship between whole grain intake and diabetes (Liu et al., 2000a). Over a 10-year follow-up period, 1,879 cases of diabetes occurred. Whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake was assessed using a 126-item FFQ. The median whole grain intake, from the lowest to the highest quintile, was 0.13, 0.43, 0.85, 1.31, and 2.70 servings/day, respectively. When the lowest with the highest quintiles of whole grain intake were compared, the adjusted RR for Type 2 diabetes was 0.73 (95% CI: 0.63, 0.85; *P* for trend < 0.001) and for refined grain intake was 1.31 (95% CI: 1.12, 1.53; *P* for trend = 0.0003).

In the HPFS, 42,898 men aged 40–75 y were followed prospectively for 12 years, during which 1,197 cases of incident Type 2 diabetes were identified (Fung et al., 2002). Whole grains were defined as described by Jacobs, Jr. et al. (1998). The median whole grain intake, from the lowest to the highest quintile, was 0.4, 0.8, 1.3, 1.9, and 3.2 servings/day, respectively. After adjusting for potential confounders, the RR of Type 2 diabetes was 0.58 (95% CI: 0.47, 0.70; *P* for trend <0.0001) when comparing the highest with the lowest quintile of whole grain intake. Adjusting for intake of magnesium, cereal fiber, and glycemic load attenuated the association between whole grain and Type 2 diabetes, RR = 0.98 (95% CI: 0.76, 1.26, *P* for trend = 0.98), suggesting that one or more of these diet attributes contributed to the association.

In a Finnish prospective cohort study, data from 2,286 men and 2,030 women aged 40–69 y initially free of diabetes were used to evaluate the relationship between whole grain and fiber intake and the incidence of Type 2 diabetes (Montonen et al., 2003). During a 10-year follow-up period, incident Type 2 diabetes cases were identified in 54 men and 102 women. The food groups considered whole grains were rye bread, rye crisp bread, and all whole-grain flours and other products (rye, whole wheat, wheat germ, rolled oats, barley, millet, and buckwheat) derived from different grain foods (*e.g.*, porridge, gruel, and Karelian pie [a national food of rice pudding baked in rye pastry and greased by butter]). In addition, breads prepared from mixtures of whole grains and refined grains were classified into the whole-grain group. The proportion of whole-grain flours in these mixtures was 25–50%, as determined from the available cook book information. Whole grain intake was assessed by conducting a dietary history interview. The quartiles (median) of whole grain intake were 79, 136, 198, and 302 g/day and for fiber were 16, 22, 29, and 40 g/day. The incidence of Type 2 diabetes between the highest and lowest quartiles of whole grain intake had an RR of 0.65 (95% CI: 0.36, 1.18; *P* for trend = 0.02). The incidence of Type 2 diabetes between the extreme quartiles of cereal fiber intake had an RR of 0.39 (95% CI: 0.20, 0.77; *P* for trend = 0.01).

The Black Women's Health Study of Boston University and Howard University reported an inverse association between whole grain intake and incidence of Type 2 diabetes (van Dam et al., 2006). In this cohort study, 41,186 African American women aged 21–69 y were prospectively followed for 8 years (1995–2003). Whole grains were dark breads, such as wheat, rye, pumpernickel and high fiber, bran or granola cereals,

shredded wheat. Whole grain intake was assessed using a 68-item Block FFQ. Whole grain was divided into 4 categories: 0.03, 0.37, 0.79, and 1.29 servings/day which resulted in a multivariate HR of Type 2 diabetes of 1, 0.84 (95% CI: 0.75, 0.93), 0.76 (95% CI: 0.65, 0.89), and 0.69 (95% CI: 0.60, 0.79) (all $p < 0.0001$), respectively.

Cross-Sectional Studies

Liese (2003) evaluated the data from the Insulin Resistance Atherosclerosis (IRAS Exam I, 1992–1994) regarding the relationship between whole grain dietary intake and insulin sensitivity. Participants in this cohort study were 978 individuals aged 40–69 y with normal (67%) and impaired (33%) glucose tolerance. Whole grain intake was assessed using a 114-item FFQ. Whole grain variable used for the analysis was compiled from 3 FFQ lines worded as follows: 1) "dark bread (including whole wheat, rye, pumpernickel, other high-fiber bread"; 2) "High-fiber bran or granola cereals, shredded wheat"; and 3) "cooked cereal (including oatmeal, cream of wheat, and grits)". The IRAS participants consumed, on average, 0.8 servings/day of whole grain. The investigators used multivariable linear regression to analyze the data. The results showed that whole grain intake was significantly associated with improved insulin sensitivity ($p = 0.0005$) and lower fasting insulin ($p = 0.019$).

In a cross-sectional study, data from 2,834 participants of the FOS study were analyzed to evaluate the effect of diets rich in whole grains or refined grain on fasting insulin (McKeown et al., 2002) and HOMA-IR (McKeown et al., 2004). In both studies, whole grains were defined as described by Jacobs, Jr. et al. (1998) and the intake assessed by a 126-item SFFQ. The median whole grain intake from the lowest to the highest quintile was 0.12, 0.50, 0.91, 1.34, and 2.91 servings/day, respectively. After adjusting for potential confounders, the lowest compared with the highest quintile of whole grain intake was inversely associated with fasting insulin (205 pmol/L and 199 pmol/L, respectively; *P* for trend = 0.03). The standard deviations for the fasting insulin values were not reported in this study. The mean HOMA-IR (range) from the lowest to the highest quintile of whole grain intake was 6.8 (6.6–7.1), 6.9 (6.6–7.1), 6.7 (6.5–7.0), 6.6 (6.4–6.8), and 6.6 (6.4–6.9) (*P* for trend = 0.05).

Two hundred-two healthy adults from the Slovak Republic with normal BMI (18.6–25), aged 19–64 y, participated in a cross-sectional study (Valachovicova et al., 2006). Metabolic indicators of diabetes were compared in 95 vegetarians and 107 non-vegetarians. Whole grain intake was assessed using a 114-item FFQ with oat (flakes, porridge) and barley pearls considered to be whole grain products. Vegetarians had a significantly higher whole grain intake compared to non-vegetarians, including oat flakes porridge, (20.3 ± 1.0 *versus* 2.4 ± 0.2), barley pearls (10.6 ± 0.6 *versus* 0), and whole grain products (176 ± 11 *versus* 41 ± 2 g/day), respectively (all $p < 0.001$). Vegetarians compared to non-vegetarians had significantly lower values for fasting serum glucose (4.47 ± 0.05 mmol/L *versus* 4.71 ± 0.07 mmol/L), fasting serum insulin (4.96 ± 0.23 mU/l *vs* 7.32 ± 0.41 mU/l), and HOMA-IR (0.99 ± 0.05 *versus* 1.59 ± 0.10; no units were reported), respectively.

In another cross-sectional study, the effect of whole grain intake on serum insulin, insulin sensitivity and fasting glucose was investigated using baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA) (Lutsey et al., 2007). Participants were 5,496 men and women aged 45–84 y. Servings *per* day of the following foods were summed to calculate total whole grain intake: whole grain breakfast cereal; oatmeal; dark bread (dark, whole grain breads or rolls hamburger buns, bagels, pita, English muffins); bran muffins; brown or wild rice. If participants reported eating cold cereal, they were asked to name the breakfast cereal that they usually ate. Breakfast cereals mentioned were then evaluated for dietary fiber and whole grain content as determined by package labels, dietary databases, such as the Nutrition Data System and the US Department of Agriculture Food Composition Data, or by records shared in 1996 by General Mills, Minneapolis, MN. Of the 144 breakfast cereals mentioned, 121 were classified as whole grain cereals (most mentioned by very few participants) as they contained ≥ 3 g dietary fiber/100 g dry weight. Whole grain intake was assessed using a 127-item SFFQ. The median whole grain intake, from the lowest to the highest quintile, was 0.02, 0.15, 0.39, 0.72, and 1.39 servings/day, respectively. After adjustment for demographic and health behavior variables, mean differences for the highest quintile of whole grain intake minus the lowest quintile of intake were 0.21 mU/L*mmol/L or 3.9% (*P* for trend = 0.002) for HOMA-IR, 0.48 mU/L or 9% (*P* for trend = 0.002) for serum insulin, and 0.14 mmol/L or 2.5 % (*P* for trend = 0.008) for fasting glucose.

In the BLSA, Newby and colleagues (2007) investigated the associations between whole grains, refined grains and cereal fiber, and chronic disease risk factors. Participants were 1,516 men and women aged 27–88 y. The authors used all dietary data from the BLSA to create a whole grain database. All foods containing grains or mixed dishes with foods containing grains, either whole or refined, were identified. The quantification of cereal fiber included fiber from whole grains (*e.g.*, wheat, rice, corn, oats) and all foods made from grains, including ready-to-eat and hot cereals, bread, pasta, crackers, sweet baked goods, and salty snacks. Dietary intakes were assessed with a 7-day dietary record. Quintiles were developed separately for each outcome because of differences in sample size. Lowest and highest quintile of whole grain intake was 0.56 and 45.4 g/day for fasting glucose (n = 1,324), and 2.2 and 51.5 g/day for fasting insulin (n = 460), respectively. In a multivariate adjusted model, whole grain intake was not associated with fasting glucose ($p = 0.21$) and fasting insulin ($p = 0.41$).

Table IX. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Diabetes**

Reference	Population	Study Design	Enrollment Dates; Follow-up	Assessment Instrument	Subjects: Sex	Subjects: Age years	Subjects: No. #	Whole Grain Intake	Type II Diabetes: RR	Type II Diabetes: 95% CI	Surrogate Endpoints: Fasting Blood Sugar mmol/l	Surrogate Endpoints: Insulin Resistance mU/l x mmol/l	Controlled Factors
FDA Definition													
de Munter et al., 2007	US	Cohort	1984; 1998	SFFQ	F	37–65	73,327	g/d		*P* for trend < 0.001			Age, smoking, physical activity, alcohol, hormone replacement therapy, oral contraceptive, family history, coffee, sugar sweetened soft drinks, fruit punch, energy intake, processed meats, fats
								3.7	1				
								8.4	0.94	0.86–1.02			
								13.2	0.83	0.76–0.91			
								19.5	0.73	0.66–0.80			
								31.2	0.63	0.57–0.69			
			1991; 1999	SFFQ	F	26–46	88,410	g/d		*P* for trend < 0.001			
								6.2	1				
								12.6	0.93	0.81–1.07			
								18.6	0.86	0.75–1.00			
								26.1	0.74	0.63–0.86			
								39.9	0.68	0.57–0.81			
Expanded Definition													
Meyer et al., 2000	US	Cohort	1986; 1992	127-item SFFQ	F	55–69	35,988	servings per day		*P* for trend = 0.0089			Age, energy intake, BMI, waist-to-hip ratio, education, smoking, alcohol, physical activity,
								0.1	1				
								0.6	0.99	0.82–1.18			
								1.0	0.98	0.81–1.18			
								1.5	0.92	0.76–1.11			
								2.9	0.79	0.65–0.96			
Liu et al., 2000	US	Cohort	1984; 1994	126-item SFFQ	F	38–63	75,521	servings per day		*P* for trend < 0.001			Age, BMI, physical activity, smoking, alcohol, family history, multivitamins, energy intake
								0.13	1				
								0.43	0.91	0.79–1.05			
								0.85	0.94	0.82–1.08			
								1.31	0.74	0.64–0.86			
								2.70	0.73	0.63–0.85			
Fung et al., 2002	US	Cohort	1986; 1998	FFQ	M	40–75	42,898	servings per day		*P* for trend < 0.0001			Age, physical activity, energy intake, smoking, alcohol, family history, fruit, vegetables
								0.4	1				
								0.8	0.9	0.76–1.05			
								1.3	0.75	0.63–0.90			
								1.9	0.73	0.60–0.87			
								3.2	0.58	0.47–0.85			
Montonen et al., 2003	Finland	Cohort	1972; 1982	Dietary history interview	F/M	40–69	4,316	g/d		*P* for trend = 0.02			Age, sex, geographic area, smoking, BMI, energy intake, fruit, vegetables
								79	1				
								136	1.05	0.71–1.55			
								198	0.52	0.31–0.88			
								302	0.65	0.36–1.18			

Table IX. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Diabetes** (*continued*)

Reference	Population	Study Design	Enrollment Dates; Follow-up	Assessment Instrument	Subjects			Whole Grain Intake	Type II Diabetes		Surrogate Endpoints		Controlled Factors
					Sex	Age years	No. #		RR	95% CI	Fasting Blood Sugar mmol/l	Insulin Resistance mU/l x mmol/l	
Expanded Definition													
van Dam et al., 2006	US	Cohort	1995; 2003	68-item FFQ	F	21–69	41,186	servings per day 0.03 0.37 0.79 1.29	 1 0.84 0.76 0.69	*P* for trend < 0.0001 0.75–0.93 0.65–0.89 0.60–0.79			Age, energy intake, BMI, smoking, physical activity, alcohol, family history, education, coffee, sugar sweetened soft drinks, processed meats
Liese et al., 2003	US	Cross-Sectional	1992-1994	114-item FFQ	F/M	40–69 y	978	0.8 servings per day				2.16 ± 1.96‡	Age, energy intake, BMI, total energy expenditure, waist circumference, family history, dietary fiber, magnesium, and zinc
McKeown et al., 2004	US	Cross-Sectional	1991 – 1995	126-item FFQ	F/M	26–82	2,834	servings per day 0.12 0.50 0.91 1.34 2.91	 1 0.81 1.09 0.82 0.67	*P* for trend = 0.01 0.60–1.08 0.82–1.44 0.61–1.10 0.48–0.91		6.8 (6.6–7.1) 6.9 (6.6–7.1) 6.7 (6.5–7.0) 6.6 (6.4–6.8) 6.6 (6.4–6.9)	Age, sex, energy intake, hypertension, smoking, multivitamin,
Valachovicova et al., 2006	Slovak	Cross-Sectional		114-item FFQ	F/M	19–64	202	g/d 41 176			4.71 ± 0.07 4.47 ± 0.05**	1.59 ± 0.10 0.99 ± 0.05*	Age

Table IX. Observational Studies on the Association of **Whole Grain Intake** on Incidence of **Diabetes** (*continued*)

Reference	Population	Study Design	Enrollment Dates; Follow-up	Assessment Instrument	Subjects			Whole Grain Intake	Type II Diabetes		Surrogate Endpoints		Controlled Factors
					Sex	Age years	No. #		RR	95% CI	Fasting Blood Sugar (mmol/l)	Insulin Resistance (mU/l x mmol/l)	
Expanded Definition													
Lutsey et al., 2007	US	Cross-Sectional	2000	127-item SFFQ	F/M	45–84	5,496	servings per day 0.02 0.15 0.39 0.72 1.39			*P* for trend = 0.008 5.52 5.50 541 5.47 5.38	*P* for trend = 0.002 **5.37** **5.42** **5.42** **5.19** **5.16**	
Newby et al., 2007	US	Cross-Sectional	1978	7-d diet record	F/M	27–88	1,516	g/d 0.56 45.4			5.49 ± 0.06 5.49 ± 0.06	2.91 2.92	Age, sex, energy, decade of visit, education, vitamin supplements, smoking, fat, alcohol, refined grain, BMI, medication, diabetes

BMI: body mass index ; ‡ insulin sensitivity; * $p < 0.05$; ** $p < 0.01$.

DISCUSSION AND CONCLUSIONS

The purpose of this report was to evaluate the effects of applying the FDA definition of whole grains on the strength of the scientific evidence in support of health claims to elucidate the relationship between whole grain consumption and the risks of CVD and diabetes. The FDA defines "whole grains" as consisting of the intact, ground, cracked or flaked fruit of the grains whose principal components—the starchy endosperm, germ and bran—are present in the same relative proportions as they exist in the intact grain (U.S. Food and Drug Administration, 2006). In evaluating scientific evidence to support a health claim, the FDA primarily focuses its review on human intervention and observational studies because these studies can provide evidence from which scientific conclusions can be drawn about substance and disease relationships in humans (U.S. Food and Drug Administration, 2007). LSRO considered five studies (Andersson et al., 2007; de Munter et al., 2007; Jensen et al., 2006; Jensen et al., 2004; Rave et al., 2007) that were in accord with FDA definition of whole grains, but later expanded the analysis to include relevant whole grain studies regardless of their definition of whole grains. A discussion on the strength of the scientific evidence to support a health claim considering the FDA and the expanded definition follows.

Cardiovascular Disease

FDA Definition

The only prospective cohort study included in the FDA definition reported an inverse association between whole grain intake and incidence of CHD (Jensen et al., 2004). While intake of whole grain foods (foods containing 51% or more of whole grain as defined by the FDA) was associated with lower CHD risk (HR = 0.82; 95% CI: 0.70, 0.96; for highest versus lowest quintiles *P* for trend = 0.01), a stronger association of low CHD risk was reported with the intake of bran that was added during processing or cooking (HR = 0.70; 95% CI: 0.60, 0.82; for highest versus lowest quintiles *P* for trend < 0.0001). The authors suggested that these results could reflect the possibility that added bran may be beneficial and, if confirmed, should cause the FDA to consider whether the health claim for whole grains should be revised to explicitly include to beneficial effects from added bran.

In a cross-sectional study using data from the HPFS and NHS II, lower levels of TC were observed with higher intake of whole grains (Jensen et al., 2006). This study had several caveats, including a relatively small study sample that contributed to a lower statistical power and may have influenced the weak and somewhat inconsistent associations observed with lipid-related measures. Furthermore, because dietary intake and blood lipid levels are measured at the same point in time, the levels of blood lipids measured might not reflect solely long-term diets; they may also reflect the influence of more recent changes in lipids due to changes in diet or medication use.

Two intervention studies were included when applying the FDA definition (Andersson et al., 2007; Rave et al., 2007). No beneficial effect of consumption of whole grains, predominately milled wheat, was observed when compared with intake of refined grain on BP and serum lipid profile (Andersson et al., 2007). This was a well-designed randomized, non-blinded crossover study conducted for 6 weeks with compliance monitored by dietary records. The authors speculated that not all types of whole grain products have the same health effect, since beneficial effects on blood TC levels were reported after consumption of oats and barley (Behall et al., 2004a; Van Horn et al., 1988). Rave and colleagues (2007) also reported no beneficial effect of consuming whole grain wheat on a hypo-caloric diet for 4 weeks on BP or lipid profile.

- There is not enough evidence to draw a firm conclusion about the effect of whole grain intake on the risk of CVD when evaluating only the few studies that met the FDA definition of whole grains. There are only two human intervention studies included. These studies were of a short-term (4-6 weeks), tested a limited variety of whole grains (predominately wheat) and only examined one or two of many pathogenic mechanisms that contribute to the risk of CVD. The body of evidence from observational studies from which a protective relationship over a long-term can be inferred is also insufficient. This is because the observational studies are limited to a small number of independent samples (including only one prospective study). Moreover, the benefit of whole grains cannot be separated from the confounding influence of other diet components that alter pathogenic mechanism that promote CVD or its multiple risk factors over many decades.

Expanded Definition

In addition to the 2 observational studies that used the FDA definition of whole grains (Jensen et al., 2006; Jensen et al., 2004), 12 observational studies were included in the evaluation when considering an expanded definition of whole grains. Of these 12 studies, 10 defined whole grains as described by Jacobs, Jr. et al. (1998): Esmaillzadeh & Azadbakht (2006), Jacobs, Jr. et al. (1998), Jacobs, Jr. et al. (1999), Liu et al. (1999), Liu et al. (2003a), Liu et al. (2000b), McKeown et al. (2002), Newby et al. (2007), Steffen et al. (2003), and Wang et al. (2007); 1 study assessed intake of whole-grain bread (Fraser et al., 1992; Fraser, 1999; Morris et al., 1977); and 1 study evaluated the effect of oats (He et al., 1995). Results of all fourteen observational studies included in the expanded definition, regardless of their whole grain source, suggested a protective association between whole grain intake and risk of CVD.

The Dietary Guidelines for Americans recommends consumption of at least three 1-ounce-equivalents, approximately 85 g/day, of whole grains (U.S. Department of Health and Human Services, 2005). This amount, corresponding to three servings/day of whole grains, is associated with 30–48% reduced risk of several CVD outcomes, including IHD (Jacobs, Jr. et al., 1998), ischemic stroke (Liu et al., 2000b; Steffen et al., 2003), incident CAD (Steffen et al., 2003), and nonfatal and fatal CHD (Fraser et al., 1992). Reductions in plasma TC and LDL-C levels were also associated with intakes of 3 or more servings/day of whole grain intake (McKeown et al., 2002). Even lower amounts of

whole grain intake were related to beneficial health effects; a minimum of 1 serving/day of whole grains was associated with reduced risk of CVD (Jacobs, Jr. et al., 1998; Jensen et al., 2004; Steffen et al., 2003) and a 20% decrease in CVD mortality (Liu et al., 2003a). Several biological mechanisms may be involved in the protective role of whole grain against CVD. For this review, we evaluated the strength of the association between whole grains and the following risk factors of CVD: BP, TC, and LDL-C.

Results from 2 out of 4 studies, conducted on a variety of individual whole grains, suggested improvements in one or more indicators of BP. One study showed no beneficial effect of consumption of whole oats or wheat cereals (60 g/day) for 12 weeks on BP in mildly hypertensive men (Davy et al., 2002b). In contrast, SBP and DBP were reduced in hypertensive men who consumed 137 g/day of oat cereals for 6 weeks (Keenan et al., 2002). These data suggested that the amount of oats consumed might be more important in reducing BP than the period of time that it was consumed. Among healthy adults, a reduction in SBP was observed when subjects consumed a hypo-caloric diet containing oats (82 g/day) for 6 weeks (Saltzman et al., 2001), but not when a mix of wheat, rye and oats (112g/day) was consumed for the same length of time (Andersson et al., 2007).

- More studies are needed to evaluate the effect of individual grains on BP taking into consideration the type and amount of grains, population health status, and length of the study.

Although the intervention study by Andersson et al. (2007) evaluated when applying the FDA definition showed no effect on CVD outcomes, additional intervention studies in the expanded definition generally reported a beneficial effect. The beneficial effect of oats was reported in 6 studies (Davidson et al., 1991; Keenan et al., 2002; Saltzman et al., 2001; Van Horn et al., 1991; Van Horn et al., 1988; Van Horn et al., 1986); only one study showed no effect (Judd & Truswell, 1981; Weickert et al., 2006). Studies that resulted in a positive effect were conducted for 6–8 weeks compared to less than 3 weeks with those studies that had no beneficial effect. Four intervention studies with barley showed a reduction in plasma TC and LDL-C levels. Three of them were published by the same research group in the US (Behall et al., 2004a; Behall et al., 2004b; Behall et al., 2006) and the other was conducted by a research group in Japan (Li et al., 2003). Two studies with a similar study design, sample size, and study duration: one of which studied a diverse population of American men with hypercholesterolemia (Behall et al., 2004b) and the other which studied healthy Japanese women (Li et al., 2003), reported similar reductions in TC (20-15%) and LDL-C (21%) levels. The positive effect of barley reported across population, gender, and health status gives strength to the evidence of a beneficial health effect of barley on plasma TC and LDL-C levels.

- The observational evidence when using the expanded definition for an inverse association of whole grain consumption and risk of CVD was conclusive. There is also consistent and reliable evidence to support a positive short term effect (6

weeks) of oats and barley intake on TC and LDL-C levels, though the effect is no longer evident by 12 weeks.

Diabetes

FDA Definition

The only observational study included when using the FDA definition showed an inverse association of whole grain intake and risk of Type 2 diabetes (de Munter et al., 2007). This study evaluated data from the NHS I and NHS II cohort studies. An in-depth comparison of cohorts showed a 5% greater risk reduction in the NHS I population, who had a lower whole grain intake than the NHS II. Therefore, the authors suggested that the benefit of adding a serving of whole grains may be greater for populations with a low intake than for those who already have a high intake of whole grains. Additionally, the authors conducted an independent analysis and reported that the intake of bran (RR = 0.70; 95% CI: 0.62, 0.79; *P* for trend < 0.001) was significantly associated with a lower risk of Type 2 diabetes. These results are in accordance with the inverse association observed with bran intake and CVD (Jensen et al. 2004). This suggests a potential benefit of consuming bran to reduce the risk of diabetes and CVD, but might also reflect confounding by the intake of other food components or health behaviors that are related to bran intake.

Results of the two intervention studies (Andersson et al., 2007; Rave et al., 2007) that met the FDA criterion of whole grains were inconsistent regarding the effects of whole grain intake on insulin response. Both studies had virtually the same sample size and used wheat as their main source of grain, however, the amount of whole grain intake and the health status of the study population differed. In a crossover study design with a sample size that provided 80% power to detect a 10% change in insulin resistance, no beneficial effect on insulin sensitivity was reported in healthy individuals who consumed 112 g/day of whole grains (mainly wheat) for 6 weeks. Conversely, Rave et al. {165 /id /d} showed a marginally beneficial effect of consuming 200 g/day of double-fermented wheat with a hypo-caloric diet for 4 weeks on insulin resistance ($p = 0.049$) and serum insulin ($p = 0.031$) in obese subjects. Therefore, no conclusion about the short-term effect of whole grains on insulin response could be drawn from analyzing the results of these two intervention studies.

- The evidence for a short-term effect of whole grain intake on blood sugar and insulin response is suggestive but inconsistent when evaluating only studies that met the FDA definition of whole grains.

Expanded Definition

The additional observational studies included in the expanded definition consistently indicated an inverse association between whole grain intake and diabetes (de Munter et al., 2007; Fung et al., 2002; Liese et al., 2003; Liu et al., 2000a; Lutsey et al., 2007; McKeown et al., 2002; McKeown et al., 2004; Meyer et al., 2000; Montonen et al., 2003; Valachovicova et al., 2006; van Dam et al., 2002; van Dam et al., 2006). Results of only 1 cross-sectional study (Newby et al., 2007) indicated no association between whole grain intake and fasting glucose or fasting insulin.

Overall, epidemiological studies included when applying the expanded definition showed a 21–42% reduction in the incidence of Type 2 diabetes to be associated with the consumption of 3 servings/day of whole grains (de Munter et al., 2007; Fung et al., 2002; Liu et al., 2000a; Meyer et al., 2000; Montonen et al., 2003). One study showed that a 31% reduction in the risk of Type 2 diabetes was associated with 1.29 servings/day of whole grains (van Dam et al., 2006). Thus, results from studies included in the expanded definition, which further considered studies that included individual bran and germ as whole grains, evidenced a greater beneficial effect on reducing the risk of Type 2 diabetes than would be predicted from results of studies included in the FDA definition.

No intervention study that met the FDA definition evaluated the effect of whole grain intake on blood glucose levels and most of the 6 studies that did in the expanded definition reported no beneficial effect. A lower postprandial blood glucose level was achieved when subjects' breakfasts included brown or milled rice (Panlasigui & Thompson, 2006) and barley kernel or rye kernel (Nilsson et al., 2008); but there was no effect from oat and barley porridge (Liljeberg et al., 1996), or whole wheat bread (Behall et al., 1999). All of these acute studies had a similar study designs, involved healthy subjects with comparable sample sizes. Even though in acute studies the short period of time to observe a change in blood glucose (2–3 hours after whole grain consumption) may be of a concern to the study's validity and relevance; studies conducted for longer periods (8 to 12 weeks) also reported no significant effect on blood glucose levels (Davy et al., 2002a; Juntunen et al., 2003).

Five additional studies included when applying the expanded definition evaluated the effect of whole grain intake on insulin resistance and serum insulin; however, the data supporting such a relationship are limited and weak. A positive effect ($p = 0.03$) on fasting insulin was reported among hyperinsulenimic subjects consuming whole grains for 6 weeks (Pereira et al., 2002). Another 2 studies showed a marginal positive effect of rye consumption for 8 weeks on acute insulin ($p = 0.047$) (Juntunen et al., 2003) and on insulin resistance ($p = 0.049$) but only after adjusting for the amount of weight loss among obese subjects (Rave et al., 2007). Three studies observed no effect of whole grain intake on blood insulin levels (Andersson et al., 2007; Davy et al., 2002a; Saltzman et al., 2001).

- The evidence when using the expanded definition for the association of whole grain intake and metabolic mechanisms that contribute to diabetes was suggestive but inconclusive.

Other Biological Mechanisms

The relationship between whole grain intake and reduced risk of diabetes may also be mediated, in part, by reduction in body weight (de Munter et al., 2007), and intake of the whole-grain components, such as fiber (Fung et al., 2002; Meyer et al., 2000; Montonen et al., 2003) and magnesium (Fung et al., 2002; van Dam et al., 2006). The health benefits conferred by whole grain intake in relation to CVD may be mediated in part by its fiber, folate, magnesium, vitamin B-6, and vitamin E constituents (Jacobs, Jr. et al., 1998; Jensen et al., 2004), endothelial health (Katz et al., 2001b; Katz et al., 2001a; Katz et al., 2004), reduction in serum homocysteine (Jensen et al., 2006; Lutsey et al., 2007) and C-reactive protein (Jensen et al., 2006; Qi et al., 2006) levels, and higher serum levels of enterolactone (Jacobs, Jr. et al., 2002; Johnsen et al., 2004). Residual confounding due to these constituents might not be fully removed by adjusting for their intake. Furthermore, other unknown constituents of whole grains or diet patterns related to whole grain intake may contribute to the additional protection of whole grains against CVD and diabetes.

The variation in constituents among types of whole grains should also be considered when associating whole grains with a health benefit. Grains differ in their amount of soluble and insoluble fiber, phenolic compounds, lignan, sterols, all compounds suggested to be associated with health benefits (Marquart et al., 2007). Some compounds are even unique to some grains, such as the phenolic avenanthramides that are present only in oats and have antioxidant activity (Chen et al. 2007). Among the intervention studies included in the expanded definition only the studies conducted with oats and barley (Behall et al., 2004b; Van Horn et al., 1991) reported reduced cholesterol levels. Milled wheat did not lower serum cholesterol levels (Andersson et al., 2007). Therefore, studying the association of individual grains rather than an entire category of whole grains to a particular health benefit would provide additional evidence about the possible beneficial components of whole grains.

Summary of Conclusions

- A consistent definition of whole grains has not been applied in existing research that investigates the health benefits of consuming whole grains. As such, drawing specific conclusions on benefits of “whole grains” in general from the body of scientific evidence is confounded, typically with bran/dietary fiber. Using the FDA definition for whole grains as a selection criterion is limiting because the vast majority of existing studies often use a broader meaning to categorize a grain product as whole grain. Applying the FDA definition of whole grains excludes the majority of observational studies because they include the intake of bran and germ to evaluate the health effect of whole grains, and a great number of

intervention studies that use individual grains because they do not explicitly state that the endosperm, bran and germ are present in the same proportion.

- The scientific evidence on the relationship of whole grain consumption and CVD can be evaluated two ways. First, there is no consistent scientific evidence to support a whole grain and CVD risk health claim if only whole grain studies that conform to the FDA whole grain definition (using native proportion of endosperm, bran and germ) are considered. In contrast, a whole grain and CVD health claim is supported using a broader concept of whole grain, typically used in the literature that includes whole grain foods containing principal components such as bran. A health claim for the relationship between soluble fiber from oats and barley and risk of CHD has been approved by the FDA (U.S. Food and Drug Administration, 2008a).

- The scientific evidence on the relationship of whole grain consumption and diabetes is suggestive but inconclusive whether the analysis was restricted to studies that defined whole grain according to the FDA definition, or included studies using a wider classification of whole grains.

- The health benefits observed from consumption of one whole grain do not necessarily reflect the same benefit or the same magnitude of benefit from other whole grains. This is because of the diversity among whole grains in terms of macronutrient, micronutrient and bioactive components.

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APPENDIX I. LIFE SCIENCES RESEARCH OFFICE

Whole Grain Review Committee

James Hoadley, Ph.D., recently retired after a distinguished 20-year career with the Food and Drug Administration (FDA). Dr. Hoadley earned his Ph.D. in Toxicology at the University of Cincinnati, College of Medicine, and did postdoctoral research in nutrition at the University of Florida. His Bachelor of Science degree is from Ohio State University with a major in agricultural education. Dr. Hoadley's FDA career, which began in 1987, included work as a research scientist in the Nutrition Division of the Center for Food Safety and Applied Nutrition (CFSAN), and later as a toxicologist, performing food additive and GRAS petition safety reviews in the Office of Premarket Approval (OPA). Over the past ten years, Dr. Hoadley worked as a regulatory scientist in the Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS) with primary responsibilities in food label claim regulations. In this role, he conducted scientific and regulatory reviews of petitions for new health claims and nutrient content claims. Dr. Hoadley was a recipient of the CFSAN Distinguished Career Service Award.

Julie Mares, M.S.P.H., Ph.D., is a Professor in the Department of Ophthalmology and Visual Sciences, University of Wisconsin, School of Medicine and Public Health. She is a nutrition scientist and epidemiologist whose research team has investigated the relationships between nutrition and common age-related eye diseases for the past 20 years. She has also worked to develop and evaluate valid and reliable estimates of diet and nutritional status that are used in epidemiological studies. Her research team has received 19 years of support from the National Institutes of Health, National Eye Institute. The results of these studies of diet and its relation to cataract, macular degeneration and diabetic retinopathy have been published in over 70 papers and book chapters.

Judith Marlett, R.D., Ph.D., is Professor Emeritus of Nutritional Sciences, University of Wisconsin-Madison. Her research, which focused on dietary fiber analysis and mechanisms of action, is summarized in over 100 publications. Other major professorial responsibilities included the instructor for 26 years of the Clinical Nutrition course for dietetic students and periodic administration of the Department's dietetics program. Throughout her career, Dr. Marlett has served on government committees and grant study sections, was a regular speaker at national and international symposia/meetings, and was a consultant for the food and pharmaceutical industries. Currently, she is an active ad hoc reviewer, an Associate editor of *The Journal of the Science of Food and Agriculture*, and an occasional consultant.

Harry Sapirstein, Ph.D., is an Associate Professor in the Department of Food Science, Faculty of Agricultural and Food Sciences, University of Manitoba. Dr. Sapirstein is a cereal scientist with a diverse program of research, focused primarily on wheat utilization for food which has spanned topics such as cultivar identification using biochemical fingerprints, digital imaging for quality control of grain and bread, genotype and environmental effects on gluten protein composition, and the physicochemical

nature of breadmaking quality. More recently his studies have focused on wheat bran and fiber composition, antioxidants, and processes to enhance bran functionality for food and health. His research has been reported in over 70 publications. A longstanding member of AACC International, Dr. Sapirstein has participated in many committees including Scientific Advisory Panel, and has served as Technical Program Chair, Chair of the Protein Division, Chair of the Canadian Prairie Section, and as Associate Editor of the journal *Cereal Chemistry.*

Life Sciences Research Office Staff

MaryBeth Bernhard, B.S., is an Associate Staff Scientist at the Life Sciences Research Office (LSRO). She graduated *summa cum laude* from Towson University, where she obtained B.S. degrees in both psychology and mass communication and communication studies, with a concentration in public relations. Ms. Bernhard completed internships in the Towson University Adult Psychology Research Lab, where she coordinated an ongoing study that contributed to a symposium presentation at the 57th Annual Scientific Meeting of the Gerontological Society of America. As Project Coordinator/Lab Manager, Ms. Bernhard collected, recorded, and analyzed data for the study and presented her research findings at the Sixth Annual Research and Scholarship Expo. Before joining LSRO, Ms. Bernhard worked in the Marketing Department of Crist Instrument Company, a research and development facility for biomedical research equipment. Ms. Bernhard has also participated in community outreach efforts through the Dowell Health Center HIV Counseling and Testing Program. Ms. Bernhard is currently working toward completing her Master of Public Health degree at the George Washington University Medical Center School of Public Health and Health Services, with a concentration in epidemiology.

Fabiana F. De Moura, Ph.D., is a LSRO Staff Scientist. She received her Ph.D. in nutrition from the University of Maryland, College Park, and completed her postdoctoral training in the Nutrition Department at the University of California, Davis. She holds an M.S. degree in food science from the State University of Campinas and a B.S. degree in food engineering from the Federal University of Viçosa, both institutions in Brazil. During her doctoral and postdoctoral training, Dr. De Moura's research focused on elucidation of human metabolism of vitamins and carotenoids. In collaboration with researchers at the National Eye Institute, she investigated the possible beneficial effects of lutein in prevention of age-related macular degeneration. Dr. De Moura is the primary author of a book chapter and she has authored and co-authored eight peer-reviewed journal articles. She is a member of the American Society for Nutritional Sciences and the International Carotenoid Society.

Michael C. Falk, Ph.D., is Executive Director of LSRO. He received his Ph.D. in biochemistry from Cornell University and completed postdoctoral training at Harvard Medical School. He was employed in various capacities at the Naval Medical Research Institute, where he supervised as many as 80 senior level scientists. As Principal Investigator, he was a key member of the Scientific Advisory Board and the Acting Director of the Institute. He was also the Director of the Wound Repair Program and

pioneered a new position as the Director of Biochemistry and Cell Biology. Also, as the Director, he rescued the Septic Shock Research Program by cutting inefficiencies and increasing productivity in terms of grant funding and publication production. He managed peer review and subject review panels in infectious diseases, environmental sciences, military medicine, and other health-related fields. He was a peer reviewer for research proposals for the National Science Foundation, Medical Research Council of Canada, and Office of Naval Research. As the Director of LSRO, Dr. Falk evaluates biomedical information and scientific opinion for regulatory and policy makers in both the public and the private sectors. Among his many accomplishments, he has produced seminal white papers on infant nutrition, food labeling, food safety, and military dental research and has organized two international conferences. Concurrently, he is with MCF Science Consultants and provides analysis and consultation on emerging technologies. Dr. Falk has published more than 60 research articles, abstracts, technical reports, and presentations.

Robin S. Feldman, B.S., M.B.A., is the LSRO Literature Specialist. She is a seasoned information specialist with experience in the electronic acquisition, analysis, and management of scientific, business, and regulatory information. Ms. Feldman obtained her B.S. from the George Washington University in Washington, D.C., with a major in zoology and her M.B.A. from the University of Maryland at College Park with a concentration in science and technology. She previously worked as a Biomedical Research Assistant at Consultants in Toxicology, Risk Assessment and Product Safety, where she obtained and researched scientific literature for private and governmental clients. At the National Alliance for the Mentally Ill, she designed and implemented a document management and retrieval system for the Biological Psychiatry Branch of the National Institute of Mental Health and served as Managing Editor of *Bipolar Network News*, a newsletter for the Stanley Foundation Bipolar Network. At Howard Hughes Medical Institute (HHMI), she oversaw the implementation of the HHMI Predoctoral Fellowship in Biological Sciences program. While serving as Science Information Specialist at the Distilled Spirits Council of the United States, she managed the installation of a local area network and participated in the development and maintenance of an electronic research database for the beverage alcohol industry. As a Report Coordinator at Microbiological Associates, Inc., she conducted statistical analyses and prepared technical reports about toxicology studies using animal models. She served as data management administrator for the National Toxicology Program's sponsored studies. Ms. Feldman currently maintains LSRO's library, responds to requests for reports, and assists LSRO's scientists in discovering, obtaining, compiling, and documenting the scientific literature required to prepare reports for sponsors.

Rebecca Johnson, Ph.D., is the LSRO Assistant Information Specialist. Dr. Johnson received her B.A. from Wesleyan University and her Ph.D. in anthropology with a concentration in archaeology from the University of Iowa. Her dissertation research examined dietary change between two Native American villages in southeastern Iowa, dated to 1950 and 100 B.P., by looking at fatty acid residues extracted from pottery. Dr. Johnson has performed fieldwork across the Mid-Atlantic and Upper Midwest, as well as in South Carolina, Great Britain, and Poland. Dr. Johnson currently assists in

maintaining the LSRO library, responding to requests for reports, and organization the scientific literature required by staff scientists for sponsored projects. Before joining LSRO, Dr. Johnson developed and maintained statewide archaeological databases for Iowa's Office of the State Archaeologist.

Kara D. Lewis, Ph.D., is a LSRO Senior Staff Scientist. She obtained her Ph.D. in biology, with a concentration in neuroscience, from Clark University and graduated *summa cum laude* with a B.S. in biology from Spelman College. Dr. Lewis completed her postdoctoral research at Yale University. Dr. Lewis has conducted research on taste and smell of the fruit fly *Drosophila melanogaster* and on molecular mechanisms of sweet taste transduction in the blowfly *Phormia regina*. She has collegiate teaching experience and three peer-reviewed publications and served as editor for LSRO's Review of Ingredients Added to Cigarettes Phase Two: Scientific Criteria for the Evaluation of Ingredients Added to Cigarettes and Exposure Assessment in the Evaluation of Potential Reduced-Risk Tobacco Product reports. She is a member of the Association for Chemoreception Sciences.

James L. Seale, Ph.D., is a LSRO Scientific Consultant. Dr. Seale earned his B.S. in mechanical engineering from the University of Arizona and his M.S. and Ph.D. in bioengineering from Texas A & M University. He served as Research Biomedical Engineer in the Diet and Human Performance Laboratory of the USDA Agricultural Research Service, Beltsville Human Nutrition Research Center, where he investigated factors affecting human energy metabolism. Dr. Seale also served as Consulting Engineer in the Custom Applications Branch of the National Institutes of Health Center for Information Technology, where he developed plans for quality assurance, change control, security, testing, and validation processes. Dr. Seale currently teaches physics in the Howard County, Maryland public school system. Dr. Seale has authored or coauthored more than 25 publications.

APPENDIX II. EXCLUDED STUDIES

Reference	Research Area	Outcome Assessed	Study Design	Population Health Status	Country	Reason for Exclusion
Bazzano et al. (2005)	Obesity	Body weight	Prospective Cohort (PHS)	Healthy	US	No validated endpoint for CVD
Halton et al. (2006)	Diabetes	Type 2 diabetes mellitus	Prospective Cohort (NHS)	Healthy	US	Not whole grain study. Whole grain was a covariate
Jacobs, Jr. et al. (2000)	Mortality	Mortality (total, CVD)	Prospective Cohort (IWHS)	Healthy	US	No validated endpoint for CVD or diabetes
Koh-Banerjee et al. (2004)	Obesity	Body weight and biomarkers of obesity	Prospective Cohort (HPFS)	Healthy	US	No validated endpoint for CVD
Liu et al. (2003b)	Obesity	Body weight	Prospective Cohort (NHS)	Healthy	US	No validated endpoint for CVD
Mozaffarian et al. 2003 (2003)	CVD	MI, fatal events consistent with IHD death, and stroke	Prospective Cohort (CHS)	Healthy	US	Fiber study
Qi et al. 2006 (2006)	Inflammation	C-reactive protein and TNF-R2	Prospective Cohort (NHS)	Diabetic	US	No validated endpoint for CVD and unhealthy population
Rimm et al. (1996)	CHD	Fatal and nonfatal MI	Prospective Cohort (HPFS)	Healthy	US	Fiber study
Schulze et al. (2006)	Obesity	Body weight	Prospective Cohort (NHS II)	Healthy	US	No validated endpoint for CVD and not a whole grain study
Lee et al. (2004)	CHD	Serum GGT	Prospective Cohort (CARDIA)	Healthy	US	No validated endpoint for CVD
Djousse & Gaziano (1999)	CVD	Incident Heart Failure	Prospective Cohort (PHS)	Healthy	US	No whole grain study. Breakfast cereal study.

Reference	Research Area	Outcome Assessed	Study Design	Population Health Status	Country	Reason for Exclusion
Wolk et al. (1999)	CHD	Incidence of acute MI or death due to CHD	Prospective Cohort (NHS)	Healthy	US	Fiber study. Not a whole grain study
Lopes-Garcia et al. (2004)	Endothelial Health and Inflammation	CRP, IL-6, E-selectin, sICAM-1, and sVCAM-1	Cross Sectional (NHS)	Healthy	US	No validated endpoint for CVD
Mantzoros et al. (2006)	Diabetes	Adiponectin	Cross Sectional (NHS)	Healthy	US	No validated endpoint for Diabetes
Davy et al. (2002a)	CVD	Lipoproteins (particle size and number)	Human Intervention	Healthy	US	No validated endpoint for CVD
Jacobs, Jr. et al. (2002)	CHD and Cancer	Serum enterolactone	Human Intervention	Overweight and hyperinsu-lemic	US	No validated endpoint for CVD and unhealthy population
Katz et al. (2004)	Endothelial Health	Flow-mediated dilation of the brachial artery	Human Intervention	Healthy	US	No validated endpoint for CVD
Katz et al. (2001a)	Endothelial Health	Brachial artery reactivity	Human Intervention	Healthy	US	No validated endpoint for CVD
Katz et al. (2001b)	Endothelial Health	Brachial artery reactivity	Human Intervention	Healthy	US	No validated endpoint for CVD
Pins et al. (2002)	Hypertension	SBP, DBP, blood lipids, fasting glucose, and insulin levels	Human Intervention	Hypertensiv e	US	No validated endpoint for CVD and unhealthy population
Agostinho Gimeno et al. (2008)	CVD and Diabetes	BMI, WHR, ankle-to-branchial systolic BP, OGTT	Cross Sectional	Not described	Brazil	Unknown population health status
Johnsen et al. (2004)	CVD and Cancer	Plasma enterolactone	Cross Sectional	Healthy	Denmark	No validated endpoint for CVD or diabetes

Reference	Research Area	Outcome Assessed	Study Design	Population Health Status	Country	Reason for Exclusion
Villegas et al. (2004)	Diabetes	Weight, WHR, fasting glucose and insulin	Cross Sectional	May have subjects with CVD and diabetes	Ireland	May have unhealthy population
Michels et al. (2002)	CVD and Mortality	death	Prospective Cohort	Healthy	Sweden	No validated endpoint for CVD or diabetes
Hoffman et al. (2004) (CORA Study)	CVD	Weight, WHR, LDL-C, BP	Case-Control	CAD	Germany	Unhealthy population
Hagander et al. (1985)	Diabetes	Blood glucose, IRI, C-peptide, GIP, HbA1, TG, glucagon, and glycerol	Human Intervention	Diabetic	Sweden	Unhealthy population
Jang et al. (2001)	CAD and Diabetes	Blood glucose and insulin, lipid profile, OGTT, Hcy, Plasma MDA and Folate	Human Intervention	CAD	Korea	Unhealthy population
Jenkins et al. (1986)	Diabetes	Blood glucose	Human Intervention	Diabetic	Canada	Unhealthy population
Jenkins et al. (1988)	Diabetes	Glycaemic index of foods	Human Intervention	Diabetic	Canada	Unhealthy population
Jenkins et al. (2002)	Diabetes	Blood glucose, HbA1, CRP, lipids profile, oxidized LDL cholesterol, clotting factors and minerals	Human Intervention	Diabetic	Canada	Unhealthy population
Jarvi et al. (1995)	Diabetes	Blood glucose, insulin, lipids profile, plasma C-	Human Intervention	Diabetic	Sweden	Unhealthy population

Reference	Research Area	Outcome Assessed	Study Design	Population Health Status	Country	Reason for Exclusion
		peptide				
Jimenez-Cruz et al. (2003)	Diabetes	BMI, TC, TG, and blood glucose	Human Intervention	Diabetic	Mexico	Unhealthy population
Kabir et al. (2002)	Diabetes	Abdominal subcutaneous adipose tissue, plasma glucose, insulin, and lipids	Human Intervention	Diabetic	France	Unhealthy population
Kallio et al. (2007)	Diabetes	Adipose tissue biopsies, OGTT and other biochemical measurements	Human Intervention	Metabolic Syndrome	Finland	Unhealthy population
Lindeberg et al. (2007)	CVD	Weight, waist circumference, glucose, and insulin	Human Intervention	IHD	Sweden	Unhealthy population
Asp et al. (1981)	Diabetes	Blood glucose	Human Intervention	Diabetic	Sweden	Unhealthy population
Vuksan et al. (2007)	CVD and Diabetes	Lipid profile, glycemic control, blood pressure	Human Intervention	Diabetic	Canada	Unhealthy population
Esposito et al. (2004)	Endothelial Health	L-arginine, CRP, IL-6, IL-7, IL-18	Human Intervention	Metabolic Syndrome	Italy	Unhealthy population

BP: blood pressure; **BMI:** body mass index; **CARDIA**: Coronary Artery Risk Development in Young Adults Study; **CORA**: Coronary Risk Factors for Atherosclerosis; **CAD**: coronary artery disease; **CHD**: coronary heart disease; **CHS**: Cardiovascular Health Study; **CRP**: C-reactive protein; **CVD**: cardiovascular disease; **GGT**: ?-glutamyltransferase; **GIP**: Gastric inhibitory polypeptide; **HPFS**: Health Professionals Follow-up study; **IHD**: ischemic heart disease; **IL**: interleukin; **IRI:** insulinemia; **IWHS**: Iowa Women's Health Study; **LDL-C**; low-density lipoprotein cholesterol; **MDA**: malondialdehyde; **MI**: myocardial infarction; **NHS**: Nurse's Health Study; **OGTT**: oral glucose tolerance test; **PHS**: Physician's Health Study; **sICAM-1**: soluble intercellular adhesion molecule-1; **sICAM-1**: soluble vascular adhesion molecule-1; **TC:** total cholesterol; **TAG**: triacylglycerol; **TNF R2:** Tumor necrosis factor-a receptor 2; **WHR**: Waist to Hip Ratio

APPENDIX III. ACRONYMS AND ABBREVIATIONS

AHA	American Heart Association
AHS	The Adventist Health Study
ARA	Arabinose
ARIC	Atherosclerosis Risk in Communities Study
AX	Arabinoxylan
BARS	Brachial artery reactivity studies
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body mass index (kg/m^2)
BP	Blood pressure
CABG	Coronary artery bypass graft
CAC	Coronary artery calcification
CAD	Coronary artery disease
CARDIA	The Coronary Artery Risk Development in Young Adults Study
CHD	Coronary heart disease
CHS	The Cardiovascular Health Study
CRP	C-reactive protein
CVD	Cardiovascular disease
CORA	Coronary Risk Factors for Atherosclerosis in Women
DBP	Diastolic Blood Pressure
F	Female
FDA	Food and Drug Administration
FDAMA	FDA Modernization Act of 1997
FDCA	U.S. Federal Food, Drug and Cosmetic Act
FFQ	Food-frequency questionnaire
FOS	The Framingham Offspring Study
GGT	?-Glutamyltransferase
GI	Glycemic index
GIP	Gastric inhibitory polypeptide
GLC	Glucose
HDL	High density lipoprotein
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPFS	The Health Professionals Follow-up Study
HR	Hazard ratio
IHD	Ischemic heart disease
IMT	Intimal medial thickness
IR	Insulin resistance
IRAS	The Insulin Resistance Atherosclerosis Study
IRI	insulinemia
IAUC	Incremental area under the curve
IWHS	The Iowa Women's Health Study
LDL	Low density lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
MRAN	Mannose
MR	Meal replacement
MAP	Mean arterial blood pressure
NHS	The Nurses' Health Study
NHSII	The Nurses' Health Study II
NLEA	Nutrition Labeling and Education Act of 1990
NMR	Nuclear magnetic resonance
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
PHS	The Physicians' Health Study
PP	Pulse pressure
PUFA	Polyunsaturated fatty acid
RAFF	Raffinose
RCT	Randomized controlled trial
RHA	Rhamnose
SBP	Systolic Blood Pressure
SFA	Saturated fatty acid
SHS	The Seventh-day Adventist Health Study
SHS-2	The Seventh-day Adventist Health Study-2
SOL	Sorbitol
STA	Stachyose
SUC	Sucrose
TG	Triglycerides
UFA	Unsaturated fatty acid
VLDL	Very low density lipoprotein
WHI	The Women's Health Initiative
WHO	World Health Organization
WHS	The Women's Health Study
XYL	Xylose

OGTT	Oral glucose tolerance test
OR	Odds ratio
PHS	The Physicians Health Study
RR	Relative risk
SBP	Systolic Blood Pressure
SFFQ	Semiquantitative food-frequency questionnaire
TC	Total cholesterol
TCI	Transient cerebral ischemia
TAG	Triacylglycerol
TNF-R2	Tumor necrosis factor-a receptor 2
VLDL	Very-low density lipoprotein
XYL	Xylose
WG	Whole grain
WHR	Waist-to-hip ratio
WHS	The Women's Health Study