

Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy¹⁻³

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ABSTRACT Evidence is synthesized that foods and food patterns act synergistically to influence the risk of several chronic diseases. Whole-grain consumption and risk of disease are presented as a model of food synergy. Food synergy is defined as additive or more than additive influences of foods and food constituents on health. Risk appears to be lower with consumption of whole grain than of refined grain; that is, benefit accrues when all edible parts of the grain are included (bran, germ, and endosperm). It appears that phytochemicals that are located in the fiber matrix, in addition to or instead of the fiber itself, are responsible for the reduced risk. Risk is further reduced if whole-grain foods are consumed in a diet otherwise high in plant foods. To gain full understanding of the pathways by which food synergies work, it is desirable to use several “top down” approaches, starting with the larger units, namely foods or food patterns, and working down to smaller units that provide protection from disease. Study of foods, food patterns, and individual nutrients or food components in reducing disease risk is seen as complementary. Epidemiologic, clinical trial, and in vitro approaches to such research are needed. *Am J Clin Nutr* 2003;78(suppl):508S–13S.

KEY WORDS Food synergy, whole grain, plant-based diet, chronic disease, epidemiology, feeding study

INTRODUCTION

Nutrition research has favored a reductionist approach (1) that emphasizes the role of single nutrients in diet-disease (or diet-health) relations. This approach has led to important steps forward, for example, in learning the basic cause of and identifying prevention strategies for vitamin deficiency diseases (2, 3), or in clarifying the influence of dietary cholesterol and fat intake on serum cholesterol (4, 5). Nevertheless, the reductionist approach must be seen as a simplification designed to facilitate the understanding of complex diet-disease relations. Metaphorically speaking, understanding one leaf in a forest does not necessarily provide insight into the entire forest. The interrelation of human physiology and of the biological activity of plant and animal foods that humans consume is incredibly complex, replete with checks, balances, and feedback loops, dependent on a myriad of substances that differ only in subtle ways from one another.

Therefore, it is likely that there are additive or more than additive influences of foods and food constituents on health—that is, food synergy, though the extent and nature of that synergy are difficult to uncover. Based on the idea that there is food synergy, this paper considers the question, What is the best way to understand the full effect of dietary intake on health?

This paper presents 1) a summary of findings relating intake of whole-grain foods to reduced chronic disease risk as an example of synergy in a single food group–disease relation, 2) the effectiveness of plant-based diets on health, and 3) considerations for research approaches to elucidate food synergies in health risk. More specifically, we propose complementary research methodology: “bottom up” to identify and characterize individual food constituents that have powerful health effects, and “top down” to study health effects of the combinations of these constituents in foods and food patterns.

HISTORICAL PERSPECTIVE

With the advent of industrialized roller milling and mass refining of grains in about 1880, worldwide epidemics of pellagra and beriberi began because of loss of B vitamins during processing of grain to remove the bran and the germ for longer shelf life (3). In 1937 scientists showed that nicotinic acid was the specific micronutrient deficiency for pellagra and thiamine for beriberi (3). These discoveries were so fundamental and startling that some believed that little remained to be investigated in the field of nutrition (1, 6). One obvious solution, protecting health and satisfying the needs of industry, was to resupply the deficient nutrients. There seemed to be no need to modify food production, because the only problem was a shortage of a few important vitamins. The net result of all these forces was overreliance on several nutrients and food enrichment, what might be called a “Wonder Bread” culture of institutionalized supplementation.

It is now clear that today’s chronic diseases, such as atherosclerosis, ischemic heart disease, and cancers, are complex diseases with multiple etiologies and not simple deficiency diseases. For example, findings of the strongly reduced risk of ischemic heart disease, diabetes, and some cancers among habitual consumers of whole-grain foods support the idea that food synergies

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TABLE 1

Hierarchical structure of dietary patterns, foods, and nutrients for study of food synergy¹

Food synergy level	Examples of dietary component at each synergy level
Level 5: dietary pattern	"Prudent diet," "Western diet," other combinations of food groups
Level 4: food groups	Whole grain, dairy, fruit, vegetables, meat
Level 3: whole grain	Whole wheat, brown rice, rolled oats
Level 2: whole wheat	Bran, germ, endosperm; extract of fat-soluble portion
Level 1: bran or a single phytochemical	Specific nutrients or phytochemicals

¹"Top down" research begins with the higher levels, searching for combinations of foods and their constituents that influence health; "bottom up" research begins at the lowest level, searching for individual constituents that influence health.

play an important role in chronic disease prevention (7). Nevertheless, the overprocessing of grains and other foods has worsened since the early 1900s. We and other health professionals continue to warn that vitamins and many other important biologically active constituents are lost in the refining of grain.

WHOLE GRAIN AND HEALTH AS AN EXAMPLE OF FOOD SYNERGY

Whole grain defined

Cereal grains are grass seeds (8). The commonly eaten grains arose from those wild grasses that were abundant and had larger seeds; they were domesticated to enhance their size. Grains commonly consumed in the Western world include wheat, oats, rye, rice, barley, and corn. Elsewhere, commonly consumed grains include millet, amaranth, spelt, triticale, and Job's tears. Buckwheat is a related food—a seed, but not a grass, eaten as a grain.

Understanding the botanical structure of the grain is helpful in understanding the concept of food synergy. The grain has an inedible husk; an outer layer called the bran; an outer section called the germ, which contains the embryonic grain plant; and a large central section called the endosperm, which serves primarily as a food sac for the potential seedling. A particularly biologically active portion of the bran is the aleurone layer. The bran and the germ perform many biological functions, including offering protection from predators such as bacteria, virus, and fungus and enabling enzyme and signaling activities that foster the growth of the seedling. In wheat, for example, the bran and the germ together constitute 17% of the total weight of the grain but include 80% of the fiber and of many other nutrients and nonnutrients. Most of these other phytochemicals are embedded in the fiber matrix; fiber plus accompanying phytochemicals might be called fiber complex. The germ contains polyunsaturated fatty acids necessary for the embryonic plant; these fatty acids have a tendency to oxidize, producing rancidity with longer storage. The bran and the germ contain few calories. The endosperm, on the other hand, is mostly starch, is energy rich, and contains cell walls but little fiber. The fiber in the cell walls within the endosperm is nutrient poor, reflective of the botanical fact that the bulk of the plant defense and activity takes place outside the food sac. These constituents of the plant act synergistically in the life of the plant;

when the whole grain is eaten, all these biologically active constituents are eaten.

A whole-grain food includes all edible parts of the grain: the bran, the germ, and the endosperm. Whole-grain foods include products such as whole-grain bread, some ready-to-eat breakfast cereals, pasta, oatmeal, brown rice, lightly pearled barley, and bulgur wheat. Related grain foods that are not cereals are wild rice and buckwheat. A refined-grain food contains only the endosperm; therefore, most of the grain's nutritional value is lost during milling. Refined-grain foods include products such as white bread, bagels, rolls, pastries, breakfast cereals, white or durum flour pasta, and white rice. The great bulk of grain is eaten as flour, that is, in small particles rather than as intact grains. The term *whole grain* has more to do with inclusion of all edible parts than with intactness of the kernel.

Framework for study of food synergy

The study of food synergy attempts to isolate which food patterns, foods, or parts of foods have health effects (**Table 1**). For example, dietary patterns have been identified as prudent, Western, or other combinations of food groups (Level 5). Whole grain is often contained in a prudent dietary pattern. Because all grains have a common botanical structure, grains may sensibly be grouped (Level 4). To understand details of the whole-grain group, specific whole grains, such as whole wheat, may be studied (Level 3). To understand the whole wheat, botanical parts of the grain, namely bran, germ, and endosperm, or biochemical extracts such as fat-soluble constituents may be studied (Level 2). Specific nutrients and phytochemicals contained in grains, or combinations thereof, are more detailed (Level 1).

Epidemiology of whole-grain consumption and risk of chronic disease

Initial epidemiologic studies grouped all whole-grain foods, that is, foods of all grain species containing bran, germ, and endosperm, however they were processed. Refined-grain foods containing only endosperm were studied in parallel. The epidemiology of whole grains and several chronic diseases began unfolding in the mid-1990s with reviews of cancer case-control studies plus one prospective study of ischemic heart disease incidence (9–11). These reviews generally suggested reduced risk in those who habitually consumed whole-grain foods. The first study to explore the relation of whole-grain consumption and risk of mortality from all causes, ischemic heart disease, cardiovascular disease generally, all cancers, and all other causes was the Iowa Women's Health Study with 10 y of follow-up (7). Food groups were formed based on a semiquantitative food frequency questionnaire (12); for example, the whole-grain group was formed as the sum of the number of servings per week of dark bread, brown rice, whole-grain breakfast cereal, bran, wheat germ, and a miscellaneous whole-grain item (13). Whole-grain intake was categorized in quintiles, each including over 7000 women (**Table 2**).

Habitual eaters of whole grains (self-report of more than 1 serving per day), compared with those who rarely ate whole-grain foods, had a healthier lifestyle, characterized by nonsmoking, physical activity, vitamin supplement taking, and hormone replacement therapy. Dietary habits were also favorable, characterized by more "desirable" plant foods and higher intake of desirable nutrients, coupled with less red meat than among those who rarely ate whole grain (13). Refined-grain eaters had a generally less healthy lifestyle. Table 2 shows an etiologic analysis, in which



TABLE 2
Total mortality in whole-grain eaters, Iowa Women's Health Study 1986–1996¹

	Quintile of whole-grain intake					<i>P</i> for trend
	1	2	3	4	5	
Servings/wk	0–3.5	4–7	7.5–10	10.5–18	> 18	—
Person-years	68 262	68 672	64 761	66 329	64 980	—
No. of deaths	914	705	583	523	595	—
Adjusted hazard rate ratio (effect of grain only)						
Etiologic analysis	1.00	0.95	0.87	0.81	0.86	0.005
Unadjusted hazard rate ratio (effect of grain and related behaviors)						
Lifestyle analysis	1.00	0.76	0.65	0.55	0.64	<0.0001

¹Exactly 38 470 women, aged 55–69 y, followed for 10 y. Adapted from Jacobs et al (7).

the potential contribution of whole-grain intake in preventing total mortality is examined, by adjusting for age, energy intake, and indicators of diet and lifestyle. About a 15% reduction in total mortality is suggested among habitual whole-grain consumers.

The lifestyle analysis in Table 2 adjusted for only age and energy intake. An ≈40% reduction in risk for total mortality was associated with the package of whole-grain consumption, higher consumption of other plant foods and lower consumption of meats, nonsmoking, increased physical activity, better education, and reduced body fatness, compared with those who rarely consumed whole grain and otherwise had a less favorable dietary and lifestyle pattern. The lifestyle analysis suggests food synergy, namely, that various aspects of a whole-grain-containing dietary pattern work together to reduce mortality risk. Of interest to food synergy, further simultaneous adjustment for dietary fiber, vitamin E, folic acid, phytic acid, iron, zinc, magnesium, and manganese intake did not explain the association of whole-grain consumption with total mortality, whether adjusting for other lifestyle characteristics or not. This analysis suggests that something else in the whole grain protects against death.

A similar study was undertaken in Norwegian men and women, with baseline between 1977 and 1983 (14), where the available whole-grain consumption questions dealt entirely with bread. Food disappearance data suggest that Norwegians eat about 4 times as much whole grain as do Americans (7, 15). The Norwegian findings (14) in men and women confirmed the Iowa findings (7, 13). Habitual Norwegian whole-grain bread eaters had a healthier lifestyle than did those who ate little whole-grain bread. Total mortality was inversely related to whole-grain bread consumption in Norway as in Iowa, but at an average level much higher than in the Iowa women. In the Norwegian data, the highest quintile of consumption corresponded to the lowest mortality, whereas the Iowa data showed a slightly higher risk ratio in the highest whole-grain consumption quintile than in the second highest (Table 2).

The Iowa and Norwegian studies were of mixed whole grains, but do all grain species contribute to reduced risk? In Iowa and Norway, the largest proportion of whole grain was wheat and oats, plus small amounts of corn and rice. A Finnish study (16) showed reduced ischemic heart disease risk in male smokers who ate more whole-grain rye bread. These data suggest that the whole grains of several different species have similar health effects.

Another aspect of the food synergy investigation is whether grain fiber or the phytochemicals that coexist with the fiber are more important in health. The Iowa data were reanalyzed to address this issue (17). For fixed total cereal fiber intake, the

total mortality rate was 17% lower if the fiber came from whole-grain foods than from refined-grain foods. This suggests that the food constituent, cereal fiber, is not the sole active component in the grain leading to reduced risk; rather, some of the phytochemicals or other food components in the fiber complex located in the bran or germ must have important disease-protecting effects, conceivably acting in synergy with each other or with the fiber itself.

Whole-grain feeding studies and risk factors for chronic disease

A feeding study (18, 19) was carried out in 11 overweight, hyperinsulinemic, nondiabetic, free-living adults fed all food for 12 wk in a crossover design. In half the people, a base diet plus whole-grain foods was fed for 6 wk, there was a washout period of self-selected diet, and then the base diet plus refined-grain substitute foods was fed for the next 6 wk. In the other half of participants, the order was reversed. Increased satiety, reduced fasting insulin, improved insulin sensitivity (18), and increased serum enterolactone levels (19) were reported on the whole-grain diet compared with the refined-grain diet. All of these intermediate factors may be associated with reduced risk for ischemic heart disease and diabetes.

Another short-term randomized study (20) closely related to whole grain was done over 16 wk in 76 men with coronary artery disease. In the treated group, the investigators added to the subjects' free-living, self-chosen diet, a powder as a food supplement that was mostly a mixture of whole grains but also included some legumes and vegetables. There were improvements in various risk factors, including insulin metabolism and lipid oxidation status.

A series of feeding or supplement studies was done with whole oats, leading to the conclusion that oats and oat bran reduce serum cholesterol, particularly in participants whose cholesterol was higher at the outset (21–23). Similar results were found for whole barley (24). These studies led to the conclusion that soluble fiber influenced serum cholesterol. The specific fiber constituent believed to be influential is β-glucan, which is abundant in oats and barley but not wheat. Oat consumption also appears to reduce blood pressure in mild or borderline hypertension (25–27).

A study of whole rye compared with refined wheat was conducted in Finland (28). In these healthy young volunteers, small effects were seen, such as reduction of low-density lipoprotein cholesterol in men only. Serum enterolactone was consistently increased on the diets incorporating whole rye (29).

Several studies involving corn bran, oat bran, rice bran, or wheat germ have found improved cholesterol or glucose tolerance



(30). However, a 12-wk randomized crossover study in type 2 diabetic patients whose diet was supplemented with wheat bran failed to find any effect in a wide variety of lipid, blood pressure, glucose tolerance, or inflammatory factors (31).

Summary of whole-grain intake as an example of food synergy

Long-term observational studies found reduced chronic disease risk associated with consumption of mixed whole grains (primarily wheat and oats, plus some corn and rice) and with rye. The benefit was not found with refined grain containing only endosperm. Furthermore, the benefit was not found with cereal fiber from the endosperm but was found with the phytochemical-rich cereal fiber found in the whole grain, when eaten as part of whole foods. Small, randomized feeding studies extend the chain of studies relating to food synergy. After several weeks of consumption, mixed whole grains, oats, rye, the bran from several grains, and wheat germ, but not wheat bran, were seen to have a direct influence on factors believed to relate to long-term disease risk. Thus, the existing evidence suggests that the various grains and their parts act synergistically. The health benefit results from consuming a variety of whole grains, or the phytochemical-rich portions of them, but not from consuming the endosperm alone, cereal fiber from the endosperm, or wheat bran alone. Nevertheless, much remains to be learned about which grains, parts of grains, or constituents of grains are effective in promoting health.

PLANT-BASED DIETARY PATTERNS AND HEALTH: EXAMPLE OF FOOD SYNERGY

As with whole grains, other plant foods such as fruit, vegetables, nuts, legumes, spices, and herbs have apparently advantageous biological activity (32–36). Several largely plant-based dietary patterns are recognized for the longevity and generally better health of the populations that consume them. The Mediterranean diet (37) is high in olive oil, a variety of fresh fruit and vegetables, and, as recently as the 1960s, whole-grain foods. The traditional Japanese diet is particularly rich in soy products and other vegetables and low in meats (38). Seventh-day Adventists and Mormons typically eat vegetarian or near-vegetarian diets (39, 40).

Dietary patterns were studied with observational epidemiology using factor analysis, resulting in prudent and Western patterns (41). The prudent pattern was characterized by higher intake of vegetables, fruit, legumes, whole grains, fish, and poultry, whereas the Western pattern was characterized by higher intake of red meat, processed meat, refined grains, sweets and dessert, French fries, and high-fat dairy products (41). Disease occurrence according to these patterns was studied. The prudent pattern was associated with lower rates of diabetes (42), ischemic heart disease (41, 43), and colorectal cancer (44) but not breast cancer (45). Risk reductions in these studies were typically greater than is found in epidemiologic studies of single foods or of nutrients; thus, synergy is suggested.

A largely plant-based diet was studied in the Lyon Diet Heart Study (37), a 46-mo randomized study comparing a Mediterranean diet supplemented with fish oil capsules with a “prudent Western diet.” The study was carried out in men who had survived myocardial infarction. Men in the Mediterranean diet group had substantially reduced mortality and morbidity, compared with men in the control diet group. Examples were given earlier of diets eaten by

entire cultures (38–40) that tend to have reduced total mortality rates. Various epidemiologic studies have examined dietary patterns and found lower risk of disease or all-cause mortality for certain plant-based diets (41–44).

Further support for the benefit of plant-based diets comes from a large, randomized feeding study of blood pressure reduction, the 8-wk DASH study in 459 people (46). It found that a fruit and vegetable diet that included fish and some whole-grain foods reduced blood pressure in borderline and mildly hypertensive men and women. In this study even larger reductions in blood pressure were attained with the addition of low-fat dairy foods and the reduction of sodium.

RESEARCH STRATEGIES TO INFER ETIOLOGIC MECHANISMS

The finding that a food or food pattern is related to an outcome reflects the synergy of the constituents of the food or food pattern. Scientists may study nutrition and disease mechanisms by examining increasingly small parts of the food, and ultimately single biochemicals. Research strategies that start with foods or food patterns (synergies), then take these larger units apart to isolate simpler pathways might be termed “research from the top down” (47). In contrast, the commonly used reductionist strategy—in which individual building blocks of pathophysiologic pathways are investigated, then put together to form a more complex picture of nutrition and health—might be termed “research from the bottom up.” We view both top-down and bottom-up strategies as important and complementary. Increased understanding of nutrition can be obtained by studying and deconstructing foods and food patterns, as well as by studying nutrients.

Biochemical studies of foods

Approaches other than epidemiologic and feeding studies can also be helpful in the study of food synergy. Construction of indexes that summarize nutrients or biological activity is a potentially useful exercise that is midway between the study of foods and the study of individual nutrients. Such indexes may point out a new way to group foods or may point to characteristics of foods that are important. In either case, the index may help to take apart and more fully understand the synergy. One example of such an index is the glycemic index, which marks the increase in blood glucose in the hours after a meal, relative to the glucose-raising effect of refined wheat bread (48–50). Theoretically, a diet high in foods that stress glucose homeostasis may result in a state somewhat like mild diabetes, in which glucose is elevated through much of a 24-h period. This index was found to predict incident diabetes in some studies (51, 52) but not in another (53). The relation of the glycemic index to whole grain is of interest: the glycemic index apparently depends greatly on the particle size of grain products; thus, the glycemic index of whole-grain flour is little different from that of refined-grain flour (54, 55). This finding, coupled with the consistently reduced risk associated with whole-grain foods, suggests a synergy between foods rich in phytochemicals and foods with a low glycemic index. It raises an interesting question about the health effects of foods that are high in phytochemicals but have a high glycemic index, such as whole-grain flour, and foods that are low in phytochemicals but have a low glycemic index, such as pastas, which tend to be composed of resistant starches.

Another index is total antioxidant capacity. Total antioxidant capacity of a wide variety of plant foods was recently published




(56). Antioxidants with different partition coefficients will likely nestle next to each other in cellular phases and interfaces and recharge neighboring antioxidants in an integrated manner. Although it is simple to test the protective effect of single antioxidants, the association between dietary antioxidants and health may be difficult to find if hundreds of carotenoids, polyphenolic acids, sulfides, flavonoids, lignans, and so on are bioactive and work synergistically. Thus, the diet's total amount of electron-donating antioxidants (ie, reductants) derived from combinations of individual antioxidants that occur naturally in foods may be a better concept than individual dietary antioxidants. These concepts have not yet been studied in an epidemiologic database.

Another approach to deconstructing the synergies inherent in the study of whole foods is to fractionate the foods and study them in *in vitro* systems. Eberhardt et al (57) have used this approach with apples, relating extracts of apple with skin, apple without skin, and purified vitamin C, an important apple constituent, in *in vitro* systems of colon and hepatic cancer cell proliferation. Per 100 g of apple with skin, they found 290 mg of total phenolic compounds, 143 mg of flavonoids, and only 6 mg of vitamin C. Corresponding amounts in apple without skin were lower, 220, 98, and 4 mg, respectively. Total antioxidant capacity per 100 g apple with skin was 83 trolox equivalents, compared with 46 for the apple without skin, and <1 for 4–6 mg of purified vitamin C, with or without the apple skin. Therefore, an apple, particularly with skin, contributes much more antioxidant capacity, from a wide variety of phytochemicals, than is available from its most studied constituent, vitamin C. A health connection was suggested by the study of percent inhibition of proliferation of human colon and hepatic cancer cell lines. Using 50 mg/mL of apple extract with skin, inhibition was 43–57%, without skin it was 29–40%, and it was negligible using 6 mg of purified vitamin C.

Such *in vitro* studies hold promise for deconstructing food synergies but are also complex. The success of such studies depends on which food fractions are studied, which phytochemicals are investigated, and which *in vitro* model of pathophysiology is used. In their review of possible health benefits of fruit and vegetables, Van Duyn and Pivonka (58) provide a long list of candidate biochemicals that may positively influence health. These include sulfides (*Allium*), carotenoids, flavonoids, glucosinolates/indoles, phytoestrogens, isothiocyanates, phytosterols, protease inhibitors, phenols, capsaicin, resveratrol, anthocyanins, tannins, terpenes, dietary fiber, vitamins, and minerals. They also provide a list of mechanisms for protection from chronic disease that may serve as research targets, including clinical disease, protection from oxidation, improved insulin and fat metabolism, antiinflammatory action, anticlotting action, improved bowel function and microbial milieu, stimulation of protective enzymes, prevention of DNA damage, and enhancement of DNA repair. These observations may be helpful in designing *in vitro* studies.

CONCLUSIONS

There is considerable evidence for the existence of food synergy, the additive or more than additive influences of foods and food constituents on health. Such food synergy is not surprising given the complexity of both dietary patterns and individual foods. This complexity, compounded by the potential measurement error in diet assessment, adds to the difficulty of dietary research. Nevertheless, the synergy points toward consumption of diverse plant foods as important in maintaining health. These synergies are of

great public health interest. Eating all edible parts of diverse plant foods, including whole grain, is recommended to maintain advantageous biological activity while hindering possible side effects. At the same time, the synergies are of great scientific interest. Complementary study of food and food patterns and of nutrients and specific food constituents will enhance the understanding of diet and health. 

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