Chapter 14
Food Synergy: A Paradigm Shift in Nutrition Science

David R. Jacobs, Jr. and Norman J. Temple

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Key Points

- A major focus of nutrition science has centered on identifying the various macronutrients, vitamins, and minerals and then discovering their mode of action.
- Many associations between diet and risk of disease are best understood by looking at food as a whole and not merely as a collection of individual nutrients and other bioactive substances.
- Because of the limitations of epidemiology, it is extremely difficult in many cases to identify the substances in food that account for protection against disease. This is especially the case with phytochemical-rich plant foods, including fruit, vegetables, nuts, legumes, and whole-grain cereal foods.
- Research into foods and dietary patterns is needed. Such findings can be directly translated into public recommendations. They also serve as a scientific anchor point to which studies of food components must conform.

This chapter critically evaluates approaches to explaining the nature of the relationship between diet and disease. Most research has focused on studying single substances: macronutrients, micronutrients, as well as the many other bioactive

D.R. Jacobs, Jr., PhD (✉)
Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South Second Street, Suite 300, Minneapolis, MN 55454, USA
e-mail: Jacobs@epi.umn.edu

N.J. Temple, PhD
Centre for Science, Athabasca University, Athabasca, AB, T9S 3A3, Canada
e-mail: normant@athabascau.ca

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substances present in food, either beneficial or harmful. Here we argue the case for turning our attention to food as a whole and to dietary patterns. This concept, known as food synergy, defined as additive or more than additive influences of foods and food constituents on health, is a powerful tool to help explain many nutrition-related diseases and how best to prevent and treat them. This chapter is based on previous publications from one of us (DJ) [1–5].

14.1 The Concept of Nutrient Deficiency Diseases

Up until the 1950s a major focus of nutrition science centered on identifying the various vitamins and minerals and then discovering their mode of action. The underlying philosophy can be summarized as follows:

1. There is a simple cause-and-effect relationship between deficiency of a nutrient and the associated specific disease.
2. Each nutrient deficiency disease can be explained in terms of the role played by that nutrient, especially in the areas of biochemistry and physiology.
3. The nutrient deficiency can be prevented (and often reversed) by giving that nutrient in an isolated (pure) form.

Classic examples are vitamin C in relation to scurvy and iron in relation to anemia. This concept is still very much alive and is seen in the vitamin and mineral chapters of every textbook used in college nutrition courses. The concept can be applied not only to vitamins and minerals but also to protein and essential fats.

In recent years the concept has shown its continuing value in several areas. Research has firmly established that supplementary folic acid (a form of folate) is protective against neural tube defects (NTD), a group of congenital disorders that include spina bifida [6]. While NTD cannot be characterized as a vitamin-deficiency disease in the mother, it seems clear that a low maternal intake of folate creates a deficiency condition in the fetus that hinders normal development of the nervous system, thereby allowing the condition to emerge [7]. As a result of this discovery addition of folic acid to refined grain products is now mandatory in the USA and Canada. Research on vitamin D is another illustrative example. There was little progress in this area for several decades after the relationship between vitamin D and rickets was discovered. But in recent years strong evidence has emerged that the vitamin has a protective action against the risk of cancer and several other diseases (Chap. 17).

The relationship between single substances and disease risk extends well beyond disease protection by micronutrients; there are many other bioactive substances in food, either beneficial or harmful. Sodium (as salt) is an especially clear example of this. A high intake of the mineral, which is the case for the great majority of the population, plays an important role in the causation of hypertension ([8, 9]; see Chap. 11) and cardiovascular disease (CVD) [9, 10]. Strong evidence also suggests that salt significantly increases the risk of stomach cancer [11]. *Trans* fatty acids are

another example. This type of dietary fat adversely affects multiple cardiovascular risk factors and increases the risk of coronary heart disease (CHD) [12, 13]. Another bioactive substance in food is alcohol. High intakes cause multiple harmful effects. But as explained in the next chapter evidence has emerged over the last 2 decades that alcohol lowers the risk of CHD and possibly several other conditions. The active ingredient is alcohol itself, not the other substances commonly found in alcoholic beverages.

In many respects this reductionist approach to nutrition, called nutritionism by Scrinis [14], has not provided satisfactory answers to nutritional questions. Of special note, as discussed below, are studies in which nutrients were derived from food intake, found to be "protective" observationally (e.g., [15]), then used in higher doses as supplements in clinical trials. The purified nutrients in relatively high dose did not work as expected according to reductionist logic.

14.2 Food Synergy: An Alternative Paradigm

14.2.1 The Emergence of the Concept of Food Synergy

A strong argument has been made that to properly explain the many associations between diet and risk of disease we should view food as a whole, and not merely as a collection of individual nutrients and other bioactive substances. Over the past couple of decades this concept has emerged as an alternative concept to the one discussed above that focuses on individual nutrients and bioactive substances in food. In a nutshell—figuratively (and literally in the case of nuts)—food synergy has provided a better explanation for many nutrition-related diseases and how best to prevent and treat them. This represents a paradigm shift in our understanding of nutrition science.

Compelling support for food synergy comes from examining complex dietary patterns in relation to disease risk. The following examples illustrate this.

14.2.2 The Mediterranean Diet

One such dietary pattern that has been much studied in relation to CHD is the Mediterranean diet. While this diet varies from country to country around the Mediterranean, major features include a relatively high intake of vegetables, fruit, legumes, nuts, fish, whole-grain cereals, and olive oil. Conversely, the diet is typically low in meat (especially red meat).

Mente and colleagues carried out a systematic review on the relationship between diet and risk of CHD [16]. They examined some 26 nutrients, foods, and dietary patterns for the strength of the associations seen in cohort studies. They reported

that of all the associations with risk of CHD, either positive or negative, the strongest one was for the Mediterranean diet. The Mediterranean diet has the following attributes: first, it manifests a strong protection against the risk of CHD; and second, it has a complex nutritional composition, rich in phytochemicals but low in saturated fat, heme iron, and many other substances found in meat. It appears highly likely that multiple dietary components and multiple pathways are responsible. Based on this it can be reasonably argued that this diet–disease association provides strong support for the food synergy concept.

14.2.3 The Alternate Healthy Eating Index

Another healthy eating dietary pattern is the Alternate Healthy Eating Index [17]. Findings from the Nurses' Health Study showed that middle-aged women adhering to this dietary pattern have a much reduced risk of death from CVDs, from cancer, and from all causes combined [18].

14.2.4 The A Priori Healthy Diet Score

A novel index based only on foods is the a priori Healthy Diet Score [19]. It was formulated as the sum of ranks of food groups that had been judged to be favorable or unfavorable for health by knowledgeable persons experienced in nutrition and nutritional epidemiology. It was related to reduced odds for myocardial infarction [19], to changes in intermediate risk markers [20, 21], to common carotid intima media thickness, mediated by waist circumference [20], and to incident diabetes, mediated by waist circumference [22].

14.2.5 Western Dietary Pattern

Just as every movie with a hero also needs a villain, so a healthy dietary pattern needs an unhealthy one. That role is played by the "Western" pattern. Such a diet is high in red meat, processed meat, refined cereals, French fries, and desserts. A publication from the Nurses' Health Study linked this dietary pattern to an elevated risk of death from CVDs, from cancer, and from all causes combined [23].

14.2.6 Meat and Health

The above dietary patterns are wide ranging. The meat content of these dietary patterns is just one factor among many. However, there has been much interest for

many decades regarding the relationship between meat consumption and health. Vegetarian diets have been advocated by many people over the years as a healthier alternative to a meat-based diet. The most compelling evidence supporting the strong health benefits of a reduced intake of meat comes from a cohort study of half a million middle-aged and elderly Americans [24]. The findings clearly show that consumption of red meat (i.e., beef and pork) and processed meat are associated with higher risk of death from CVDs, from cancer, and from all causes combined.

There are several possible food constituent-based reasons that might explain these results, including the dietary intake of saturated fat, iron, and of various amino acids, and low intake of phytochemicals. The researchers in this study did adjust their hazard ratios for many confounding variables. This is important as meat consumption in this population was associated with a generally poor diet and unhealthy lifestyle. Many nutritional factors are probably involved in the connection between meat and risk of death from diverse causes. Accordingly, meat consumption should best be viewed from the perspective of food synergy.

14.2.7 DASH Diet

This diet was developed as a treatment for hypertension [25]. Key features are a generous intake of fruit, vegetables, and low-fat dairy products, combined with a reduced intake of meat, and therefore saturated fat. As described in Chap. 11 this food synergy approach has proven effective as a treatment for hypertension [25].

14.2.8 Food Synergy and Disease

In each of the above cases we see strong evidence that the relationship between diet and disease risk is best explained by focusing on foods rather than substances present in food. This applies both to prevention and to treatment. It also applies both to dietary patterns and to single food groups, such as meat. Our best explanation lies in the great complexity of food and dietary patterns, the thousands of different substances present, and the many pathways that connect food with the etiology of disease.

14.3 Food Synergy: A Research Pespective

14.3.1 The Limitations of Epidemiology

The evidence considered above supports the case for food synergy as an explanation for many diet–disease associations. However, there is a separate line of argument that also supports the food synergy concept. Nutrition research methods have

limited power to identify which nutrients or other bioactive substances in a complex food are likely to be responsible for particular health benefits. The reasons for this were explained in Chap. 1 by the authors of this chapter. The major problem is that nutrients and other bioactive substances are not distributed randomly in foods. Instead, they are mostly associated with each other. In other words, focusing on one substance causes confounding due to the presence of many other substances. This problem is especially acute with the multitude of substances found in fruit and vegetables and other phytochemical-rich plant foods. These include folate, vitamin C, potassium, fiber, and, of course, a great many other phytochemicals, many of which have been little studied or not even identified. Because of this, it is unlikely that epidemiological studies will ever be able to identify, for example, whether lycopene prevents prostate cancer or if α-carotene prevents colon cancer.

Cereal fiber and whole-grain cereal foods pose a similar challenge and an interesting counterpoint. This was illustrated in a study by Jacobs et al. [26]. They observed that dietary fiber from whole-grain cereals has a stronger protective association with disease than does the same amount of fiber from refined cereals. The proposed explanation is because of the phytochemicals present in whole grains. This indicates that epidemiological studies cannot even state with confidence whether dietary fiber really has an independent protective association with disease risk, beyond its direct effect in the large intestine. However, the suggestion is that there is something of health value in the whole grain, which is a conclusion about a food, rather than a nutrient.

We see, therefore, that the problem of confounding makes it extremely difficult to identify which nutrients or other bioactive substances deserve the credit for the health benefits of fruit, vegetables, and whole-grain cereals.

One obvious way to circumvent this problem is to carry out randomized clinical trials (RCTs) on single substances. However, these are extremely costly and usually take several years. They are only appropriate, therefore, when dealing with dietary components where there is already strong supporting evidence. Besides, as argued in depth in Chap. 1 on research design, the many differences between drugs and foods heavily influence research design. One must be very careful when undertaking an RCT on a single substance derived from food to be clear about whether it is even possible to answer the question being asked about the health implications of a single nutritional substance. As well, one must consider whether that RCT answer would help elucidate what food people should eat. We will now illustrate these points with some examples.

The saga of antioxidants provides perhaps the best illustration of the limits of epidemiology. It was discovered that β-carotene (derived as a weighted average of β-carotene-containing foods) was inversely related to lung cancer [15]. Subsequent epidemiological studies led to the widely held view that β-carotene may be effective as a chemopreventive agent against a range of cancers [27]. At around the same time epidemiological evidence linked two other antioxidant vitamins—vitamins C and E—with protection against disease. Vitamin C was reported to have a negative association with risk of cancer [28] while several cohort studies observed that intake of

vitamin E has a modest protective association with risk of CHD [16, 29]. Following these findings all three antioxidant vitamins were studied as disease preventatives; this involved administering these substances in a purified form at doses typically several times higher than the RDA. The results of long-term RCTs on β-carotene appeared in the mid-1990s and these have consistently shown that supplements are ineffective for the prevention of cancer [30]. Likewise, supplements of vitamin E have little or no preventive action against CHD [16]. Findings for all three antioxidants were actually adverse: an increase in total mortality of about 5–6% [31, 32]. The likely explanation for these findings is that the negative associations seen in epidemiological studies were entirely due to confounding by or interaction with phytochemicals and other substances that are found in the same foods as the antioxidant vitamins.

It is very likely that there is a complex food synergy at work in all the examples discussed above. In other words, the true reason that fruit, vegetables, and wholegrain cereals are protective against cancer and CHD is because of a complex interaction induced by a wide variety of nutrients and other bioactive substances. But let us suppose for one moment that the active ingredients are limited to a mere three or four phytochemicals. Because of the limitations of epidemiology, as explained above, it is extremely difficult to identify these substances with any confidence. For that reason, it hardly matters if the actual number of anticarcinogenic phytochemicals is 3 or 300. In contrast, a finding that a certain food or dietary pattern influences health is feasible, informative for future thinking, and of great practical value.

The limitations of epidemiology are also shown by studies investigating the relationship between homocysteine, folate, and CHD. Several epidemiological studies had revealed that blood homocysteine levels are correlated with risk of CHD and other CVDs [33, 34]. As supplements of folic acid (the form of folate used in supplements) are effective at lowering the blood homocysteine level [35, 36], it was hypothesized that this intervention will therefore be protective against CHD. Separate from this, epidemiological studies had indicated that dietary intake of folate has a strong inverse association with risk of CHD [16]. Indeed, in the systematic review carried out by Mente et al. [16], of all the nutrients, foods, and dietary patterns examined, folate had one of the strongest associations with risk of CHD, based on the findings from cohort studies. However, when the results of RCTs appeared, the optimistically expected results showed no indication that folic acid supplements prevent CHD [16, 35], and some RCTs have even suggested adverse effects on cancer and other diseases ([36, 37]; see Chap. 12 by Davis and Milner). The lesson here is that the studies that attempted to explain the association between blood homocysteine levels and risk of CHD did not confirm a simple, critical, causal role for homocysteine. The protective association between folate and CHD is most likely explained as one more case of confounding. These supplement studies do not necessarily imply no value for folate when obtained from foods, because nutrients obtained from (whole) foods are in natural balance, certified by evolution.

14.3.2 The Limitations of Mechanistic Research in Explaining the Effects of Food on Health

Some might argue that what cannot be achieved by epidemiology can be accomplished by laboratory-based research with the goal of explaining disease in terms of its causative mechanisms. For example, studies of the biochemical action of diverse phytochemicals on the processes of carcinogenesis will (supposedly) help identify which ones are potentially chemopreventive and should therefore be tested in RCTs. Similarly, while epidemiological research has provided indications that particular vitamins prevent CHD (and therefore, by implication, also help prevent atherosclerosis), this can be firmly established by studies of the processes of atherosclerosis at a cellular level.

Chapter 1 explained the serious limitations of mechanistic research on nutrients, often referred to as reductionism. We will illustrate this by returning to two of the antioxidant vitamins discussed above. Many studies were carried out during the 1980s that investigated the effects of β-carotene on body systems possibly related to cancer. This included studies of antioxidant action [38] and immune function [39, 40]. However, the dubious relevance of these studies to the relationship between diet and cancer became obvious when RCTs demonstrated that supplemental β-carotene does not prevent human cancer likewise with vitamin E. Here, the focus of research was on the ability of vitamin E to retard the oxidation of LDL [41]. But as vitamin E has shown little or no effectiveness in preventing CHD, it is hard to discern the practical value of the mechanistic research.

14.4 Future Research Directions

While there is nothing intrinsically wrong with an approach that searches for simple answers and roles of specific molecules, there is much to be said for accepting a finding about a food or food pattern as important information that answers a nutritional question. It is not necessary to reduce foods to constituents in order to understand that diet does affect health and to make policy for better eating. We should take a food synergy perspective, think foods first [4], working on the assumption that as we have little idea which substances are involved, the only practical approach is to assume that all nutrients and other bioactive substances in phytochemical-rich plant foods play a role in giving protection against cancer, CHD, and other chronic diseases. Even if there are simple reductionist answers to nutritional questions in generally well-nourished people, due to practical circumstances of solving the immensely complex problem of interacting food constituents, we are unlikely to make major progress in the reductionist mode in the near future.

What is the best way for researchers to design investigations to achieve a better understanding of how to maintain health? Based on the arguments presented here the answer lies in a two-stage strategy. First, epidemiological studies are required

to identify which dietary patterns or foods have an apparent cause-and-effect relationship with disease. Such studies are quite reliable for that purpose. In the second stage RCTs need to be carried out in order to test either whole diets or individual foods.

Carrying out such RCTs presents serious challenges. These would need to be long term. Moreover, blinding is all but impossible as it is fairly obvious what is being eaten. Compliance to fixed diets may be an even larger problem. Imagine requiring that for several years coffee drinkers abstain from coffee or those who dislike coffee consume it regularly; or that meat lovers become vegetarian or vegetarians omnivores. However, such studies are feasible. For example, a 4-month trial using the DASH diet as a treatment for elevated blood pressure achieved excellent compliance [42]. The Women's Health Initiative set a much more ambitious target with the aim of persuading healthy women to make major changes in their diets and maintain them for 6 year [43]. For example, they aimed to reduce total fat intake to 20% of calories. However, the actual change was only about half of this.

14.5 Conclusions

Food which emanates from a living organism is a mixture of constituents, but not a random mixture. Rather, the particular mixture has proven adequate through evolution for the life of the organism eaten. To the extent that the organism has been eaten for a long time, evolution has also tested the mixture of constituents as a food for the eater.

There is still much to be gained from research that investigates individual nutrients and bioactive substances in food and then attempts to determine their role in health and disease. This is especially valuable in cases where problems of confounding are relatively small and it is therefore possible to investigate nutrients or other substances as single variables. An interesting example is vitamin D, where sun exposure is important in addition to food.

In several cases research on single nutrients has lead to important measures that have improved public health. We see this with folate in relation to spina bifida, although there are reservations about whether the good findings for NTDs carry over to the whole population for protection from chronic diseases of adulthood. Other notable cases of single-nutrient solutions to health problems are iron supplementation for iron deficiency anemia and vitamin B_{12} supplementation for the elderly. However, these instances usually occur in situations of relative deficiency.

We must stay open to the possibility of more such cases appearing. It is entirely possible that a small number of phytochemicals will be proven to have valuable health-enhancing actions. In such cases they could have potential as drugs. Indeed, some evidence of this has already been documented: lutein is showing promise for improving eye health [44, 45] and soy isoflavones for improving bone health [46]. Whether these nutrients would be useful as supplements in the general population is an unanswered question; or, perhaps they should be thought of as drugs.

But, increasingly, we are seeing the limitations of this approach. There is a strong case for placing much more emphasis on food synergy and regarding findings for foods or dietary patterns as final answers to questions. This can include dietary patterns, such as the Mediterranean diet, or single foods, such as red meat. It is not clear whether food synergy reflects a true mathematical synergistic relationship (i.e., the whole risk or benefit is greater than the sum of the parts) or else is simply an additive effect. At minimum, though, even in the absence of mathematical synergy, foods are complex mixtures, tested by evolution, which we would not come to by constituting them de novo from individual constituents.

We are sympathetic to attempts to properly understand the detailed causes of chronic diseases. However, we believe that the complexity of metabolism and pathology is such that nutrition research is a long way from being able to achieve this goal. Epidemiologic studies of nutrients are often misleading because they miss the context of the whole food and diet pattern. In other words, both epidemiologic study of nutrients and mechanistic research are inferior strategies for achieving valuable breakthroughs that lead to improvements in public health through improved diet. Despite that, mechanistic research attracts far more resources than food-based research. We conclude, therefore, that improved infrastructure for food-oriented research would be most valuable.

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