Food Synergy: A Paradigm Shift in Nutrition Science

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Key Points

- A major focus of nutrition science has centered on identifying the various macronutrients, vitamins, and minerals and then investigating 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.
- More research into foods and dietary patterns is needed.
- The findings can be directly translated into dietary 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 historically has focused on studying single substances: macronutrients, micronutrients, as well as the many other bioactive 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. The constituents of foods and patterns act in concert to influence health. This concept, known as food synergy, defined as an 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. Many ideas in this chapter were stated some years ago by one of us (DJ) [1–5]. Other authors endorse this concept [6–8].

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

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action [7]. 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. Folate illustrates this well. 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 [9]. 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 [10]. As a result of this discovery, mandatory addition of folic acid to refined grain products started in 1998 in the USA and Canada.

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 ([11, 12]; see Chap. 9) and cardiovascular disease (CVD) [12, 13]. Strong evidence also suggests that salt significantly increases the risk of stomach cancer [14]. Jacobson described the practical and political issues, and some limited success, in working towards salt reduction by the food industry [15]. *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) [16, 17]. Another bioactive substance in food is alcohol. High intakes cause multiple harmful effects. The adverse effect of the alcohol itself is almost certainly the cause of higher disease rates in heavy drinkers. But as explained in Chap. 12 evidence has emerged over recent decades that alcohol lowers the risk of CHD and possibly several other conditions. The active ingredient could be alcohol itself, but the production of alcoholic beverages extracts many phytochemicals from the plant from which it is made, such as barley or corn [18], and these might explain the epidemiologic associations. The small amount of alcohol in a single drink could be beneficial or adverse, but if it is adverse, the simultaneous provision of phytochemicals may provide a net benefit up to a certain amount drunk. In fact, this interplay between the alcohol and phytochemical constituents of alcoholic beverages is a good example of food synergy.

In many respects, this reductionist approach to nutrition, called nutritionism by Scrinis [19], 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., [20]), then used in higher doses as supplements in clinical trials. The purified nutrients in relatively high dose did not work as predicted according to reductionist logic.

Food Synergy: An Alternative Paradigm

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.

The Mediterranean Diet

One such dietary pattern that has been much studied in relation to CHD is the Mediterranean diet. This diet and its effects on health is discussed in detail in Chap. 16. While this diet varies from country to country around the Mediterranean, major features include a relatively high intake of vegetables, fruit, legumes, nuts, fish, cereals, and olive oil. Conversely, the diet is typically low in meat, especially red meat, such as beef and pork, and processed meat.

Mente and colleagues carried out a systematic review on the relationship between diet and risk of CHD [21]. 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 diet has the following attributes: first, it manifests 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. Indeed, the large, long-term PREDIMED randomized controlled trial found that the Mediterranean diet protects against total CVD [22].

The Alternate Healthy Eating Index

Another healthy eating dietary pattern is the Alternate Healthy Eating Index, as revised in 2010 [23]. 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 [24], as well as other outcomes such as physical function impairment [25].

The A Priori Diet Quality Score

A novel index based only on foods is the A Priori Diet Quality Score [26]. 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 reported as being related to reduced odds for myocardial infarction [26], CVD [27], changes in intermediate risk markers [28, 29], common carotid intima media thickness, mediated by waist circumference [28], incident diabetes [30, 31], and loss of kidney function [32].

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, cancer, and all causes combined [33].

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 [34]. The findings clearly show that consumption of red meat and processed meat are associated with a higher risk of death from CVDs, from cancer, and from all causes combined.

The Seventh-Day Adventist religion includes scriptural mandates to eat a vegetarian diet. Findings from the Adventist Health Study 2, in which many participants ate a vegetarian diet, observed lower all-cause mortality for vegetarians [35], and that in this population both ultra-processed food and red meat consumption are associated with excess total mortality [36].

There are several possible food constituents that might explain these results, including saturated fat, iron, and various amino acids, and a 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 is 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.

DASH Diet

This diet was developed as a treatment for hypertension [37]. 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. 17 this food synergy approach has proven effective as a treatment for hypertension [37].

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 to both prevention and 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.

Food Synergy: A Research Perspective

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 or for increasing the risk of particular diseases. 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 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 determine, for

example, whether lycopene prevents prostate cancer or if alpha-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. [38]. 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 the findings from that RCT 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 beta-carotene (derived as a weighted average of beta-carotene-containing foods) was inversely related to lung cancer [20]. Subsequent epidemiological studies led to the widely held view that beta-carotene may be effective as a chemopreventive agent against a range of cancers [39]. At around the same time epidemiological evidence linked two other antioxidant vitamins—C and E—with protection against disease. Vitamin C was reported to have a negative association with risk of cancer [40] while several cohort studies observed that intake of vitamin E has a modest protective association with risk of CHD [41]. 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 beta-carotene appeared in the mid-1990s and these have consistently shown that supplements are ineffective for the prevention of cancer [42]. Likewise, supplements of vitamin E have little or no preventive action against CHD [21]. Findings for all three antioxidants were actually adverse: an increase in total mortality of about 2–5% [43]. 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 fruits, vegetables, and whole-grain 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 [44, 45]. As supplements of folic acid (the form of folate used in supplements) are effective at lowering the blood homocysteine level [46, 47], 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 [21]. Indeed, in the systematic review carried out by Mente et al. [21], based on the findings from cohort studies, of all the nutrients, foods, and dietary patterns examined, folate had one of the strongest associations with risk of CHD. However, when the results of RCTs appeared, contrary to expectations, results showed no indication that folic acid supplements prevent CHD [21, 46], and some RCTs have even suggested adverse effects on cancer and other diseases ([47, 48]; see Chap. 10). 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. In other words, folate is present in the same foods as the substances in foods that are protective against CHD. 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.

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 beta-carotene on body systems possibly related to cancer. This included studies of antioxidant action [49] and immune function [50, 51]. However, the dubious relevance of these studies to the relationship between diet and cancer became obvious when RCTs demonstrated that supplemental beta-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 [52]. But as vitamin E has shown little or no effectiveness in preventing CHD, it is hard to discern the practical value of mechanistic research.

Future Research Directions

There is nothing intrinsically wrong with an approach that searches for the roles of specific molecules. But there is much to be said for seeking findings about foods or food patterns; this is because this can generate valuable information that answers nutritional questions. It is not necessary to reduce foods to constituents in order to understand that diet does affect health and to formulate 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 near future based on a strategy that centers on a reductionist approach.

What is the best way for researchers to design investigations in order 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 [53]. 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 years [54]. For example, they aimed to reduce total fat intake to 20% of calories. However, the actual change was only about half of this. The PREDIMED study [22] was successfully carried out with a mean follow-up of approximately 5 years.

Top Down Approach

Tapsell et al. [6] pointed out that dietary guidelines are intended to promote healthy eating so as to avoid chronic disease. They expressed a need for statements about specific foods or food groups. Following a recommendation by Jacobs and Steffen [3], they carefully detailed investigations that use a "top down approach" of diet patterns, then individual foods, and then nutrients in order to understand mechanisms. On the one hand, membership of a food group within a diet pattern is a sort of endorsement of that food group as a part of the diet pattern. That level of endorsement might be sufficient advice to justify consumption or not of a food in question. However, it may be useful to make statements about individual food groups without much reference to the overall diet (that is, no matter what the rest of the diet is). Tapsell et al. [6] then asserted that statements about nutrients may be helpful in understanding the mechanics of diet and health, and working from the bottom up in making recommendations for what foods to consume. This scenario may also be applied in the case of Fardet and Rock's [8] 3 V's: "vegetal" (eat plant foods), "varie" (vary what you eat), and "vrai" (eat real food, in a form close to "as grown"). In making food choices, which "vegetal" foods should be preferred? Does eating a lot of brands or types of junk food satisfy "varie"? And is "vrai" violated if whole-grain food is ground into meal or flour?

These issues lead to a desire to go beyond diet patterns, and a suggestion to endorse nutrient-based guidelines. Tapsell et al. [6] focused on three examples where they consider that a nutrient is important in dietary guidelines. These are saturated fat, refined and added sugar, and salt. They noted that the food industry has capitalized on the fact that fat, sugar, and salt tend to make food more palatable. For saturated fat, they argued that a dietary guideline limitation is needed and effective because saturated fat is a strong indicator of demonized foods, such as cheese pizza (also high in refined grain and salt). But Choi et al. [55] showed that purely limiting saturated fat was not related to future CVD, even though it was related to lower low-density lipoprotein cholesterol, whereas a general plant-centered pattern was related to incident CHD and stroke, and to incident total CVD [36]. Furthermore, perhaps in order to further simplify the message, Fardet and Rock [56] asserted that

the matrix of real food is the single most important aspect of food. While we agree that the food matrix is an important consideration, we think that this assertion [56] dilutes the power of the food synergy argument. Thus, we acknowledge the need for greater depth of understanding of what to eat and support further research into the subtleties of the resulting arguments.

Conclusion

Food that 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 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 nutrient 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 some 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 [57, 58] and soy isoflavones for improving bone health [59]. Whether these substances 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 a 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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