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**Supplement–What Comes First: The Food or the Nutrient?**

# What Comes First: The Food or the Nutrient? Executive Summary of a Symposium[1–3]

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## Abstract

This article summarizes background materials and presentations at a symposium that considered the issue of the role of foods and dietary patterns vs. nutrients in relation to chronic disease risk. A model of food synergy is presented as a basis for studying whole foods and dietary patterns. Findings from a series of studies of walnuts were presented and support the concept that walnuts are a healthy food, with specific benefits in a mouse model of breast cancer growth, reductions in cardiovascular disease risk factors in humans, and motor performance and in vitro, in vivo, and ex vivo cellular response to challenge in an aged-rat model. J. Nutr. 144: 543S–546S, 2014.

## Introduction

The history of nutrition research and communication of nutrition policy with the public since the early 1900s was punctuated with the remarkable chemical understanding of vitamins and that deficiency of these vitamins could cause severe diseases such as scurvy, pellagra, beri-beri, and rickets. At the same time, the role of the food industry expanded greatly as food science and technology progressed to the point where food could be tailored for a desired taste, texture, and shelf life. In the case of grains, roller milling allowed industry to centralize business, and white flour became very popular, despite the recognition that excluding the bran and the germ from the flour led to loss of vitamins. These 2 streams—recognition of the importance of selected nutrients in protection against disease and industrialization of food production and delivery to consumers—came together in enrichment and fortification programs, wherein isolated vitamins and minerals were added back to food. This series of events has been well documented by many authors; for example, Messina et al. (1) and Jacobs and Steffen (2) discussed these points.

The view of using nutrients as a way to solve disease problems extended to heart disease; it was fostered by cross-country ecologic studies (3,4) [see Blackburn and Labarthe (5) for a description of the controversy concerning these studies]. There followed a series of elegant and influential experiments (6) that pointed to total fat or saturated fat as good indices of an atherogenic diet. Studies of micronutrients and other bioactive substances raised interest in individual substances that could be important in cancer (7). In totality, the focus on nutrients has led to a way of thinking about diet from low fat to low carbohydrate to low glycemic index to functional foods. Each of these foci might be considered a search for a "silver bullet," the 1 component of the diet that is most important, or at least has substantial importance in and of itself. In recent years, there has been a call to return to food as the unit of analysis in nutrition (8–10). Thus, the concept of the different roles of foods vs. nutrients in nutrition research and in public messaging is in need of discussion.

A scientific symposium was organized on the theme, "Do we need nutrients to talk about food?" This symposium, entitled "What Comes First: The Food or the Nutrient?," was held as a

[1] Presented at ''What Comes First: The Food or the Nutrient?,'' as a satellite session to the American Society for Nutrition Scientific Sessions and Annual Meeting at Experimental Biology held in Boston, MA, on 19 April 2013. The satellite session and supplement publication were supported by the California Walnut Commission (CWC). All session speakers received travel funding and/or honoraria for participation in the meeting and manuscript preparation. The views expressed are those of the authors. Because the symposium was held on the day of the city lockdown in the search for the Boston Marathon bomber, presentation was to a limited audience; Dr. Katz was not present. The recorded presentations are available at http://www.nutrition.org/education-and-professional-development/archived-content-from-past-meetings-and-professional-development-events/asn-at-eb-2013/recorded-sessions/satellite-session-what-comes-first-the-food-or-the-nutrient/. The CWC and all of the presenters express their solidarity with the people of Boston, and particularly with those killed or injured at the Boston Marathon. The Supplement Coordinator for this supplement was David R. Jacobs Jr. Supplement Coordinator disclosures: David R. Jacobs Jr., PhD, is a consultant at the California Walnut Commission (member of the Scientific Advisory Council). Dr. Jacobs' travel expense to Experimental Biology 2013 was paid by the California Walnut Commission. Dr. Jacobs is otherwise employed by the University of Minnesota and is supported by government grants. This supplement is the responsibility of the Guest Editor to whom the Editor of *The Journal of Nutrition* has delegated supervision of both technical conformity to the published regulations of *The Journal of Nutrition* and general oversight of the scientific merit of each article. The Guest Editor for this supplement was Kevin Schalinske. Guest Editor disclosure: Kevin Schalinske had no conflicts to disclose. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of *The Journal of Nutrition*.

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satellite session before the ASN and Experimental Biology meetings on 19 April 2013.

Presenting at the conference were the following:

- David R. Jacobs Jr., PhD, Professor, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota (moderator)
- W. Elaine Hardman, PhD, Professor, Department of Biochemistry and Microbiology, Byrd Biotechnology Science Center, Marshall University School of Medicine
- Penny M. Kris-Etherton, PhD, RD, Distinguished Professor of Nutrition, Department of Nutritional Sciences, Penn State University
- Barbara Shukitt-Hale, PhD, Research Psychologist, Neuroscience Lab, USDA, Human Nutrition Research Center on Aging at Tufts University
- David L. Katz, MD, MPH, FACPM, FACP, Director, Yale University Prevention Research Center, and Director, Integrative Medicine Center at Griffin Hospital

This article presents background materials for this symposium and an overview of the 3 presentations, which are published as separate articles in this supplement (11–13). A fifth article included herein was scheduled but was not actually presented at the symposium (14).

## Conceptual Basis for Food and Diet Pattern as the Appropriate Unit of Conceptualization and Communication

The concept of food synergy leads to the conclusion that each food is a fundamental and integral unit for both study and communication. "Food synergy" is defined as the concerted action on health of compounds within foods and of foods working together in diet patterns in health. This concept is based on the observation that food consists of complex, nonrandom mixtures of compounds that serve the life of the organism eaten, as developed under evolutionary control (15,16). Just as the chemical compounds in food function act as a unit, epidemiologic studies have identified dietary patterns that consistently predict future chronic disease, probably for similar reasons of combining non–randomly selected mixtures.

Food is extraordinarily complex. Although a few foods are a single molecule (e.g., $H_2O$, NaCl), most foods are organisms or derived from organisms in all the complexity that life requires. Furthermore, even small differences in molecules can matter, considering as 1 example the tiny difference of the location of a single double bond in 18:1 *cis* vs. 18:1 *trans*. There are at least thousands of compounds in each morsel of most food, counting every possible variant in each molecule.

Digestion breaks down dietary protein, fat, and carbohydrate into simpler compounds. However, other compounds, such as polyphenols, do survive digestion, at least in conjugated form, and reach cellular targets in vivo. For example, Natella et al. (17) showed that hydroxycinnamic acids in coffee are absorbed and bind to LDL particles and reduce oxidation. In this acute study, after ingestion of a single cup of coffee, the concentrations of conjugated caffeic acid, p-coumaric acid, and ferulic acid in LDL particles resembled that of the original dietary compounds in coffee. Jacobs and Tapsell (8) reviewed other studies in which the whole food was biologically more than the sum of the parts. However, many randomized clinical trials of isolated supplemental nutrients have not been successful. $\beta$-Carotene estimated from food (thereby indicating a diet high in plant food) predicted lung cancer, whereas supplemental isolated $\beta$-carotene increased mortality in randomized clinical trials (18).

## A Comprehensive Mathematical Model for Food Synergy

A mathematical view of food synergy would model it as additive or as more than additive health effects of food constituents and dietary patterns. Here the entire diet is modeled in food groups or in compounds. For example, in the purely additive model for a dietary pattern with $k$ food groups (denoted by $F_j$, $j$ = 1 to $k$, with $k$ being a number such as 10, 30, or 50, depending on how many food groups are selected to represent the full diet), a regression equation would be as follows:

$$\text{Disease Risk} = a + \sum_{j=1 \text{ to } k} b_j F_j.$$

In the same algebraic equation, $F_j$ could denote compounds in the assemblage of foods in the whole diet, but here, $k$ would be a number in the thousands. This model assumes independence of all components, with the coefficients $b_j$ reflecting the correlations among the variables $F_j$. This model would seem at first look to support statements about individual foods, nutrients, or other compounds. Yet, risk varies by food or diet pattern even in this simplistic formulation, which does not contain any terms for mathematical synergy, because different patterns contain different foods, different foods contain different compounds, and all of this (composition of a dietary pattern and, even more so, composition of a food) is not random. Thus, even without formal mathematical synergy, disease risk is an extremely complex phenomenon if the whole diet is considered. Introducing mathematical interactions into the equation leads to the following equation:

$$\begin{aligned}\text{Disease Risk} = {} & a + \sum_{j=1 \text{ to } k} b_j F_j \\ & + \sum_{j=1 \text{ to } k} \sum_{m=j+1 \text{ to } k} b_{jm} F_j F_m \\ & + \sum_{j=1 \text{ to } k} \sum_{m=j+1 \text{ to } k} \sum_{s=m+1 \text{ to } k} b_{jms} F_j F_m F_s \ldots,\end{aligned}$$

where the coefficients $b_{jm}$ and $b_{jms}$ represent interactive effects (where a positive coefficient represents synergy and a negative coefficient represents antagonism). Is it believable that all of these are 0 or even small? In a sense, dietary pattern formulations represent whole diets, and statements about coefficients of individual food groups would be feasible in the purely additive model (although not necessarily easy to interpret), but it is difficult even to imagine a model representing all of the thousands of compounds in a whole diet.

## Consequences of Nutrient Focus

There are some positive aspects from a nutrient focus. Such a focus helps to avoid deficiency conditions, which is perhaps most important in those with the least resources, and in that way fosters public health equity. It is relatively simple to ensure or at least assess dietary adequacy, taking this problem 1 nutrient at a time. For the food industry, it is relatively easy to characterize each product in a uniform way, as is evidenced by current nutrition labels. Also, for the scientist, the nutrient focus may help to uncover simple, independent associations.

However, there are clear downsides to a nutrient focus. Some would say that even scientists are confused when thinking purely in nutrient terms. Studies of nutrients have a tendency to contradict each other depending on whether they are performed in vitro, in vivo in animals, or in vivo in humans. Epidemiologic studies are often inconsistent. The statement that a food focus would be less confusing assumes that at some food level, most likely the level of

dietary patterns, findings would be consistent. A high level of consistency is indeed seen for dietary pattern studies of disease risk (19,20). Ensuring adequacy of a whole diet is not as simple as avoiding deficiency. Regulators require clear and legally defensible rules, yet these can be internally inconsistent and difficult for the food industry, which is the source of virtually all of our food. The regulatory problem is not simple in part because a nutrient focus is important to regulation in some cases—for example, for food safety—but may not actually represent disease risk well. Industry, which is trying to make a profit (needed to keep companies in business to supply food to the world), thinks of ways to increase nutrients, without necessarily focusing on foods. Marketing is not simple, and the bottom-line financial focus can lead to advertising aimed at attaining a market edge over competitors. A breakfast cereal box that advertises food (e.g., whole grain, nuts, and berries), less processed, high fiber, antioxidants (e.g., vitamins C and E), and low fat (e.g., 3 g total) must be interpreted by consumers. Such a label may well appeal to consumers with different personal knowledge bases and priorities in life, but there are subtle meanings and scientific questions about all of these items except for the simple fact of what foods are contained in the product. The public is definitely confused. The low-fat message promulgated in earlier versions of the U.S. *Dietary Guidelines for Americans* would logically recommend avoiding fatty olives and nuts, although there is much evidence that they are valuable foods. The proliferation of popular diets [in addition to low-fat, low-carbohydrate, and low-glycemic–index diets there are the Paleolithic diet, variations on vegetarian diets, the Portfolio diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and the Mediterranean diet, to mention just a few] may contribute to this confusion.

## What Do We Need for Nutrition Knowledge and Public Health to Advance?

People talk about "basic nutrition" as if it were something simple. In the food synergy view, there is no such thing as basic nutrition; food and nutrition are very complex. Food is much more complex than drugs, yet is much less researched (and is much harder to research) (16). It is questionable whether the consumer can correctly put together a diet based on an understanding of how to get needed nutrients from combinations of foods. It would at least be more direct to give advice specifically about foods. It can be argued that the most important consumer knowledge would be which foods relate to what long-term health outcomes.

## Does a Study Have to Have a Nutrient or Mechanistic Answer to Be Valuable?

This symposium is a discussion of the assertion that a primary point for nutritional discovery is how food relates to chronic disease, using the walnut as a focus for this discussion. It is not easy to fund research that has a purely food focus; indeed, 3 of the articles in this symposium (11–13) discuss walnuts and other food from the perspective of alternative food constituents vs. the whole walnut. Furthermore, although the food synergy concept does promote food as the primary unit of analysis in nutrition research, it is recognized that food does consist of biocompounds, and that at some level the effect of food on health is through those compounds. In this author's experience as a grant reviewer, the idea that a food or diet pattern effect is a complete answer to a question is not well accepted. Many scientists believe that a finding about food or diet pattern in relation to health is only a hint, the beginning of the process, a statement of the question, and that the more important question is why the food or diet pattern is related to health or disease. Hardman (11), Kris-Etherton (12), and Poulose et al. (13) all report studies in which walnuts had a variety of beneficial effects. An example of a highly successful food-based study of long-term cardiovascular diseases is the randomized clinical trial Prevención con Dieta Mediterránea (PREDIMED) (21). Participants included >7000 Spanish men and women at high cardiovascular disease risk, but who were free of any known previous cardiovascular disease event. They were advised to eat a low(er) fat diet or to eat a Mediterranean diet, the latter coupled with either supplemental extra-virgin olive oil or a supplemental mixture of walnuts, almonds, and hazelnuts, then followed for ~5 y. Cardiovascular disease incidence was reduced in both of the Mediterranean diet groups compared with the group that received advice for a lower-fat diet (although the reference group did not achieve what most consider to be "low fat"). This study has added information about many aspects of the development of different conditions that lead to cardiovascular disease events, including inflammatory conditions, metabolic syndrome, and diabetes, but did not look at specific aspects of the Mediterranean diet, olive oil, or tree nuts. There is ambiguity as to whether the advice to eat a Mediterranean diet, the extra-virgin olive oil supplement, or the tree nut supplement is the basis for the cardiovascular benefits of this highly successful study. Yet, in this author's opinion, this type of study sets important mileposts for knowing certain aspects of how food affects long-term health.

The 2015 Dietary Guidelines Advisory Committee established 3 work groups to shape the report. Work groups are as follows: *1*) Environmental Determinants of Food, Diet, and Health; *2*) Dietary Patterns and Quality and Optimization through Lifestyle Behavior Change; and *3*) Foods, Beverages, and Nutrients and Their Impact on Health Outcomes. The *5* primary topic areas to be addressed by the 2015 Dietary Guidelines Advisory Committee are food environment, physical activity environment, agriculture/aquaculture sustainability, food systems, and food safety. Walnuts/walnut production relate to all of these areas. Relative to the food environment, walnut production in the United States has increased from 298,000 metric tons in 2007/2008 to 451,000 metric tons in 2012/2013 (22,23), which reflects an increase in consumption. The California Walnut Sustainable Program is economically viable for walnut growers, follows environmentally responsible practices, and is socially acceptable because it improves quality of life for growers, neighbors, consumers, and the public. The California walnut industry's sustainability project defines best production practices by focusing on integrated pest management, energy efficiency, water quality, air quality, nutrient efficiency, and food safety. By using these best practices, the walnut food system has provided consumers with safe and nutritious walnuts and walnut products. Relative to the impact of walnut consumption on diet quality, there is research that shows that the nutrient profile of the diet is improved with both nut consumption (24,25) and walnut consumption (26). Walnut consumption is associated with higher intakes of PUFAs, omega-3 FAs, and dietary fiber. Finally, there is an impressive evidence base that indicates that walnuts have many health benefits, which are addressed in the current supplement and summarized below.

## Symposium Papers

Hardman (11) presented findings from a series of murine experiments with walnuts added to the diet, compared with either corn

oil or canola oil. The animal model relied on implanted breast cancer tumors. She showed that tumor growth inhibition was greater with whole walnuts than with canola oil supplementation, thereby ruling out $\alpha$-linolenic acid (18:3n−3) as the sole effector. Both walnut and canola oil treatments were superior to the reference treatment, corn oil, in terms of implanted tumor growth.

Kris-Etherton (12) briefly reviewed epidemiologic evidence for the long-term benefits of tree nut consumption, as well as making a comprehensive statement about the PREDIMED study. She comprehensively reviewed acute or short-term studies in which walnuts decreased LDL cholesterol and blood pressure, as well as improving endothelial function, decreasing oxidative stress and inflammation, and increasing cholesterol efflux. Most of these findings were dose-dependent (increased with increasing walnut intake, up to ~56 g/d). In many studies, walnut oil also was studied and showed effects similar to or smaller than the results for whole walnut.

Poulose et al. (13) studied an aged-rat model of stress-induced neurotoxicity in BV-2 microglial cells. The authors reviewed earlier in vitro and in vivo studies of walnut consumption on age-associated declines in cognition and neural function in rats, using outcomes such as motor performance in the in vivo studies. They then reported ex vivo studies of BV-2 cells extracted from 19-mo-old rats fed a walnut diet or a control diet. They stated that serum from the walnut diet (6% and 9%) significantly attenuated LPS-induced nitrite release and reduced proinflammatory TNF-$\alpha$, cyclooxygenase 2 (COX-2), and inducible NO synthase.

Katz (14) briefly reviewed studies of walnuts and general dietary pattern and lifestyle studies in relation to type 2 diabetes and related chronic diseases. His own studies with walnut intake in middle-aged men and women with diabetes, or without diabetes but with central obesity, found improved flow-mediated dilation, a measure of endothelial function. In general, his opinion is that many chronic diseases in Western countries are caused by diet. He stated, in line with the food synergy concept, that we cannot say with any degree of confidence what "best practices" are for dietary intake, but that the general answer is well understood. He recommended eating preferably "minimally processed foods direct from nature, and food made up of such ingredients" in a plant-centered diet.

The presenters at this symposium concluded that studies of foods and dietary patterns are much needed for improving understanding of nutrition and for providing good advice to consumers. A series of theoretical models were presented that support this contention. Furthermore, empirical studies were presented showing that the walnut is an example of a well-studied food that has a variety of short- and long-term beneficial effects on disease risk.


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