



# Integrating the Totality of Food and Nutrition Evidence for Public Health Decision Making and Communication

JUAN L. NAVIA,<sup>1</sup> TIM BYERS,<sup>2</sup> DARINKA DJORDJEVIC,<sup>3</sup> ERIC HENTGES,<sup>3</sup>  
JANET KING,<sup>4</sup> DAVID KLURFELD,<sup>5</sup> CRAIG LLEWELLYN,<sup>6</sup> JOHN MILNER,<sup>7</sup>  
DANIEL SKRYPEC,<sup>6</sup> and DOUGLAS WEED<sup>8</sup>

<sup>1</sup>McNeil Nutritionals LLC, 601 Office Center Drive, Ft. Washington, Pennsylvania

<sup>2</sup>University of Colorado, MS F-519, Room W6112, P.O. Box 6508, 13001 East 17th Place Aurora, Colorado

<sup>3</sup>ILSI North America, 1156 Fifteenth Street, NW, Suite 200, Washington, DC

<sup>4</sup>Children's Hospital Oakland Research Institute, 5700 MLK Jr. Way, Oakland, California

<sup>5</sup>USDA Agricultural Research Service, 5601 Sunnyside Avenue, Beltsville, Maryland

<sup>6</sup>Kraft Foods, 801 Waukegan Road, Glenview, Illinois

<sup>7</sup>National Institutes of Health, 6130 Executive Blvd., Suite 3160, Rockville, Maryland

<sup>8</sup>DLW Consulting Services LLC, 3706 Farragut Avenue, Kensington, Maryland

*The interpretation and integration of epidemiological studies detecting weak associations (RR <2) with data from other study designs (e.g., animal models and human intervention trials) is both challenging and vital for making science-based dietary recommendations in the nutrition and food safety communities. The 2008 ILSI North America "Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research" workshop provided an overview of epidemiological methods, and case-study examples of how weak associations have been incorporated into decision making for nutritional recommendations. Based on the workshop presentations and dialogue among the participants, three clear strategies were provided for the use of weak associations in informing nutritional recommendations for optimal health. First, enable more effective integration of data from all sources through the use of genetic and nutritional biomarkers; second, minimize the risk of bias and confounding through the adoption of rigorous quality-control standards, greater emphasis on the replication of study results, and better integration of results from independent studies, perhaps using adaptive study designs and Bayesian meta-analysis methods; and third, emphasize more effective and truthful communication to the public about the evolving understanding of the often complex relationship between nutrition, lifestyle, and optimal health.*

**Keywords** epidemiology, weak associations, dietary guidelines, decision making, communication, nutrition, Bayesian, biomarker

## INTRODUCTION

Population-based dietary guidance is faced with the continual challenge of appropriately considering the totality of evidence, including preclinical, epidemiological, clinical, and translational research. Nutritional epidemiology studies have served as a vital signal of associations that sometimes point to the need for additional investigations using animal models and/or human intervention trials. Relative risk (RR) measurements less

than 2.0, classified as "weak associations" in the broader field of epidemiology, are common in nutritional epidemiology. In some cases, conclusions about causality have been inappropriately interpreted from such associations; in others, the results have been completely dismissed.

Recognizing the important contribution that epidemiology makes to nutrition science, as well as the need to explore avenues for reducing bias and confounding, *the North American Branch of the International Life Sciences Institute (ILSI) North America* organized a 1997 workshop entitled "The Role of Epidemiology in Determining When the Evidence Is Sufficient to Support Nutrition Recommendations" (Byers, 1999). The two-day workshop, held in Washington, DC, provided a

Address correspondence to Juan L. Navia, PhD, McNeil Nutritionals LLC, 601 Office Center Drive, Ft. Washington, PA 19034. Tel: 215-273-4954. E-mail: jnavia@its.jnj.com

forum for nutritional epidemiologists, nutritional scientists, and food-policy experts from academia, industry, and government to discuss the role of epidemiology in the formulation of dietary advice for the public. The summary statement prepared by the organizers briefly addressed the issue of weak associations in nutritional epidemiology and concluded that: “The challenge, then, is to distinguish the moderate effects that are real and have important public health consequences from those that are artifacts. A change of 50% in risk (e.g., a relative risk of 1.5) may be considered strong in nutritional epidemiology, so the commonly cited criterion of relative risks < 2.0 being suspect does not necessarily apply to nutritional epidemiology” (Byers et al., 1999). Indeed, the relative risk of a nutritional exposure at a smaller magnitude than is commonly seen in chemical toxicology may have considerable potential for public health impact, because the effect is multiplied by broad exposure within the population.

A decade later, ILSI North America revisited the subject by convening the “Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research” workshop in December 2008, in Washington DC. Participants representing the nutrition and food safety communities in academia, industry, and government shared current practices in the interpretation of weak epidemiological associations, and explored avenues for appropriate interpretation and integration of animal study data, human intervention, and epidemiological data in the development of public health recommendations (Boffetta, 2008; Colditz, 2008; Ioannidis, 2008; Kris-Etherton, 2008; Liang, 2008; Livesey, 2008; Marantz, 2008; Picciano, 2008; Rowe, 2008; Russell, 2008; Schneeman, 2008; Squires, 2008; Wiseman, 2008). This report is a summary of the workshop dialogue, and does not necessarily reflect the opinions of all of the members of the organizing committee or the presenters.

## **CONFERENCE SUMMARY**

According to the widely accepted hierarchy of scientific evidence, research along the continuum should lead to the randomized, controlled trial (RCT), with epidemiology and other types of study considered as supportive of the RCT. However, the perception of the RCT as the definitive research method is challenged by the prevalence of publication and reporting bias of clinical studies. In an empirical investigation of the prevalence of outcomes reporting bias in clinical investigations, Chan and colleagues (2004) identified 274 RCT protocols approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark between 1994 and 1995; however, only 102 trials resulted in one or more publications. A comparison of outcomes reported in the resultant 122 published articles to those originally stated in the study protocols found that 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Furthermore, 86% of survey responders denied the existence of unreported outcomes despite evidence to the contrary (Chan et al., 2004). Although some may find Chan and colleagues’ assessment of the state of clinical trial reporting difficult to ac-

cept for a variety of reasons, these results should be seen less as an indictment of RCTs as a whole but more as a sobering recognition that wholesale acceptance of the conclusions of a study simply because it uses randomization and placebo controls may not always be warranted. RCTs can be as flawed as any other study design. Extrapolation of results from a single RCT to form conclusions beyond the controlled conditions of the RCT, perhaps to refute an association observed in one or more observational studies, may not give the truest picture of the biology underlying a perceived association. As discussed in later sections of the current report, the true association may be better discerned by combining multiple independent lines of evidence, such as RCTs, epidemiology, and data from model systems. Laboratory studies using appropriate model systems are essential for the study of metabolic pathways and mechanisms of action at the cellular or organ level; clinical studies are well suited to answer questions about a specific intervention in a defined population over a limited span of time; and epidemiology is better suited to address questions about a broader population over several years or decades. Interventional studies present an opportunity to examine whether a change in behavior can produce the same benefit as persistent behavior in observational studies. These three fields of study each provide a portion of the true health impact of nutrients on overall health. To paraphrase British mathematician, logician, and philosopher Alfred North Whitehead (1861–1947), in nutrition research there are no whole truths; all truths are half-truths. It is trying to treat them as whole truths that plays the devil (Whitehead, date unknown).

A. Bradford Hill’s (Hill, 1965) criteria for inferring causality provide a means for judging the merit of an association between food or nutrient intake and a health outcome. The durable usefulness of these criteria is in the explicit acknowledgment that no one line of evidence is sufficient to infer a causal relationship. Rather, it is in examining the totality of the currently available data (from biological model systems, clinical intervention trials, and epidemiology) that one can, until new and better evidence comes to light, infer a causal association.

## ***Epidemiological Methods and Applications: An Overview***

The appropriate interpretation of weak associations is an important aspect of epidemiology, and is particularly challenging in nutrition. Although there is no sharp delineation between strong or weak effects, “strong associations” tend to be viewed as being more suggestive of a causal relation than “moderate” or “weak” associations. Weak associations are more likely to be perceived simply as the result of chance or the play of uncontrolled sources of systematic error. Discerning the true association between nutrient intake or dietary pattern and a health outcome may be complicated by bias or confounding effects. One particular challenge in nutritional epidemiology is that there are essentially no completely treatment-naïve subjects with respect to diet or lifestyle. Therefore, investigators can only compare high and low exposures when evaluating

health benefits. Particularly in the case of chronic diseases with long latency, the study design must reflect whether the nutrient or lifestyle exposure is being considered in terms of primary versus secondary prevention, because the two are not interchangeable (Boffetta, 2008; Colditz, 2008).

Differences in study methodology and design contribute to variability in the overall body of evidence. Conversely, study design and methodology can be used to limit the effects of bias and confounding in the study of weak associations. One way to increase the ability to detect small effects, as well as to reduce recall bias, is to use a prospective study design with repeated measures. Replicating studies in different populations can help to confirm or refute the finding of a weak association. Along these lines, the formation of research consortia could enable concurrent planning of smaller studies with compatible designs. Using this approach would allow results to be more easily compared. Large international research consortia, requiring public deposition of data and deliberate steps to avoid selective reporting of data, would also minimize the risk of bias. Similar consortia have been implemented over the past 10 years in genetic epidemiology. The most important potential advantage to nutritional epidemiology would be the replication of results (Ioannidis, 2008).

Bayesian inference methods may be well adapted to the analysis of data from multiple independent studies, in contrast to the current reliance on statistical significance of individual studies. Provocative new data may trigger a so-called bandwagon effect in which a series of publications favoring one outcome beget other articles with like outcomes, although sometimes with progressively weaker associations. Once data have been published in the literature, there is a resistance to refutation by subsequent studies. Even discredited associations tend to be resurrected periodically by “new statistically significant” results. Statistical significance may be less important with respect to weak associations, and may be more practically replaced by the Bayes Factor (Goodman, 1999) as a measure of probability of an effect. The Bayes Factor may in fact enable investigators and policy makers alike to make the best use of present and accumulating data on weak associations.

### ***Applications of Epidemiological Data for Decision Making: Discerning the Link***

It is important to understand the difference between the considerations of acute toxic exposures and long-term chronic exposures. The use of epidemiological methods in tracking down foodborne disease outbreaks is an example of acute exposures where the cost of inaction to human health can be so great that decisions must be made, even if causal relations are difficult to establish (Liang, 2008). Food safety outbreaks tend to show very strong but imprecise RRs because the number of individuals affected is usually small. The *Salmonella* outbreak in peanut products that began in 2007 (Centers for Disease Control and Prevention (CDC), 2007) illustrates how epidemiological meth-

ods were applied to identify the cause of illness and issue public health alerts. Causal links between food and acute illness are inferred from an integration of epidemiologic data, laboratory work, and the judgment of public health professionals. Such investigations can still be challenged by incomplete data (e.g., the source of contamination may be eradicated, intentionally or unintentionally, before investigators can get to it; or cases or controls may be reluctant to participate for a variety of reasons).

Long-term health consequences present a particularly difficult challenge to the epidemiologist. Whereas foodborne disease outbreaks typically identify strong associations when close to the source, dietary patterns assert subtle effects on health outcomes such as cancer only with prolonged exposure. Furthermore, there are multiple contributions to chronic health outcomes, including genomic and lifestyle confounders. Therefore, asserting that a particular quality of dietary exposure causes a health outcome is exceedingly difficult.

The evolution of U.S. Food and Drug Administration (FDA) regulation of food and dietary supplement labeling regarding such claims demonstrates the challenge of balancing the right of the consumer to accurate health-related information with protecting them from misleading information or harmful products. From the Nutrition Labeling and Education Act of 1990 (NLEA, 1990) to qualified health claims in the 1990s, the heart of the controversy lies in defining the type of evidence that will be accepted in establishing a credible link between the intake of a nutrient and a health outcome. For health claims to appear on a food label without caveat regarding the level of evidence backing the statement, the FDA has retained the standard of significant scientific agreement with respect to the relevant nutrient and “disease or health-related condition.” A systematic evaluation of published intervention and observational studies in humans considers the strength of the evidence in terms of study design, methodological quality, study sample sizes, relevance to the target population, replication of results, and the quantity and overall consistency of the evidence (FDA, 2009).

### ***Forming Dietary Recommendations for the Public***

The adoption of evidence-based decision making in public health recommendations was intended to move the profession away from reliance on “expert opinion” and toward consideration of the sum of evidence. However, the demand for guidance, even in the face of weak associations and incomplete data, can be considerably challenging to regulators and expert panels dealing in the public health arena.

For example, a recent analysis of data on the relationships between intakes of particular foods and the risk for cancer revealed that most were weak ( $RR < 2.0$ ), and were judged by the expert panel to understate the true effects (Wiseman, 2008). Because these were the best available data at the time, the panel made dietary recommendations that they judged to be consistent with helping to reduce the incidence of cancers. In such cases, the need for subsequent monitoring and evaluation of the impact of such recommendations is important.

The evidence standards for dietary guidelines should appropriately be as high as or higher than for pharmaceuticals because of the large numbers of people, including children, who are affected by the recommendations. Pointing to the case of recommendations in the 1990s to reduce fat intake to less than 30% of one's daily calories, it was not anticipated that dietary choices that were intended to reduce fat would translate into higher carbohydrate and calorie intakes. During the period from 1980 to 2000, fat intake as a percentage of calories declined. However, energy intake and carbohydrates as a percentage of calories increased significantly (CDC, 2004), and at the same time, the incidences of obesity (Flegal et al., 2002) and diabetes also increased (CDC, 2008; Cowie et al., 2009; Engelgau et al., 2004). Dietary recommendations can have unintended effects; the imperative should be, "first, do no harm." Published dietary recommendations tend to persist in the public domain as entrenched eating habits and commercially available prepared foods, even when superseded by new recommendations. An appropriate level of conservatism seems prudent when making such recommendations.

Whether the public has a fundamental (ethical, legal, or moral) right to health information, even if it is incomplete, to be able to make personal decisions is an ethical issue that cannot be dismissed. A decision to make, or withhold from making, a recommendation can have public health consequences for good or ill. Dietary recommendations are intended to inform the public about the best current understanding of food choices to support good nutrition and good health, but may also be used to provide nutritionally balanced meals for individuals who cannot make autonomous, informed decisions about food choices.

For example, some have questioned the current practice of revisiting the U.S. Dietary Guidelines for Americans every five years. A three-step process has been proposed and comprises a technical advisory committee that would provide the scientific rationale for the recommendations; a users' committee that would review the recommendations for economic, commercial, and public health impacts; and a federal dietary guidelines committee that would formulate the recommendations. Advocates of this approach argue that it would provide a staged forum for vetting possible unintended consequences from recommendations (King, 2007).

Using epidemiology alone to define dietary reference intakes (DRI) would be problematic, in that such reference values target risk reduction for a particular chronic disease (Russell, 2008). Although observational studies can provide valuable support in establishing links between nutrient intakes and risk for chronic diseases, they are of limited value alone in establishing causality. Because the development of chronic disease can have a long latency, the selection of suitable surrogate markers is critical to the usefulness of observational and clinical studies of limited duration. It is also important to integrate findings from different types of studies that use similar biomarkers, as well as from systematic reviews and meta-analyses of such studies.

### ***Recent and Emerging Issues***

Three examples of the interpretation of weak associations in nutritional epidemiology include—vitamin D supplementation for optimal health (Picciano, 2008), the health effects of fructose intake (Livesey, 2008), and the cardiovascular effects of an incidental component of partially hydrogenated oils, *trans* fat (Kris-Etherton, 2008).

Vitamin D status has been linked to a reduced risk for some types of cancer, cardiovascular disease, diabetes, osteoporosis, and other chronic diseases; however, the data are highly variable in some cases. Increased awareness of widespread vitamin D insufficiency may well result in significant increases in vitamin D intakes beyond the recommended levels, and thus in a potential increase in cases of vitamin D toxicity from over supplementation. There is currently little scientific agreement on what can be considered an "optimal" intake of vitamin D, although accumulating evidence supports the need for supplementation for some individuals (Mithal, 2009). To address these issues, the Institute of Medicine has convened a group of experts to re-evaluate the vitamin D and calcium DRIs.

The analysis of fructose-intake data illustrates the potential for both the use and misuse of weak associations in epidemiological data. It is effectively impossible to tease out the specific effect of fructose in the diet because it is typically consumed on a nearly equimolar basis with glucose (e.g., as sucrose, or as a mixture in high-fructose corn syrup). Other confounders may include lower magnesium intake, reduced fiber intake, and less physical activity coincident with increasing energy intake. It may be that fructose intake is actually a marker for some other dietary pattern, such as excessive carbohydrate intake, or a combination of factors, rather than the causative agent. The public health risk associated with misattributing the rise in incidence in diabetes to overconsumption of a single dietary component highlights the lack of attention being paid to other factors that are associated with the increasing incidence of obesity, particularly among the young.

The story of *trans* fats and the risk for coronary heart disease is a success story for the use of epidemiology in identifying a public health risk and guiding well-designed clinical studies to establish a clear causal link. The current recommendation to avoid *trans* fats is based on more than 15 years of supporting epidemiological and clinical research. The story is presently evolving as ongoing research investigates other possible causal links between the intake of *trans* fats and the risk for diabetes and other chronic diseases.

### ***CRITICAL EVALUATION OF TOTALITY OF DATA AND PERSPECTIVES: TOWARD A POSITION STATEMENT***

#### ***Opportunities and Challenges***

The ILSI North America workshop, both the presentations summarized above and the dialogue among participants,

provided three clear strategies for understanding weak associations in nutritional epidemiology:

1. Enable more effective integration of data from all sources through the development and use of robust nutritional and genetic biomarkers;
2. Minimize the risk of bias and confounding through the adoption of rigorous quality-control standards, greater emphasis on replication of study results, and integration of results from independent studies, possibly using adaptive study designs and Bayesian meta-analysis methods; and
3. Emphasize effective communication of study results to the public in relation to existing knowledge across the spectrum of research design, and to the public health significance of the results.

### *Integrate Data from All Sources*

The interactions of genetics, nutrition, and lifestyle over a lifetime is complex and beyond the scope of any one study design. In an article published more than a decade ago in the *American Journal of Clinical Nutrition*, Gladys Block (1995) provided the following summary:

“We would like to answer the following questions regarding health and disease. 1) Can we cure a disease? 2) Can we modify the course of a disease? 3) Can we prevent a disease? The first two important questions can be studied well with clinical trials. However, the third question is the one at issue here. In the context of dietary factors, we would like to know whether by eating a certain way throughout our life or consuming certain nutrients we can reduce our risk for disease. This is a question . . . that clinical trials are not suited to answer.”

The logistical reasons for this are mainly cost, compliance, and duration. For this reason, epidemiology can be an effective tool in addressing questions related to disease prevention and risk reduction, but is by no means the only tool; RCTs are another tool, but can be more difficult to use in long-term studies. The most effective use of study data is not to treat each study as a separate event, but to treat them collectively as pieces in the complex puzzle of nutrition and health. No single line of experimental evidence can illuminate every aspect of a causal relationship. Rather, the study of complex nutrient–health interactions demands the integration of both various effective, although limited, experimental approaches and multiple lines of evidence. Integration of study results may be greatly facilitated by using similar outcomes measured by compatible instruments that are comparable across various studies.

The Bradford-Hill criteria may be misused if these are employed as a “checklist for causal criteria” (Höfler, 2005). Rather, these criteria emphasize the imperative of including data from multiple lines of evidence, particularly studies that delve into the biological plausibility of an association. The importance of preclinical research is hard to overemphasize, but in an environment in which the formation of health policy recommendations tends to exclude studies in model systems, an integral element of the totality of the data may frequently be ignored.

### *Nutritional Biomarkers*

Two commonly used methods to assess nutritional status include dietary recall, typically using food frequency questionnaires (FFQ), or measurement of biomarkers for nutritional status. Several FFQ are available to investigators to use as a tool for assessing the frequency and amount of nutrient intake. Validated FFQ are designed for a specific population or to look for specific items, and are not necessarily suitable for every new circumstance. An appropriate validation will typically evaluate whether the FFQ provides results that are consistent with other, more rigorous methods of measuring food intake, but usually not against an objective biochemical indicator or intake for most nutrients. Investigators must consider if the FFQ was designed to assess the dietary substance that is of interest for a possible health claim and whether it is validated to predict the food intake of interest.

Changes in nutritional biomarkers of exposure in blood, urine, or other tissues can help elucidate biological effects of nutrient intakes, independently or jointly with dietary recall data, and enhance interpretation of observational study results. Nutritional biomarkers may also further enable researchers to relate results from observational studies to those of interventional studies. Certain challenges will remain, including the need for methods to reliably assess the nutritional status of an individual and to measure the true range of intakes in the study, regardless of the study design.

### *Genetic Markers*

Nutrient–gene interactions may be grouped into three categories: 1) direct interactions, wherein a nutrient directly affects gene expression; 2) epigenetic interactions, in which nutrients act to chronically alter gene expression; and 3) genetic variations that can affect the structure or function of a protein product or whether a protein is produced (Zeisel, 2007). The latter category is of particular importance to the design and interpretation of population studies and the understanding of the real importance of small effects. Human genetic variability is such that a given exposure to a nutrient may present no measurable health effects in one part of the population, but can elicit a significant decrease or increase in disease risk in a different genetic population. These differences profoundly complicate policy decisions regarding nutrient intakes.

Nutritional studies tend to focus on comparing extremes of exposure or nutrient intake partly because differences at an acceptable level of significance can be easier to detect when comparing the highest versus the lowest intakes. Even when studying intake extremes, associations may be very strong in some cases and weak in others. What is the effect of comparing extremes on the dose-response curve? Should policy makers make recommendations for the general population, in which intakes may predominately fall in the middle range, on the basis of data that represent extremes?

Replication of studies of various populations provides an empirical solution to the study of nutrition and health in various

genotypes. Rather than seeking to diversify the study population in each study, would designing smaller studies with more homogenous study populations and replicating them in various geographic areas be more effective?

### *Minimize Bias and Confounding*

The complexity of interacting effects in free-living humans among genetics, lifestyle, and nutrition (e.g., quality of the diet and history of intake) can result in serious confounding effects. For example, these effects may be illustrated by studies of vitamin D and various health outcomes, in which intake is assessed by dietary recall or supplementation without measuring serum vitamin D levels. Such studies may fail to detect significant protective benefits compared with studies that implicitly consider the contribution from photosynthesis (related to age, ethnicity, lifestyle, geography, and season) by measuring serum levels.

The interaction of nutrition and lifestyle has been well studied for several decades and has provided enormous dividends in improving both health and longevity, notwithstanding the accelerating increase in obesity and diabetes worldwide. Many diseases related to malnutrition have been eliminated in most developed and many developing countries, and efforts continue to address these diseases effectively in the regions in which they still occur. Great progress has also been made in the past 10 years in the area of human genomics and metabolomics. More and better tools are needed for the study of nutrient–gene interactions in laboratory systems, clinical trials, and observational studies to allow a more complete picture to emerge of how good nutrition can best support good health. Such advances offer great promise in reducing confounding.

Statistical significance is important when evaluating associations, with some caveats. The size of the study population is among the factors that contribute to a lower  $P$  value. Should an association be discounted because the study is underpowered to find a statistically significant effect? Conversely, statistical significance is commonly held to be a requisite, but is not sufficient alone to either establish a link or to discount the possibility of bias. All studies are susceptible to bias. Can several studies that are all susceptible to a similar source of bias, most of which with results that do not reach the level of statistical significance ( $0.05 < P < 0.1$ ), be credibly combined to provide the additional power needed for statistical significance? In addition to the adoption of strict quality-control measures, better methods for data analysis are needed to effectively combine results from multiple studies.

The scientific method is essentially a process for conducting systematic observation and testing a new prediction (hypothesis) consistent with the observation. Clinical investigators and epidemiologists alike often find a situation in which they discern a pattern or trend in the data that is suggestive, but not statistically significant. There are two commonly used statistical approaches to treat the data: classical and Bayesian inference. Classical inference is the more common approach, using hypothesis testing and statistical significance to accept or reject a null hypothesis

that implicitly encompasses external information. Weak associations and small effects, assuming they are plausible and supported by laboratory studies, present a particular difficulty to classical inference methods. Large studies may be better able to detect associations of small to moderate size, but a larger group of study participants ( $N$ ) also risks overpowering the study to detect more false-positive associations.

Bayesian inference accepts external scientific information as a prior distribution. The usefulness of Bayesian meta-analysis is illustrated in a recent analysis by Berry et al. (2009), which was composed of several publications that examined vitamin E supplementation and mortality. Two previous analyses found an increase in all-cause mortality associated with vitamin E supplementation (Bjelakovic et al., 2007; Miller et al., 2005). Berry et al. (2009) included the same articles that were cited in Miller et al. (2005) and used Bayesian hierarchical-model averaging to combine data from the studies that met the inclusion criteria and Markov chain Monte Carlo computational techniques for the analyses. Unlike the previous meta-analyses (Bjelakovic et al., 2007; Miller et al., 2005), the Bayesian analysis showed no association between vitamin E supplementation and all-cause mortality, regardless of the dose (Berry et al., 2009). The implications of this difference are considerable and merit further attention.

### *Communication*

Because assertions regarding dietary effects on health, or the lack thereof, can considerably impact public health, the manner in which they are communicated to the consumer has been the subject of controversy for almost two decades. Great emphasis is currently placed on developing health policies, including dietary guidelines (King, 2007), using an evidence-based approach. There are two components to this process: 1) conducting the research to provide the evidence, and 2) communicating the science to enable informed decision making. Nutrition and food safety decisions are no better than the quality of the science and the related communications.

The communication of study results can be complicated by terse or incomplete reporting of the statistical methods and models used in the analysis of study results. Authors may seem to arbitrarily select a method of assessing and evaluating dietary data, and apply various corrections. Statements noting that something was “adjusted for energy intake,” for example, may leave the reader to speculate about how and why the adjustment was made. Indeed, authors face a difficult choice between providing details and complying with a publication’s tight word limit. Complete reporting of mathematical and statistical terms and models is important, and can be provided in supplementary documents if not in the full article.

Although statistical methods can be difficult for the professional, they are all the more confusing to a lay reader. For example, epidemiology has historically used odds ratios (ORs) or RRs as a measure of association between exposure (e.g., to a nutrient) and a health effect across retrospective, case-control

studies and prospective cohort studies. Some researchers report the attributable risk or population-attributable risk as a measure of attribution of disease to a given nutritional exposure or deficiency. Public media reporting on health research can serve its readers well by not only accurately reporting risk, but also by explaining the meanings and nuances of these various statistical methods.

When the results of the Women's Health Initiative study of the effects of low-fat dietary patterns on the risk for breast cancer (Prentice et al., 2006) and cardiovascular disease (Howard et al., 2006) was reported in the *New York Times* online edition (Kolata, 2006), the first line in the article announced: "The largest study ever to ask whether a low-fat diet reduces the risk of getting cancer or heart disease has found that diet has no effect." The article ignored many other findings that support health benefits from a low-fat diet and the fact that most participants did not reduce their dietary fat to the target level. Rather than focus on accurately reporting the complete results in the scientific publication, the article quoted several selected opinion leaders as if the scientific merit of the study could be determined by popular vote. If epidemiologists are to be criticized for not presenting results in a more accessible manner, the media may well be criticized for grossly oversimplifying for the public the complex interactions between diet, lifestyle, and genetics. The nutrition research community understands the limitations of a given finding, but the public listens for answers and makes decisions on the basis of single studies. With food news in the headlines daily, consumers are at risk of ignoring useful health advice and adopting unhealthy or ineffective dietary changes.

Another aspect of informed decision making involves the ethical and political aspects of nutritional recommendations. These are areas outside of scientific methodology, but nevertheless profoundly affect the credibility of the science, regardless of how unimpeachable the methodology. Refraining from making a recommendation because of inconclusive evidence may be interpreted as a recommendation in itself (i.e., a decision to perpetuate current practice), which carries its own inherent ethical and health-related consequences. Finally, the integrity of even the soundest science will surely be called into question if the funding is considered to be from a biased or partisan source, such as industry, or the study seems to be politically motivated. Forming research consortia, perhaps comprising investigators from industry, government, and academia, and sharing responsibility for the analysis and communication of the results from nutrition research may enable clearer understanding of experimental results, and effective communication of nutrition recommendations.

## SUMMARY

In summary, it is important to consider the totality of data in decision making. Studying nutrition is different from studying drugs. There are challenges unique to nutrition studies, including

the complexity of different types of diets and subtle differences among various nutrients and among individuals, both of which are multiplied when addressing a chronic health outcome. Better integration and critical evaluation of all data, including pre-clinical, epidemiology, and RCTs, can be accomplished in part through efforts to improve research standards for all study types, such as improved outcomes reporting, as well as collaboration to facilitate comparability and replication through study design and the use of nutritional biomarkers and genetic information.

## ACKNOWLEDGMENT

This work was supported by the Technical Committees on Food and Chemical Safety, Carbohydrates and Dietary Lipids of the North American Branch of the International Life Sciences Institute (ILSI). ILSI North America is a public, non-profit foundation that provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops, and publications. ILSI North America receives support primarily from its industry membership. Partial financial contribution was provided by the American Meat Institute Foundation. We acknowledge Dr. Sanjiv Agarwal for his contributions to early drafts of this manuscript, and we thank Ms. Cheryl Toner for all of her help in finalizing this manuscript. We also acknowledge scientific input from all of the Committees' members and workshop speakers for their helpful suggestions during development of the 2008 workshop and review of the manuscript.

## REFERENCES

- Berry, D., Wathen, J. K., and Newell, M. (2009). Bayesian model averaging in meta-analysis: vitamin E supplementation and mortality. *Clin. Trials*. **6**(1): 28–41.
- Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G., and Gluud, C. (2007). Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. **297**(8): 842–857.
- Block, G. (1995). Are clinical trials really the answer? *Am. J. Clin. Nutr.* **62**(6 suppl): 1517S–1520S.
- Boffetta, P. (2008). Causation in the presence of weak associations. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Byers, T. (ed). (1999). The role of epidemiology in determining when evidence is sufficient to support nutrition recommendations. Proceedings of a workshop. Washington DC, USA. October 7-8, 1997. *Am. J. Clin. Nutr.* **69**(6 suppl): 1297S–1367S.
- Byers, T., Lyle, B., and Workshop Participants. (1999). The role of epidemiology in determining when evidence is sufficient to support nutrition recommendations. Summary statement. *Am. J. Clin. Nutr.* **69**(6 suppl): 1365S–1367S.
- Centers for Disease Control and Prevention (CDC). (2004). Trends in intake of energy and macronutrients—United States, 1971–2000. *MMWR Morb. Mortal. Wkly. Rep.* **53**(4): 80–82.
- Centers for Disease Control and Prevention (CDC). (2007). Multistate outbreak of Salmonella serotype Tennessee infections associated with peanut butter—

- United States, 2006–2007. *MMWR Morb. Mortal. Wkly. Rep.* **56**(21): 521–524.
- Centers for Disease Control and Prevention (CDC). (2008) Percentage of civilian, noninstitutionalized population with diagnosed diabetes, by age, United States, 1980–2006. Available: <http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm> [Updated October 8, 2008; Accessed December 11, 2009].
- Chan, A. W., Hróbjartsson, A., Haahr, M. T., Gøtzsche, P. C., and Altman, D. G. (2004). Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. *JAMA.* **291**(20): 2457–2465.
- Colditz, G. (2008). Overview of the epidemiology methods and applications: strengths and limitations of observational study designs. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Cowie, C. C., Rust, K. F., Ford, E. S., Eberhardt, M. S., Byrd-Holt, D. D., Li, C., Williams, D. E., Gregg, E. W., Bainbridge, K. E., Saydah, S. H., and Geiss, L. S. (2009). Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care.* **32**(2): 287–294.
- Engelgau, M. M., Geiss, L. S., Saaddine, J. B., Boyle, J. P., Benjamin, S. M., Gregg, E. W., Tierney, E. F., Rios-Burrows, N., Mokdad, A. H., Ford, E. S., Imperatore, G., and Narayan, K. M. (2004). The evolving diabetes burden in the United States. *Ann Intern Med.* **140**(11): 945–950.
- Flegal, K. M., Carroll, M. D., Ogden, C. L., and Johnson, C. L. (2002). Prevalence and trends in obesity among US adults, 1999–2000. *JAMA.* **288**(14): 1723–1727.
- Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition. (2009). Guidance for industry: evidence-based review system for the scientific evaluation of health claims – final. Available: <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm> [Accessed December 10, 2009].
- Goodman, S. N. (1999). Toward evidence-based medical statistics. 2: The Bayes factor. *Ann. Intern. Med.* **130**(12): 1005–1013.
- Hill, A. B. (1965). The environment and disease: association or causation? *Proc. R. Soc. Med.* **58**: 295–300.
- Höfler, M. (2005). The Bradford Hill considerations of causality: a counterfactual perspective. *Emerg. Themes Epidemiol.* **2**: 11–19. Available: <http://www.ete-online.com/content/2/1/11> [Accessed December 11, 2009].
- Howard, B. V., Van Horn, L., Hsia, J., Manson, J. E., Stefanick, M. L., Wassertheil-Smoller, S., Kuller, L. H., LaCroix, A. Z., Langer, R. D., Lasser, N. L., Lewis, C. E., Limacher, M. C., Margolis, K. L., Mysiw, W. J., Ockene, J. K., Parker, L. M., Perri, M. G., Phillips, L., Prentice, R. L., Robbins, J., Rossouw, J. E., Sarto, G. E., Schatz, I. J., Snetelaar, L. G., Stevens, V. J., Tinker, L. F., Trevisan, M., Vitolins, M. Z., Anderson, G. L., Assaf, A. R., Bassford, T., Beresford, S. A., Black, H. R., Brunner, R. L., Brzyski, R. G., Caan, B., Chlebowski, R. T., Gass, M., Granek, I., Greenland, P., Hays, J., Heber, D., Heiss, G., Hendrix, S. L., Hubbell, F. A., Johnson, K. C., and Kotchen, J. M. (2006). Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA.* **295**(6): 655–666.
- Ioannidis, J. (2008). Can lessons learned from genome-wide research be applied to nutrition-wide and exposure-wide evidence? Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- King, J. C., and the Dietary Guidelines Advisory Committee. (2007). An evidence-based approach for establishing dietary guidelines. *J. Nutr.* **137**(2): 480–483.
- Kolata, G. (2006). Low-fat diet does not cut health risks, study finds. Available: <http://www.nytimes.com/2006/02/08/health/08fat.html> [Published February 8, 2006; Accessed December 11, 2009].
- Kris-Etherton, P. (2008). Trans-fats and CHD. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Liang, A. (2008). Decision-making: food safety applications. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Livesey, G. (2008). Fructose, obesity and related epidemiology. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Marantz, P. (2008). Compare and contrast methods applied for public health decision-making/policy development: rethinking dietary guidelines. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Miller, E. R. 3rd, Pastor-Barriuso, R., Dalal, D., Riemersma, R. A., Appel, L. J., and Guallar, E. (2005). Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann. Intern. Med.* **142**(1): 37–46.
- Mithal, A., Wahl, D. A., Bonjour, J. P., Burckhardt, P., Dawson-Hughes, B., Eisman, J. A., El-Hajj Fuleihan, G., Josse, R. G., Lips, P., Morales-Torres, J., and the IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. (2009). Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos. Int.* **20**(11): 1807–1820.
- NLEA. (1990). The Nutrition Labeling and Education Act of 1990. Public Law No. 101–535, 104 Stat. 2253.
- Picciano, M. F. (2008). Vitamin D and health. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Prentice, R. L., Caan, B., Chlebowski, R. T., Patterson, R., Kuller, L. H., Ockene, J. K., Margolis, K. L., Limacher, M. C., Manson, J. E., Parker, L. M., Paskett, E., Phillips, L., Robbins, J., Rossouw, J. E., Sarto, G. E., Shikany, J. M., Stefanick, M. L., Thomson, C. A., Van Horn, L., Vitolins, M. Z., Wactawski-Wende, J., Wallace, R. B., Wassertheil-Smoller, S., Whitlock, E., Yano, K., Adams-Campbell, L., Anderson, G. L., Assaf, A. R., Beresford, S. A., Black, H. R., Brunner, R. L., Brzyski, R. G., Ford, L., Gass, M., Hays, J., Heber, D., Heiss, G., Hendrix, S. L., Hsia, J., Hubbell, F. A., Jackson, R. D., Johnson, K. C., Kotchen, J. M., LaCroix, A. Z., Lane, D. S., Langer, R. D., Lasser, N. L., and Henderson, M. M. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA.* **295**(6): 629–642.
- Rowe, S. (2008). Communicating science: media, scientists and consumers. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Russell, R. M. (2008). Integration of epidemiologic and other types of data into dietary reference intake development. Presented at the ILSI North America workshop on Decision-making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Schneeman, B. (2008). Application of epidemiological data for decision-making: Health claims. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Squires, S. (2008). Evolution of science journalism. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Whitehead, A. N. (date unknown). Wisdom Quotes [Internet]. Available: <http://www.wisdomquotes.com/quote/alfred-north-whitehead-2.html> [Accessed December 10, 2009].
- Wiseman, M. (2008). Deriving policy from evidence: experience from the WCRF/AICR report. Presented at the ILSI North America Workshop on Decision-Making for Recommendations and Communication Based on Totality of Food-Related Research; December 15, 2008; Washington, D.C.
- Zeisel, S. H. (2007). Nutrigenomics and metabolomics will change clinical nutrition and public health practice: insights from studies on dietary requirements for choline. *Am. J. Clin. Nutr.* **86**(3): 542–548.