The Challenge of Connecting Dietary Changes to Improved Disease Outcomes: The Balance between Positive, Neutral, and Negative Publication Results

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EVIDENCE-BASED HEALTH CARE RESEARCH IS THE basis for developing public health policies and recommendations. Reimbursement for products and services is directly linked to research evidence that produce desired outcomes. Nutrition is recognized as a key component in national clinical practice guidelines for the prevention and treatment of chronic diseases, such as cardiovascular disease, diabetes, and cancer.[1] The Centers for Medicare and Medicaid Services has approved payment for specific nutrition services in selected disease conditions (eg, chronic kidney disease, diabetes, kidney transplantation) for adults receiving Medicare benefits.[2]

In this issue, Haring and colleagues[3] report on a nonsignificant relationship between dietary patterns and cognitive decline in a cohort of postmenopausal women participating in the Womens' Health Initiative Memory Study. The authors suggest that their results should not be viewed as discouraging. Rather, they continue to encourage practitioners to make appropriate dietary modifications following current guidelines and recommendations for the preservation of health, despite the inability to generate evidence in this cohort.[3] Why is it so challenging to connect positive changes in diet to improved disease outcomes?

There is a perceived peer-review publication bias of a higher rate of acceptance of manuscripts with positive results compared with neutral or negative research findings.[4] Yet, it might be important to know both what can and cannot be correlated using the rigor of scientific inquiry between diet and disease. The purpose of this research commentary is to explore selected practical challenges in conducting, evaluating, and applying nutrition research that might not find a strong correlation between diet patterns and disease outcomes.

CHALLENGES TO CONDUCTING DIET–DISEASE RESEARCH

Research Design: Methodological Issues

Selecting the appropriate research design is necessary to identify information needed to address the research question. Existing datasets are rich sources of detailed information that offer opportunities to examine relationships between dietary patterns and disease outcomes. It might be less expensive and more efficient to analyze an existing dataset than to conduct a new clinical trial. Several large cohort datasets with longitudinal follow-up are commonly used from the Nurses' Health Study, the Framingham protocols, the US Renal Data System, and the Womens' Health Initiative. It is important to clearly understand the differences between statistical inferences of cause and effect, correlations, or just observations of trends when reading and conducting research.

There are inherent limitations to our current dietary assessment methodologies. The choice of how to collect dietary information is driven by variables such as time frame, budget, number of study participants, and limitations of personnel and resources. Practitioners need to know the strengths and weaknesses, for example, of using a validated food frequency questionnaire vs a protocol-driven 24-hour diet recall facilitated by trained investigators.[5] The selection of the software program to analyze the data might be adequate to estimate a wide scope of nutrients or might need to be customized to include foods and nutrients matched to potential risks of the population of interest.[6]

When using an existing dataset, researchers are often constricted by the initial research protocol that might not clearly interface with the new research question. For example, dietary recall might have been collected as foods consumed, not as meals eaten. This provides a challenge if meals need to be reconstructed.[7]

Newer research in dietary assessment has focused on the use of electronic devices to "record" diet intake in a more meaningful visual manner. Digital pictures from smartphones and other visual technology can help in secondary analysis when diet–disease relationships were not fully explored in the initial protocol.[8] In our own practices, we

have seen more participant involvement if they can record intake by technology rather than recording written information or trying to remember retrospective details. This has been especially valuable in maintaining adherence to an intervention because trials often promote self-monitoring as a means to create awareness of one's dietary consumption.

Asking the Right Question: Prospective and Retrospective Challenges

Foods and their terminology can change over time. Coffee consumption is an example of a concept changing over decades. The correlation between dietary intake of coffee and disease outcomes has been widely investigated.[9-11] In 1980, when the first food frequency questionnaire was administered in the Nurses' Health Study, coffee consumption was characterized by grocery store coffee sold in cans being prepared using electric percolator-type systems. If coffee consumption data would have been collected in Italy at the same time, the researcher would have more typically encountered an espresso-type beverage being created on a stovetop using a manual two-section espresso metal pot. The mean number of cups of coffee consumed would have been collected as a "number." The caffeine measure could not have been estimated without more information of what a "cup of coffee" meant in portion size and composition. Today, consumption includes a wide cohort of beverages that vary from use of coffee "pods" to a diverse menu of commercial coffee-containing beverages with additives. Changes have been seen in frequency, portion size, and brewing methodology. Unless the question is updated or defined, the researcher may be asking a question that is not consistently collecting the same outcome measure for data comparison over time periods. In the case of coffee consumption, the number of cups consumed might not be a simple question or measure all of the intended risk factors with disease outcome. Researchers need to clarify the variable(s) being studied, such as milligrams of caffeine consumed per day from all sources (diet, supplements, etc).

Connecting Self-Reported Information with an Objective Measure

Datasets often contain both subjective (self-reported) and objective measures. The concept of validated and reliable subjective measures is beyond the scope of this commentary and has been addressed elsewhere.[12] However, a subjective measure may have been valid when collected within the concept of the original research question, but can lose some credibility in subsequent use. To subsequently validate these findings, an appropriate measure would be to match a known biomarker with a self-reported measure. In a recent paper by Thomson and colleagues,[13] a food frequency questionnaire was used to capture and quantify fruit and vegetable consumption. Serum carotenoids were then used as a biomarker to validate these self-reports and to establish the quality of intake.[13] Research is progressing in using a serum biomarker to quantify and validate gluten or whole-grain intake.[14] Using objective measures to validate the subjective measures gives stronger evidence of correlation than self-reported data alone.

Measuring Exposure: Timing, Duration, and Effect

Nutritional metabolomics is evolving.[15] Measuring any variable at a single point in time may lack understanding of its systemic effect. For example, serum calcium is not a valid indicator of bone composition. It represents <1% of total calcium in the body and the serum level is maintained in tight metabolic range regardless of calcium bone storage.[16]

Another unknown is whether exposure to certain dietary variables results in delayed onset or reduced severity of a specific disease. Haring and colleagues[3] discussed how a 9-year follow-up in postmenopausal women might be insufficient to show a change in cognitive function. Genetic factors related to aging and cognition are not clearly understood. They may play a more prominent role in the development of specific diseases than is presently known.[17] Epigenetics seeks to look for relationships with diet and disease over time. Depending on the disease and dietary variation of interest, it may be the exposure during the study time frame is of minor consequence when compared with exposures and epigenetics programming that occurred during decades or generations earlier.[18,19]

Folic acid consumption in pregnant women is an example of dietary exposure research. There is an inter-relationship between dietary intake and serum levels, but also between exposure duration and deficiency during critical periods of growth in the fetus.[20,21] This scenario also illustrates when dataset analysis might be the only way to answer a research question compared with a clinical trial. It would be unethical to withhold folic acid consumption in a cohort of pregnant women to measure the incidence of spinal cord defects in the fetus when the potential risk is known from prior research.

Control and Lack of Control When Tracking Long-Term Cohorts

Each research design has its own strengths and limitations. Research design attempts to control numerous important variables. Post hoc research identifies important variables that were not controlled when cohorts are re-sorted by other variables to find new trends.[22] Reporting of negative or neutral data can aid in future research.

Reporting Results: Statistical and Bias Issues

The last decade has seen a huge rise in the number of available peer-reviewed publications. In 2010, Bastian and colleagues[23] estimated 75 clinical trials and 11 systematic reviews were published each day. In 2012, more than 28,000 peer-reviewed science-based publications resulted in more than 2 million articles a year. The rise of online journals will further increase the number of published findings. Peer review is meant to establish scientific value and merit of publication. It has been suggested that some of the bias occurs before manuscript submission. Authors might not pursue publication of negative or neutral results.[4]

CHALLENGES TO EVALUATING DIET–DISEASE RESEARCH

When a negative finding is reported, it is prudent to look at the full scope of published research in the field. A meta-analysis, systematic or Cochrane review, or a commentary might be available to explore the issues. Examine