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# Dietary Assessment and Opportunities to Enhance Nutritional Epidemiology Evidence

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Dietary guidelines are promulgated periodically by the U.S. government (for example, reference 1), as well as by other authoritative bodies, with content substantially based on expert review of pertinent biological considerations and the world nutritional epidemiology literature. These sources contribute to widely held beliefs that adherence to dietary guidelines will reduce the risk for major chronic diseases, including cardiovascular disease, cancer, and diabetes. However, systematic reviews of specific recommended dietary behaviors often conclude that evidence for chronic disease benefits is of low certainty and that any benefits are probably small. Recent examples are provided by systematic reviews of sodium (2), eggs (3), and red and processed meat (4). Vigorous debate typically ensues, with opinions differing on the reliability of the epidemiologic data underlying the dietary recommendations.

These arguments usually provide valid points on which both sides can agree. One may concur that systematic reviews generally have been well conducted and that under the criteria applied, which weight randomized controlled trials much more heavily than observational studies, the evidence for benefits on chronic disease risk obtained from adherence to dietary recommendations may be classified as being of low certainty, and then only for modest benefits. At the same time, one might ask how such weak and uncertain data can support any related dietary recommendations by authors of systematic reviews (for example, reference 4), especially if these recommendations contradict dietary guidelines.

On the other side of the argument, one may acknowledge that dietary guidelines developed by multidisciplinary groups over many years are eminently sensible and noteworthy. However, one also may ask whether dietary guidelines have been developed from a convincing body of scientific evidence.

The last question gets to the heart of the agenda of nutritional epidemiology research, which for the past 50 years has relied primarily on observational studies in conjunction with self-reported dietary behavior. A substantial reliance on observational studies may be justified, given the many important hypotheses related to the health benefits and risks of foods, nutrients, and dietary patterns, as well as the cost and logistic challenges of carrying out long-term randomized controlled dietary intervention trials to test such hypotheses. However, observational studies, including the carefully conducted cohort studies that have been central to nutritional epidemiology reporting, can never be certain about the extent of confounding control, and ascertaining outcomes equally across dietary exposure categories may be challenging in the absence of a clinical context.

Furthermore, in the author's opinion, the biggest impediment to reliable disease association information from observational studies, and one that merits greater emphasis in systematic reviews, is that of measurement error in dietary assessment. The random component of measurement error may substantially attenuate estimated associations, so that a recommendation to consume a nutrient or food that seems to convey a small health benefit may reflect a much stronger disease prevention potential. Of importance, concurrent systematic bias in dietary assessment may fundamentally distort disease association results. Hence, although one may accept a central role for observational studies in nutritional epidemiology, no compelling argument exists for accepting self-reported dietary data.

To amplify, although many epidemiologic reports claim the use of "validated" dietary assessment tools—predominantly food-frequency questionnaires—these claims almost universally arise from repeatability, on the basis of positive correlations between intake estimates when the same or different assessment tools are applied to individual study participants. In contrast, a validity claim requires a close correspondence with actual intake.

Intake biomarkers (5), based on measures in urine, blood, or other biospecimens, may provide the opportunity for a stronger assessment of diet. Such biomarkers may be able to be applied directly in disease association analyses (for example, reference 6), or may be used to calibrate self-report assessments to reduce systematic and random measurement error influences. An important special case of the latter is provided by the doubly labeled water (DLW) assessment of total energy consumption. The DLW method accurately assesses energy intake over 2 weeks among weight-stable study participants (7). Comparisons of DLW energy with self-reported energy in Women's Health Initiative cohorts reveal weak associations and strong systematic biases, with energy intake substantially underestimated among overweight and obese participants (8). Moreover, these measurement problems are evident regardless of whether food-frequency questionnaires, dietary recalls, or dietary records are used (9). However, these weak assessments may combine with body mass index and other participant characteristics to yield measurement error–corrected energy intake estimates that have strong, positive estimated associations with major chronic diseases (10).

The set of established nutritional biomarkers is small and primarily includes DLW (for energy), urinary

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nitrogen (for protein), 24-hour urinary sodium and potassium, and recently proposed serum concentration–based micronutrient biomarkers (6). A great need exists for additional intake biomarkers to be developed, perhaps by using metabolomics, microbiomics, or other high-dimensional platforms. Doing so may help ensure that the dietary assessment limitations do not imply another 50 years of disease associations of uncertain interpretation.

Other research initiatives merit exploration for strengthening nutritional epidemiology evidence. For example, small-scale intervention trials of promising dietary changes, in conjunction with a broad array of intermediate outcomes and nutritional biomarkers, may be able to be paired with cohort studies with these same measurements from stored biospecimens from case and control participants. Together, they may usefully project intervention influences on health outcomes in studies having acceptable cost and duration.

Nutritional epidemiology research is not at all easy. Even without the measurement error problem, sorting out the contribution of specific dietary factors to health outcomes would be statistically challenging given the complex mixture of nutrients, foods, patterns, and practices that constitute the human diet. Add to that major systematic and random biases in intake assessment, and the challenge may seem overwhelming. However, research avenues are available that may lead to a fresh perspective on a broad range of diet and disease association topics, including the health implications of sodium, eggs, and red meat, if the considerable capabilities of the multidisciplinary nutrition science community, especially those able to conduct human feeding studies and small-scale human intervention trials, are directed to current opportunities.

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