VIEWPOINT

The Challenge of Reforming Nutritional Epidemiologic Research

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Some nutrition scientists and much of the public often consider epidemiologic associations of nutritional factors to represent causal effects that can inform public health policy and guidelines. However, the emerging picture of nutritional epidemiology is difficult to reconcile with good scientific principles. The field needs radical reform.

In recent updated meta-analyses of prospective cohort studies, almost all foods revealed statistically significant associations with mortality risk.[1] Substantial deficiencies of key nutrients (eg, vitamins), extreme overconsumption of food, and obesity from excessive calories may indeed increase mortality risk. However, can small intake differences of specific nutrients, foods, or diet patterns with similar calories causally, markedly, and almost ubiquitously affect survival?

Assuming the meta-analyzed evidence from cohort studies represents life span–long causal associations, for a baseline life expectancy of 80 years, eating 12 hazelnuts daily (1 oz) would prolong life by 12 years (ie, 1 year per hazelnut),[1] drinking 3 cups of coffee daily would achieve a similar gain of 12 extra years,[2] and eating a single mandarin orange daily (80 g) would add 5 years of life.[1] Conversely, consuming 1 egg daily would reduce life expectancy by 6 years, and eating 2 slices of bacon (30 g) daily would shorten life by a decade, an effect worse than smoking.[1] Could these results possibly be true? Authors often use causal language when reporting the findings from these studies (eg, "optimal consumption of risk-decreasing foods results in a 56% reduction of all-cause mortality").[1] Burden-of-disease studies and guidelines endorse these estimates. Even when authors add caveats, results are still often presented by the media as causal.

These implausible estimates of benefits or risks associated with diet probably reflect almost exclusively the magnitude of the cumulative biases in this type of research, with extensive residual confounding and selective reporting.[3] Almost all nutritional variables are correlated with one another; thus, if one variable is causally related to health outcomes, many other variables will also yield significant associations in large enough data sets. With more research involving big data, almost all nutritional variables will be associated with almost all outcomes. Moreover, given the complicated associations of eating behaviors and patterns with many time-varying social and behavioral factors that also affect health, no currently available cohort includes sufficient information to address confounding in nutritional associations.

Furthermore, the literature is shaped by investigators who report nonprespecified results that are possible to analyze in very different ways.[4] Consequently, meta-analyses become weighted averages of expert opinions. In an inverse sequence, instead of carefully conducted primary studies informing guidelines, expert-driven guidelines shaped by advocates dictate what primary studies should report. Not surprisingly, an independent assessment by the National Academies of Sciences, Engineering, and Medicine of the national dietary guidelines suggested major redesign of the development process for these guidelines: improving transparency, promoting diversity of expertise and experience, supporting a more deliberative process, managing biases and conflicts, and adopting state-of-the-art processes.[5]

Proponents of the status quo may maintain that the true associations are even larger than what are reported because of attenuation from nondifferential misclassification. Indeed, self-reported data have error,[6] but there is no guarantee it is nondifferential. Nevertheless, if error is nondifferential and estimated effects are attenuated, reported results become even more implausible: eating 12 hazelnuts daily would increase life expectancy by 20 to 30 years, not just 12 years.

Individuals consume thousands of chemicals in millions of possible daily combinations. For instance, there are more than 250 000 different foods and even more potentially edible items, with 300 000 edible plants alone. Seemingly similar foods vary in exact chemical signatures (eg, more than 500 different polyphenols). Much of the literature silently assumes disease risk is modulated by the most abundant substances; for example, carbohydrates or fats. However, relatively uncommon chemicals within food, circumstantial contaminants, serendipitous toxicants, or components that appear only under specific conditions or food preparation methods (eg, red meat cooking) may be influential. Risk-conferring nutritional combinations may vary by an individual's genetic background, metabolic profile, age, or environmental exposures. Disentangling the potential influence on health outcomes of a single dietary component from these other variables is challenging, if not impossible.

To use an analogy from genetics, studying associations of specific foods is like studying whether large chromosomal regions increase mortality risk. For decades, genome linkage scans struggled to link large chromosomal areas to disease risk. According to current knowledge, these previous efforts were doomed: each chromosomal area contains thousands of genetic variants. Linkage scans resulted in numerous articles, but limited useful information. Retrospectively, using a few hundred microsatellite markers to study an entire genome with many million polymorphisms seems naive. Similarly, limited self-reported nutrition data ascertained with a handful of questions and self-reported items fail to acknowledge or accurately measure a system that matches or exceeds the genome in complexity.

Beyond food studies, results of single-nutrient studies have largely failed to be corroborated in randomized trials. False-positive associations are common in the literature. For example, updated meta-analyses of published

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data from prospective cohort studies have demonstrated that a single antioxidant, beta carotene, has a stronger protective effect on mortality than all the foods mentioned above.[7] The relative risk of death for the highest vs lowest group of beta carotene levels in serum or plasma was 0.69 (95% CI, 0.59-0.80).[7] Even when measurement error is mitigated with biochemical assays (as in this example), nutritional epidemiology remains intrinsically unreliable. These results cannot be considered causal, especially after multiple large trials have yielded CIs excluding even a small benefit.

Proponents of the status quo of nutritional epidemiology point to occasional small trials with surrogate or metabolic outcomes (eg, lipids, diabetes, composite end points) whose results agree with epidemiologic findings. However, these small trials often have selective reporting bias similar to that of nutritional epidemiology.

Nutritional research may have adversely affected the public perception of science. Resources for some of these studies could have been better spent on unambiguous, directly manageable threats to health such as smoking, lack of exercise, air pollution, or climate change. Moreover, the perpetuated nutritional epidemiologic model probably also harms public health nutrition. Unfounded beliefs that justify eating more food, provided "quality food" is consumed, confuse the public and detract from the agenda of preventing and treating obesity.

Confusion is further enhanced by some approaches to publication in this field. Slices of data are often published from a cohort without accounting for other findings from the same cohort. A single article reporting a significant effect of a dietary component may seem plausible in isolation but would be untenable if all results were available. Given the vast space of analyzable associations, some prolific cohorts (eg, European Prospective Investigation Into Cancer and Nutrition, Nurses' Health Study) have yielded more than 1000 articles each. Nutritional epidemiology articles also attract attention because the public is very interested in (and perpetually misinformed about) nutrition. For example, one of the 20 highest Altmetric scores in 2017 was for a study reporting major survival benefits from coffee.[8] Despite important limitations and shortcomings, such studies also accrue substantial numbers of citations.

Some additional, large-scale, long-term, randomized trials on nutrition may be useful, especially for assessing diet patterns.[3] The most promising large trial to date, Prevención con Dieta Mediterránea (PREDIMED), a trial of Mediterranean diet, had shown a benefit on a composite end point but was recently retracted and republished[9] after it was realized that there were multiple subversions of randomization. Findings from the reanalysis showed results similar to those of the initially reported findings; however, the study should no longer be considered a randomized trial. Regardless, the trial showed no survival benefit. Large pragmatic trials for more complex diet patterns also may yield largely negative results. Nevertheless, their outcomes may help inform nutritional guidelines with some pragmatic "intention-to-eat" data.

Reform has long been due. Data from existing cohorts should become available for reanalysis by independent investigators. Their results should be presented in their totality for all nutritional factors measured, with standardized methods and standardized exploration of the sensitivity of conclusions to model and analysis choices. Readers and guideline developers may ignore hasty statements of causal inference and advocacy to public policy made by past nutritional epidemiology articles.[10] Such statements should be avoided in the future.

The nutritional epidemiology community includes superb scientists. The best of them should take ownership of this reform process. They can further lead by example (eg, by correcting their own articles that have misleading claims). Such corrections would herald high scientific standards and public responsibility. A flawed methodological approach has dominated research questions that have proved particularly difficult to answer, more difficult than those of other epidemiologic disciplines.

A counterargument may be, by analogy, that genome linkage scan publications have not been corrected, so why correct nutritional epidemiology? The difference is that genomic scans performed with a handful of microsatellite markers have been replaced by better methods and generally did not affect public policy and people's lives. Conversely, studies of nutritional epidemiology continue to be published regularly, spuriously affect guidelines, and confuse the public through heated advocacy by experts and nonexperts.

Nutritional epidemiologists who espouse reform in past and future work should be rewarded, for example, with continued funding to conduct pivotal trials, widely share their cohort data, conduct transparent all-encompassing analyses, and explore entirely new avenues of nutrition research. Funding agencies should support the reform agenda and thereby rejuvenate the field of nutritional research.

ARTICLE INFORMATION

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