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COMMENTARY

Unreformed nutritional epidemiology: a lamp post in the dark forest

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Giovannucci disagrees [1] that reform is needed [2–4] in nutritional epidemiology. He argues that nutritional effects are large, and that traditional means of measuring exposure and handling confounding secure reliable answers. Complexity is manageable through readily definable diet patterns, important questions are obvious, we pretty much know the answers. Analyses demonstrate the wisdom of our hypotheses. Giovannucci eloquently admits searching under the lamp post, confident that whatever is worth finding is right there.

Nutritional epidemiologists valiantly work in an important, challenging frontier of science and health. However, methods used to-date (even by the best scientists with best intentions) have yielded little reliable, useful information. The growing obesity pandemic suggests that we have little reliable knowledge to communicate about optimal diet, people are not convinced and/or cannot adhere to act on it. Probably we fail on all those fronts. Superimposed financial conflicts, fervent allegiance beliefs and group-think diminish further the odds of success. Optimizing our science is necessary under these circumstances.

Large randomized trials

Repeatedly, large randomized trials using clinical outcomes have yielded null results for dozens of nutritional exposure-outcome assessments where epidemiological studies had suggested major benefits [5, 6]. Young and Karr [5] list 52 epidemiological claims none of which were validated when assessed in randomized trials. An overview co-authored by Giovannucci admits that after 179 randomized trials "conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency) was not demonstrated" [6]. Rare exceptions are tenuous. E.g. beneficial effects of folate for stroke risk appear on small studies and a large Chinese trial [7], while two other large trials (British and multinational) showed no benefit [6].

Dietary interventions that Giovannucci highlights as promising are largely failures. E.g. the largest trial on calcium and vitamin D showed no benefit for colorectal adenomas [8]. The overall evidence on vitamin D is weak [9, 10], even causation for fractures has been challenged [11], and results on cancer and cardiovascular outcomes are negative [9]. Omega-3 fatty acids failed multiple randomized trials [12–15].

Some "classics" of nutritional guidelines have mostly weak evidence and small (or null) effects. E.g., trials suggest that decreasing saturated fats decreases cardiovascular risk without affecting all-cause or cardiovascular mortality [16]. However, one meta-analysis [17] concluded that the adequately controlled trials show no benefit from replacing saturated with poly-unsaturated fatty acids. Meta-analyses with more favorable conclusions are often crafted by investigators with strong allegiance to specific hypotheses.

For other guideline "classics", we lack large, well-designed, pragmatic trials. PREDIMED, the iconic trial on Mediterranean diet, was retracted and republished after it was realized that randomization had been subverted.

Even the epidemiological evidence for the "classics" is often debatable. E.g. in contrast to Giovannucci's narrative, optimal sodium/potassium intake remains controversial [18]. Many effect estimates have shrunk tremendously over time. E.g. alluded benefits of fruits and vegetables on cancer prevention decreased from huge benefits in early studies to hazard ratios of 0.999 per serving or null effects in latest studies.

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Diet complexity versus oversimplified hypotheses

Giovannucci asserts that "among the 250,000 potential foods that exist globally, the exposure is zero or close to zero for 99.99%". My quote [4] of 259,143 foods pertained only the small subset of branded foods included in the USDA Branded Food Products Database [19], which are sold and consumed. There are millions of non-branded foods and trillions of combinations. Even though many foods are indeed rarely consumed, assuming that only common foods matter resembles thinking that neurological disease is explainable by skull size or the dimensions of large brain areas. However, toxins, e.g. aflatoxins, in food can kill or cause cancer even in miniscule amounts.

Each "food" is composed of combinations of hundreds and thousands of chemicals that exhibit a range of ratios for the very same food. The same food differs in different restaurants or even the same restaurant on two different occasions. Farming, debugging, and harvesting of raw materials, transportation, processing, cooking, and delivery introduce further diversity for what individuals swallow (and what the consequences on the planet are). E.g. one study recently claimed that organic farming (rather than specific foods) reduces cancer risk [20]. Possible combinations of foods consumed and circumstances of their consumption over a lifetime are astronomical. Conversely, the genome is fixed. Polymorphisms are not farmed, debugged, harvested, transported, processed, cooked and delivered. Finally, even for a purified, standard bolus of glucose, metabolic and other responses vary markedly across individuals [21].

Diet patterns are poorly defined and/or still reductionist

Focusing on inclusive diet patterns may indeed be more informative than focusing on single nutrients and we should welcome large, pragmatic trials on diet patterns. However, there are multiple ways that such patterns can be defined and analyzed. E.g. what exactly constitutes a Mediterranean diet? The best effort to test Mediterranean diet by top Mediterranean diet experts was rightly criticized that it did not really test Mediterranean diet [22]. Literature reviews shows many different conceptual definitions of Mediterranean diet and even more numerous different implementations thereof [23, 24]. In theory, there are millions of ways of defining Mediterranean diet depending on what components are included in the definition and what quantitative thresholds are set.

Moreover, when extremely complex patterns are reduced to one or few dimensions, as in many key questions tabulated by Giovannucci (e.g. saturated versus monounsaturated fat, specific types of fiber, omega-three fatty acids, potassium/sodium ratio, or sugar), oversimplified reductionism is re-appearing. Zillions of variables are ignored simply because we believe to know a priori which variable matters.

What is the architecture of nutritional causal effects?

We need some modest consensus about the size and distribution of causal effects of nutritional risk factors. What are we searching for? E.g. in genetics, the median genome-wide significant SNP discovered in the UK biobank explains less than 0.0005 of the risk variance [25]. Genetic factors explaining > 1% of common disease risk are unusual. For convenience, let us bin causal nutritional risk factors as infinitesimal, tiny, small, modest, and large if they change life expectancy < 10 days, 10–30 days, 1–3 months, 3 months–1 year, and > 1 year, respectively. How many risk factors fall in each bin? Giovannucci believes that we search for dietary silver bullets equivalent to smoking that is expected to cause 1 billion deaths within a century. I fear that equating any "bad" food combo to cigarettes is misinforming the public so much than no tobacco marketing department could ever imagine.

Data from the Harvard team suggest that 5 optimal health behaviors, including good diet, increase life expectancy by 12–14 years [26]. Although lifestyle behaviors are correlated and difficult to disentangle, this might suggest a net benefit of < 2–3 years by "good quality" diet alone. We have numerous dietary candidates that each alone seems to explain this entire benefit in inflated observational claims. E.g. it is claimed that red and processed meat alone cause 2.4 million deaths annually [27]. The claimed mortality impact is huge with almost anything: single serving of whole grain, minute amounts of beta-carotene, or three cups of coffee have been reported to each cut mortality risk by 15–20% [28–30], each alone adding 2–3 years of life expectancy. Implausible relative risks get translated to implausible burden of disease estimates that are quoted and circulated widely without acknowledging their uncertainty, let alone bias. Misleading policy and guidelines follow.

The totality of reported nutrients, foods, and diet patterns that have reported modest or large benefits in the hypothesis-venerating epidemiological literature is simply ludicrous [31], even accounting for considerable correlation. Correlation between nutritional factors suggests further that most of these exaggerated factors are probably not causal. Focusing intervention efforts on non-causal exposures may be a waste.

Measurement errors and unaccounted multiplicity

Giovannucci acknowledges that nutritional questionnaire tools incur significant measurement error but considers them adequate for most circumstances. This argument depends critically on the untenable assumption of very large effects. Measurement problems have been repeatedly discussed [2, 32–36]. Actually, if errors are non-differential, the effects corrected for non-differential misclassification become even stronger and even more implausible. Moreover, given large inaccuracy [32], one cannot fully account for imbalances in caloric intake and examine the impact of food "quality" beyond simply caloric intake differences.

Furthermore, even though diet measurement tools by default encompass extreme multiplicity, this is rarely accounted in analyses; most nutritional epidemiological studies use $P < 0.05$ thresholds. The 10 papers evaluating sugar sweetened beverages and diabetes had a median of 196,608 (range, 3072–117,117,952) comparisons that could have been made [37]. Even $P < 0.0001$ means nothing in such settings.

Speculated tolerance to confounding

Giovannucci believes that confounding in nutritional epidemiology is as manageable as for other established lifestyle risks. Again, this argument presumes effects of specific dietary factors as large as those of smoking or heavy alcohol consumption. However, most dietary effects probably resemble those of 1 drink/day for alcohol—answering whether 1 drink/day increases disease risk is similarly extremely difficult in cohort studies.

Even well-trained scientists pick different designs and adjust for very different covariates and in very different ways in analyzing observational data [38–40]. The range of different results obtained ("vibration of effects") is wide, including results in opposite directions, the so-called Janus phenomenon [41]. E.g. simple multivariable adjustment choices in the same database can infer that vitamin E increases or decreases mortality [41]. Unsurprisingly, early claims for huge benefits from vitamin E [42] were not subsequently validated [43].

Giovannucci claims that studying integrated dietary patterns solves the problem. Again, this presumes huge effects for diet patterns and assumes that zillions of other effects embedded in these patterns (which are not even well-defined) cancel themselves by unexplainable magic.

I sympathize with Giovannucci's speculation that exercise is overall most important and diet choices may matter mostly for those with little/no physical activity. Still, nutritional epidemiology seeking "good quality" silver bullets is equivalent to probing questions like "is playing frisbee more beneficial than taking your dog for a walk", dilemmas rather intractable to our research armamentarium.

Option 1: just run large pragmatic trials

Perhaps observational designs are simply unsuitable for nutritional questions. Perhaps, we should simply shift emphasis to more, better, larger, pragmatic randomized trials. These have their own weaknesses, e.g. they are affected by non-adherence. This means they are still excellent choices to study effectiveness (which incorporates also potential non-adherence), i.e. what matters for practical guidance on what to eat ("intention-to-eat") [2, 4, 44]. Most questions that Giovannucci tabulates are suitable for randomized trials with hard clinical and death outcomes, not just metabolic surrogates.

Option 2: give epidemiology a chance

Instead of discarding observational designs, we should allow them their best shot removing selective analysis and reporting bias [45] and optimize choice of interventions to test in trials. This requires performing nutrition-wide analyses across all available measured exposures [46–50]. These analyses should consider systematically both single chemicals/nutrients, as well as foods, and diet patterns, i.e. leaves, trees, and tree clusters in the forest. This approach is applicable to both current and future (hopefully better) measurement tools. Nutrition is not the same as genomics; if anything, the differences [51] make the need for systematic, unbiased approach more imperative.

Nutrition-wide assessments, transparency and trust

These analyses should be done both by investigators holding the primary data and, independently, by seasoned methodologists with contrarian views. The big picture of the published literature is highly compatible with selective analysis and publication bias. Grand-scale bias is exactly what one expects when extremely smart and competent scientists like Giovannucci and his colleagues "know" where the important results should lie and search devotedly for them under a lamp post in what is a large, dark forest. Visualizing the full architecture of associations and correlation patterns across variables at different levels of aggregation is an indispensable first step.

Leading nutritional epidemiology teams should share their raw data with scientists espousing different narratives. Nutritional epidemiology cohorts have already published thousands of papers highlighted single/few associations. Nutritional epidemiologists represent the most populous group among the most prolific authors across all biomedical science [52]. Independent methodologists should be allowed to perform all-encompassing nutrition-wide analyses from each of these cohorts.

Transparency, sharing, and independent analyses will vastly upgrade the credibility of the field. E.g. a key feature distinguishes air pollution epidemiology whose credibility is strong versus nutritional epidemiology where even minimal credibility is routinely questioned. In the former, raw data have been independently re-analyzed and results were mostly robust [53] to different analyses explored by independent analysts, including contrarians. Independent validation and demonstration of robustness to different assumptions gained widespread consensus on air pollution. Nutritional epidemiology needs to make the same step.

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