

Nutritional epidemiology, extinction or evolution? It is all about balance and moderation

Sanne Verhoog¹, Pedro Marques-Vidal², Oscar H. Franco¹

¹ Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

² Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Correspondence to: Sanne Verhoog, Mittelstrasse 43, 3012 Bern, Switzerland.

sanne.verhoog@ispm.unibe.ch

Word count without abstract: 1456

Word count abstract: 264

Abstract:

There is ongoing debate regarding the contribution, role and future of nutritional epidemiology and whether the field needs radical reform. We believe this debate is like diet: the key factors are balance and moderation. Diet and its assessment are both extremely complex. In addition, obtaining biomarkers is equally complex, and the time required to estimate true average nutrient intake varies dramatically. Despite these challenges, there have been great advances in nutritional epidemiology. However, the majority of evidence has been generated by observational studies and contradictory findings are not often replicated. The future of nutritional epidemiology is jeopardized by the quality of the findings and the characteristics of the existing efforts. Although diet remains important and research into diet essential for prevention and care, how the future efforts of nutritional epidemiology should be designed and conducted remain a subject of heated debate. Should the *status quo* be preserved with few modifications? Or should nutritional epidemiology evolve, invoke parallel efforts in similar fields and substantially reform its strategy and design? An approach merging both sides of the debate is required. Extinction or evolution? The field of nutritional epidemiology could be witnessing an event equivalent to the Triassic-Jurassic extinction with the disappearance of “single” studies (single-nutrient, single-population, single-observation) vacating the field for dinosaurian efforts (gargantuan RCTs, multiple replication studies combined in one, megalodontic individual participant-based meta-analyses) equivalent to a Jurassic era in nutritional epidemiology. What will follow is unknown, but in advance of better evidence materializing, let us enjoy what we eat—of course in balance and moderation. Despite the differences of opinion, the old advice prevails.

In an editorial published in the September 2018 edition of JAMA, Ioannidis discussed the status of nutritional epidemiology and stated that radical reform is needed.¹ Diet is complex, the methods currently available to assess it are inadequate and randomized controlled trials (RCTs) do not support the findings from observational studies.

In this issue of the European Journal of Epidemiology (EJE), Giovannucci contradicts the arguments of Ioannidis by stating that current methodologies such as food frequency questionnaires and hypothesis-based approaches are sufficient to overcome the complexity of diet and deal sufficiently with confounding, and that considerable RCT data link common dietary factors to risk factors for major diseases. In response, also in this issue of EJE, Ioannidis cautions that diet complexity should not be oversimplified and mentions again the shortcomings of current methods. Ioannidis suggests two options for a radical reform: 1) large pragmatic randomized trials, and 2) giving nutritional epidemiology a chance by adopting a transparent approach of nutrition-wide analyses of single nutrients, foods, and dietary patterns simultaneously that test their robustness to different analytical choices.

Antipodal opinions need not be irreconcilable. We believe debates in nutritional epidemiology are just like diet: the key factors are balance and moderation.

On one hand, Ioannidis is correct: diet and its assessment are extremely complex for several reasons. First, regardless of whether food is branded or harvested, its composition is extremely varied. Cans of Coke and other top brand fizzy drinks contain widely differing amounts of sugar depending on where they are sold.² The median Selenium (Se) concentration in Brazil nuts varies from 2.07 mg kg⁻¹ (in Mato Grosso state) to 68.15 mg kg⁻¹ (in Amazonas state); depending on its origin, a single Brazil nut could provide from 11% (in Mato Grosso) up to 288% (in Amazonas) of the daily Se requirement for an adult man; and this is just nuts.³ Foods can also contain pesticides, mycotoxins, food additives, heavy metals, and environmental contaminants that are rarely measured or taken into account when assessing diet.^{4,5} Second, due to food processing the bioavailability of nutrients may be increased or decreased depending on the process and the food itself.⁶ Thermal processing including bleaching, retorting, and freezing can cause loss of lycopene in tomato-based foods.⁷ Third, interactions between foods or nutrients are rarely taken into account. Various types of fiber can affect the bioavailability of calcium, iron, and zinc in both positive and negative ways.⁸⁻¹¹ Fourth, relying on biological markers as a solution for the complexity of foods is not a panacea: a single 24-h urine collection cannot predict sodium, potassium, or chloride intake; multiple collections are necessary.¹² Finally, adequate assessment of diet might take much longer than initially planned: a Japanese study reported that the number of days necessary to estimate true average nutrient intake

exceeds 50 days for vitamins such as retinol and carotene, and more than a year to adequately estimate intake of seldom consumed foods such as nuts and seeds.¹³ A similar conclusion had been reached in a study conducted in the United Kingdom in which the number of days of survey required for an 80%-reliable classification of individuals varied from 2-3 days for sugar or total carbohydrates, to 2-3 weeks for dietary cholesterol or the ratio of polyunsaturated to saturated fatty acids.¹⁴ A single day's survey classified no nutrients with 80% reliability, whereas one week's survey classified most nutrients with 80% reliability or better.

On the other hand, Giovannucci is correct in stating that studies supplementing specific nutrients are effective when such nutrients are definitely lacking. The treatment of scurvy by oranges and lemons in the eighteenth century by James Lind¹⁵ and the iodine supplementation of salt in Switzerland¹⁶ are striking examples. Conversely, changes in staple food can lead to dramatic issues: in 2004, shifting from untreated to polished rice caused 20 deaths among new-borns in Mayotte.¹⁷ In addition, there are some "natural" experiments showing the impact of diet on cardiovascular disease. The decrease in purchasing power in Poland in the late 1980s led to considerable changes in dietary intake and a 20% decrease in CVD mortality rates.¹⁸ Similarly, "non-natural" experiments such as the Finnish North Karelia Project reduced coronary mortality by 84% between 1971 and 2014, whereby two-thirds of the decline was explained by risk factor changes, including diet.¹⁹ Nutritional epidemiology over the past decades has provided us with a distinction between low and high quality foods. Weight gain has been associated with the intake of potato chips, potatoes, sugar-sweetened beverages, and processed and unprocessed red meats, while weight loss has been associated with the intake of vegetables, whole grains, fruits, nuts and yoghurt.²⁰ Replacing low quality foods with those of high quality is essential in the prevention of obesity and its related diseases. Ultimately, diet does not act alone on health but interacts with physical activity and other lifestyle factors, such as alcohol use, smoking and sleep. High levels of physical activity might mitigate some consequences of poor diet, while sedentariness could counteract the benefits of a good diet. Yet, the largest part of the population fulfils an overall sedentary lifestyle, even if they meet the physical activity guidelines, showing deleterious associations with cardiometabolic health and mortality, highlighting the need to establish and maintain compensatory factors.²¹ In order to prevent non-communicable diseases and improve, maintain and recover health effectively, these lifestyle factors should be neither studied nor intervened in isolation.

It will take further efforts and innovative, thorough approaches to be able to capture the complexity of food intake. Still, there have been undeniably great advances in nutritional epidemiology. Having both

solutions and agreements in the near future of nutritional epidemiology, although desirable, is not essential. Ioannidis suggested two options towards the future, but pragmatic randomized trials still present fundamental challenges unless we control for almost everything and rely on humongous samples; those challenges are insurmountable without colossal efforts requiring gigantic resources. The period needed to obtain sufficient endpoints also precludes any stability in diet. The most achievable experiments might focus on entire countries or communities in which food policies have been dramatically changed due to political, religious, or economic pressure.²² To address Ioannidis's second option, nutritional epidemiology should definitely be given a chance—provided there is also a “radical reform” in the way that journals publish results. Statistically significant results are privileged, while non-significant findings are mostly ignored.²³ Publishing results on a vast range of nutrients, foods, and dietary patterns should become the norm, instead of putting specific (and mostly chance) findings in the limelight and avoiding the not very nutritional habit of salami slicing.²⁴ Ioannidis is also correct in stating that most effects of diet are overrated, and more replication is necessary. With the increasing number of studies conducted worldwide and the increasingly collaborative nature of science, there are few excuses for not seeking external replications of one's findings.

Debate on nutritional epidemiology will not end soon and its existence is a healthy sign of the field. As the debate continues, billions of people in the world are eating every day. Until the controversies are resolved, guidance on what is preferable to eat and what is advisable not to eat, given the overwhelming number of foods available to us, is necessary. Guidelines should theoretically be based on RCTs, but this will require time, great effort, and generous funding before results are available. Therefore, results from well-conducted, long-term prospective studies should be prioritized—provided they correspond to the dietary habits of the country or countries of interest, or they have been replicated across settings.

In the end, it does not matter who is right or wrong. As we said, with diet, balance and moderation are key. Nevertheless, the era of nutritional epidemiology is just beginning. Extinction or evolution? Both, perhaps we are living the end of the Rhaetian age of nutritional epidemiology. Without noticing it, we are witnessing an event equivalent to the Triassic-Jurassic extinction with the gradual disappearance of “single” studies (that is, single-nutrient, single-population, single-observation) which are vacating the field for the domination of dinosaurian efforts (which is to say, gargantuan RCTs, multiple replication studies combined in one, megalodontic individual participant-based meta-analyses) equivalent to a Jurassic era in nutritional epidemiology. Not to mention, an era that could observe the genesis and proliferation of a new species within the WAS genus, the ACEWAS: Anything that Can be Eaten-Wide Association Studies.

What will follow the Jurassic era of nutritional epidemiology is unknown, but in the meantime we all need adequate advice and solutions today, to learn from mistakes incurred in the past, and to not lose sight of a better future. In advance of better evidence materializing, let us at least try to enjoy what we eat—of course in balance and moderation. Despite the debates and differences of opinion, the old advice prevails.

REFERENCES:

1. Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. *Jama*. 2018;320(10):969-970.
2. Action on Sugar. International Sugar-Sweetened Soft Drink Survey 2015. <http://www.actiononsugar.org/media/actiononsugar/news-centre/surveys-/2015/International-Drinks-Data.pdf>. Accessed January 28, 2019.
3. Silva Junior EC, Wadt LHO, Silva KE, et al. Natural variation of selenium in Brazil nuts and soils from the Amazon region. *Chemosphere*. 2017;188:650-658.
4. Caldas ED, Jardim AN. Exposure to toxic chemicals in the diet: is the Brazilian population at risk? *Journal of exposure science & environmental epidemiology*. 2012;22(1):1-15.
5. Nougadere A, Sirot V, Kadar A, et al. Total diet study on pesticide residues in France: levels in food as consumed and chronic dietary risk to consumers. *Environment international*. 2012;45:135-150.
6. Amalraj A, Pius A. Bioavailability of calcium and its absorption inhibitors in raw and cooked green leafy vegetables commonly consumed in India--an in vitro study. *Food chemistry*. 2015;170:430-436.
7. Shi J, Le Maguer M. Lycopene in tomatoes: chemical and physical properties affected by food processing. *Critical reviews in biotechnology*. 2000;20(4):293-334.
8. Bosscher D, Van Caillie-Bertrand M, Van Cauwenbergh R, Deelstra H. Availabilities of calcium, iron, and zinc from dairy infant formulas is affected by soluble dietary fibers and modified starch fractions. *Nutrition (Burbank, Los Angeles County, Calif)*. 2003;19(7-8):641-645.
9. Harland BF. Dietary fibre and mineral bioavailability. *Nutrition research reviews*. 1989;2(1):133-147.
10. Palafox-Carlos H, Ayala-Zavala JF, González-Aguilar GA. The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. *Journal of food science*. 2011;76(1):R6-R15.
11. Reinhold JG, Garcia JS, Garzon P. Binding of iron by fiber of wheat and maize. *The American journal of clinical nutrition*. 1981;34(7):1384-1391.
12. Birukov A, Rakova N, Lerchl K, et al. Ultra-long-term human salt balance studies reveal interrelations between sodium, potassium, and chloride intake and excretion. *The American journal of clinical nutrition*. 2016;104(1):49-57.
13. Egami I, Wakai K, Kaitoh K, et al. [Intra- and inter-individual variations in diets of the middle-aged and the elderly]. [*Nihon koshu eisei zasshi*] *Japanese journal of public health*. 1999;46(9):828-837.
14. Marr JW, Heady JA. Within- and between-person variation in dietary surveys: number of days needed to classify individuals. *Human nutrition Applied nutrition*. 1986;40(5):347-364.
15. Lind J. A treatise of the scurvy. In three parts. Containing an inquiry into the nature, causes and cure, of that disease. 1753; <http://www.jameslindlibrary.org/lind-j-1753/>. Accessed January 28, 2019.
16. Nicod JL. [Endemic goiter in Switzerland and its prevention with iodized salt]. *Bulletin of the World Health Organization*. 1953;9(2):259-273.
17. Quatresous I, Tajahmady A, Sissoko D. *Epidémie de bérubéri infantile à Mayotte - rapport d'investigation 25 mai - 25 juin 2004 [Child beriberi epidemic in Mayotte - report 25 May - 25 June 2004]*. Paris, France: Institut de Veille Sanitaire, Département international et tropical;2004.

18. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991. *BMJ (Clinical research ed)*. 1998;316(7137):1047-1051.
19. Vartiainen E. The North Karelia Project: Cardiovascular disease prevention in Finland. *Global cardiology science & practice*. 2018;2018(2):13-13.
20. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *The New England journal of medicine*. 2011;364(25):2392-2404.
21. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. *Exercise and sport sciences reviews*. 2010;38(3):105-113.
22. Reid S. Why Bhutan's 'hardline vegetarian right' wants everyone in the country to stop eating meat. 2017; <https://www.independent.co.uk/travel/asia/bhutan-hardline-vegetarian-right-stop-eating-meat-travel-tours-holiday-a7608141.html>. Accessed January 28, 2019.
23. Dwan K, Gamble C, Williamson PR, Kirkham JJ. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. *PloS one*. 2013;8(7):e66844.
24. Berlin L. Plagiarism, salami slicing, and Lobachevsky. *Skeletal radiology*. 2009;38(1):1-4.