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COMMENTARY

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

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In an editorial published in September 2018 in 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, 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 Lind [15] and the iodine supplementation of salt in Switzerland

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[16] 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 newborns 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.

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