Review Article

The State of Nutritional Epidemiology: Why We Are Still Unsure of What We Should Eat?

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Abstract

Most people want to know how they can improve their health by implementation of a proper diet. Therefore nutritional epidemiology studies, which correlate the intake of specific nutrients, food items, or dietary patterns with health outcomes, receive substantial interest in the media. However, the results of many nutritional epidemiology studies have not been replicated in subsequent studies. This paper reviews the primary methodological problems in nutritional epidemiology that result in lack of replicability and inconsistency across studies. The problematic methodological issues include substantial measurement error, confounding, the variable effects of food items, variable reference groups, interactions, and multiple testing.

Keywords: Confounding, epidemiology, measurement error, nutrition

"What should I eat to prevent cancer?" is one of the common questions about food that people ask health professionals. Food is a major part of our daily lives and most want to know how to improve health by consuming the proper foods.

The desire to find and consume the proper food to prevent disease or to remedy existing maladies has a long history. Approximately 1000 years ago, Avicenna considered diet to be one the main contributors to health. According to Avicenna, in the *Canon of Medicine*, "Most illnesses arise solely from long-continued errors of diet and regimen."[1] However, Avicenna's specific recommendations would not be considered good health practice today. For example, he counseled that: "The meal should include: (i) flesh, especially that of baby kids of goats, veal, and year-old lamb; (2) wheat, which is cleaned of extraneous matter and gathered during a healthy harvest without ever having been exposed to injurious influences . . . ."[1]

One might assume that Avicenna's recommendations did not stand the test of time because his tools were limited. He did not have many scientific collaborators, a sophisticated laboratory, or elaborate dietary measurement instruments. He could not study large numbers of people over long periods of time, nor did he have access to computers and regression modeling techniques. The question remains if these modern scientific advances have made our knowledge of the relationship between food and health more reliable. The answer is perhaps yes, but not by much.

Despite advances in laboratory science, statistical analysis, and population research, nutritional epidemiology – the science that correlates food and nutrient intake to the occurrence of disease – still suffers from several major limitations regarding the reliability of many of its findings. Examples abound. A highly publicized study published in the *New England Journal of Medicine* in 1981 suggested a strong association between coffee consumption and an elevated risk of pancreatic cancer.[2] This study caused people to temporarily decrease their coffee intake. However, more recent studies have suggested that no association exists between coffee consumption and pancreatic cancer[3,4]; instead it may reduce the overall risk of cancer and all-cause mortality.[5] Similarly, in the early 1980s, animal and human studies suggested that intake of alpha-tocopherol, a form of vitamin E, may protect against lung cancer. However subsequent studies showed that alpha-tocopherol supplementation has no effect on the risk of lung cancer.[6] Research on other vitamins and supplements, too, has generated contradictory results.[7] Despite decades of research in many countries, it is still unclear if higher fat intake, whether overall or of specific types, increases breast cancer risk.[8,9] The role of fruits and vegetables in reducing cancer risk, once thought to be relatively well established, has been questioned.[10] This instability and confusion was reflected in the International Food Information Council's 2012 *Food & Health Survey* that reported more than half of Americans, including 55% of men, think it easier to do their own taxes than to know how to eat healthy.[11]

These examples are not outliers. Numerous associations found in nutritional epidemiology, particularly with respect to chronic diseases such as cancer, have not been replicable, which leaves us in a state of confusion over what to eat and what not to eat. Why is this so? There are a number of reasons why nutritional epidemiology has produced less consistent results than other disciplines, such as infectious disease epidemiology. Among the issues plaguing nutritional epidemiology are: 1) measurement error; 2) confounders; 3) variable effects of food items; 4) variable reference groups; 5) interactions; and 6) multiple testing, all of which are briefly reviewed.

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Measurement error

Lord Kelvin once said: ". . . when you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind".[12] Measuring diet over extended periods of time is possible, but only with substantial error. As explained below, this substantial error renders our knowledge "of a meager and unsatisfactory kind".

The most commonly used tools in nutritional epidemiology are food frequency questionnaires. These questionnaires attempt to assess the habitual dietary intake of study participants over prescribed periods of time, typically one year. The questionnaires are usually lengthy, including between 80 and 200 items, because they need to cover a range of food groups and food items. Measurements using these questionnaires are subject to several errors. First, the study participant might not remember the exact amount of each item (e.g., apples or tomatoes) consumed each week during the past year. Second, people's food intake during the previous year does not necessarily reflect their behavior over their lifetime; they might have changed diets several times for various reasons. Third, the questionnaires are long, and the respondents may not carefully or truthfully answer all questions.

Measuring the diet by other methods is also possible, such as the 24-hour dietary recall. In this method, the study participant provides information about foods and beverages consumed during 24 hours prior to the interview. People may reasonably, although not completely accurately, recollect what they ate and drank over the past 24 hours. A major limitation of this method is that it captures only one day, which may not be a "typical" day. It is possible to do multiple 24-hour recalls (e.g., twelve) over a year. However, some of the issues, such as errors in recall and the time period not representing intake over the life span, still remain. Conducting twelve 24-hour recalls is time-consuming for study participants and expensive for researchers. Only recently have some investigators attempted to reduce the cost of multiple 24-hour recalls by asking study participants to complete self-administered questionnaires over the Internet.[13,14]

Other innovative methods are in use,[13,15,16] but their success remains to be seen. As of yet, no method can measure the entirety of an individual's dietary experience with sufficiently small measurement errors. In some studies the errors are substantial enough to produce serious underestimations of relative risks. For example, validation studies have shown that if the true relative risk for the association between total energy intake or protein intake and a specific disease is 2.0, the apparent relative risk (the one obtained with errors) will be 1.1 or smaller,[17] which may not be statistically significant. Even if a relative risk of 1.1 is statistically significant because of large sample sizes, it might be attributed to potential cofounders and easily dismissed.

Confounders

Confounders are a major issue in all observational epidemiologic studies,[18] and observational studies in nutritional epidemiology are no exception. For example, over the past few decades, coffee drinkers have been more likely to smoke cigarettes. Therefore, coffee intake might be statistically associated with certain cancers, even if it is not the real culprit. Unfortunately confound-ers are difficult to measure and often remain hidden, which may bias the results[18] and lead to erroneous conclusions.

Variable effects of food items

Another source of error is that food items grown and prepared in different parts of the world, or at different times, may have different specific ingredients that change their effects on the human body. For example, if one compares brown to white rice, brown rice has more fibers, a lower glycemic index, and is considered to be less diabetogenic.[19] Therefore, it may be a healthier choice. However, some recent data show that the brown rice currently available in the United States market may have higher arsenic concentrations than white rice,[20] which may change the balance of health effects. How and where the rice is grown and prepared may vary this balance.

Case-control studies have shown that drinking maté, an infusion of the herb ilex paraguarensis, is associated with a higher risk of esophageal cancer.[21] It has been suggested that maté's carcinogenicity is related to its high concentration of polycyclic aromatic hydrocarbons,[22] which are mainly acquired when maté leaves are smoke-dried. However, the concentration of these hydrocarbons can be substantially reduced by changing the method of drying the leaves,[23] perhaps making maté drinks much less harmful.

Variable reference groups

Epidemiological studies compare a specific exposure to an alternative (the reference group). For example, the risk of lung cancer in smokers can be compared to the risk of lung cancer in non-smokers (the reference group).

In nutritional epidemiology, finding a clear-cut reference group is often difficult. Research on the effect of eating rice on diabetes could compare those who eat rice to those who do not, or perhaps those who eat large quantities of rice to those who eat relatively little rice. However, such comparisons are quite different from comparing smokers to non-smokers. One can quit smoking and not replace it with anything. However those who eat little or no rice would have to eat something else to survive. The alternative might be potatoes, bread, soya beans, or a number of other foods. If, in any specific population, the main alternative to rice is boiled potatoes, which have an equal or even higher glycemic index than rice,[24] then eating rice may not be associated with a higher risk of diabetes in that population. By contrast, if the alternative is soya beans, which have a much lower glycemic index,[24] research might find that rice intake is associated with an increase in the risk of diabetes.

The issue of variable reference groups is potentially problematic. To make a decision on causality, researchers often rely on consistency of results across studies. However, variable reference groups may lead to different results, which could make accurate conclusions about causality quite difficult.

Interactions

As in other fields of epidemiology, interactions are also possible in nutritional epidemiology. Intake of a specific nutrient source (e.g., tomatoes, a source of lycopene) may be important if that nutrient is not available from other sources. However, tomatoes may not be an important food item if lycopene is available

through other sources. There may also be other sources of interaction. For example, for reasons that are not clear, beta-carotene supplementation increases the risk of cancer incidence and death in heavy smokers,[6,25] but not in other groups.[26]

Investigating interactions often requires large sample sizes[27] and it is not always clear whether the statistically significant interactions are real or simply results of type I error (i.e., incorrect rejection of a true null hypothesis). Uncertainty about the presence of interactions, when they exist, appears as inconsistency across studies, making accurate causal conclusions difficult.

Multiple testing

Although the problem of finding false positive associations due to multiple testing is not limited to nutritional epidemiology, it may be a more serious issue in nutritional epidemiology compared to other fields. A large number of exposures and outcomes can be examined in nutritional epidemiology. Food frequency questionnaires, which typically have between 80 and 200 items, provide measurements of a large number of exposures that are available for statistical analysis. In addition to food items, nutrients, food groups, and food patterns can be recorded, calculated, and analyzed. Also, foods are examined in relation to nearly all diseases in all organs. These false positive associations, which are often reported in the media with enthusiasm, incorrectly make a food appear sometimes as healthy and at other times as unhealthy.

Conclusion

Nutritional epidemiology has enjoyed important successes over the past few decades. The collective information gathered thus far suggests that avoiding excessive calories, eating white meat rather than red meat (particularly processed red meat), increasing consumption of fruits and vegetables, and replacing saturated fat with mono- and poly-unsaturated fats are good for overall health. However, progress in this field has been slowed by the contradictory results that have frequently emerged in peer-reviewed literature. Questions of what specific food items (e.g., apples or oranges) are healthiest remain almost completely unanswered. The slow progress and controversial results are due to numerous limitations of nutritional epidemiology, including substantial measurement error, confounders, the variable effects of food items, variable reference groups, interactions, and multiple testing. Measurement error usually attenuates relative risks toward null, which generates false negative results. On the other hand, multiple testing results in false positive findings. Other problems (e.g., confounders) can make the results both false positive and false negative. Therefore, in nutritional epidemiology, a large proportion of both positive and negative findings may be false. Research is ongoing to reduce measurement errors and to identify statistical methods that reduce the impact of such errors. Until substantial improvements are made in these fields, nutritional epidemiology studies will likely continue to produce inconsistent results.

Acknowledgments

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