Mostly, mothers are concerned about food. Mothers tell you what to eat and what not to eat, how much of it to eat or not eat, when to eat it, and why you should or should not eat it. Mothers seem to know. The question is, who knows more about good nutrition, mothers or nutritional epidemiologists?

Knowledge and common wisdom about the importance of diet have been handed down from generation to generation for millennia. While the formal study of diet and health is only a few decades old, the importance of diet to maintain health was already known to the ancient Greeks. As Hippocrates (460–377 BC), the father of Western medicine, put it: 'If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.'

The first population-based studies collecting information on nutrition were conducted in the 20th century. Data on only a few foods were collected generally and were cross-classified with disease outcomes. More detailed dietary assessment instruments were subsequently developed, the most popular of which are the 24-hour recall, a food diary kept for several days, and the food frequency questionnaire (FFQ).

Nutritional epidemiology is one of the younger disciplines in epidemiology. This may be partially due to the difficulties in measuring diet as an exposure. Diet and physical activity are arguably the most difficult exposures to assess in observational research and are plagued by considerable measurement error. We all eat, we all eat many different foods, we tend to forget rather quickly what we ate, and we often do not know the ingredients of the dishes we consume. Hence we are all exposed, and the variation may be more subtle than with other, more distinct exposures such as smoking or use of hormone replacement therapy. Few people maintain extreme diets; thus assessing diet within fairly homogeneous populations makes it difficult to detect associations between dietary patterns (or particular foods and nutrients) and health or disease due to the lack of sufficient variation.

Over the past couple of decades, a large number of observational studies have attempted to elucidate the role of diet in health and disease. Most of these studies were based on a case-control design. Unfortunately, case-control studies of diet are generally problematic since participants are asked to remember their diet prior to a particular time in the past, and cases are asked to recall their diet prior to the date of their diagnosis. Remembering past diet is difficult, participants' reports are influenced by their current diet, and the differential recall among diseased and non-diseased individuals presents an inherent bias that is difficult to overcome. Prospective cohort studies with real-time assessment of diet offer the best opportunity to gather valid and reliable information on nutrition.

Can humans be randomized to strict diet schemes? Historically, the first controlled trials of which we are aware were dietary interventions. Reference to a dietary trial was made in the Bible: Daniel and his friends were to be trained at court and assigned a daily allowance of food and wine from the royal table. Daniel, determined not to contaminate himself, convinced the guard to give them only vegetables to eat and water to drink for 10 days. At the end of the 10 days they looked healthier and were better nourished than all the young men who had lived on the food assigned to them by the king. So the guard put aside the food and wine that was allocated to them and gave them vegetables.

In 1747, Captain James Lind on the HMS Salisbury, found himself losing his sailors to a mysterious disease. Suspecting that dietary deficiency was the culprit, he decided to allocate six different diets to 12 of his crew members. Everyone received the same basic diet, but each of the six groups received different additional foods. One group was given oranges and lemons. This group quickly recovered from the mysterious disease later identified as scurvy.
Captain Lind’s experiment may be one of the few examples of a dietary allocation that worked. It was a short-term intervention that led to fast recovery from a disease. Randomized controlled allocation of diet is likely to be successful only for severe dietary deficiencies that can be reversed in a short period of time, or for allocation of dietary supplements. Studying the effects of dietary composition on long-term health using randomization presents a serious challenge. Ethical principles do not permit randomizing individuals to a diet that, according to scientific evidence, may have harmful effects. Participants can be randomized only to maintaining their diet or to a diet with uncertain impact on the health outcome of interest. Adhering to an altered diet over an extended time period presents an unreasonable challenge for most people, and sufficient differences in diet between intervention and control groups are extremely difficult to maintain.

What then have we learned from observational studies—in particular, prospective cohorts—about the effect of diet on health? We have been able to determine that diet plays an important role in coronary heart disease prevention with transfats, saturated fats, and a high glycaemic index promoting heart disease and a diet high in fibre, fish oil, and polyunsaturated fats decreasing the risk. Not surprisingly, diet has been found to be a crucial factor in the aetiology of type 2 diabetes. One of the most important questions that remains unanswered is what role diet plays in cancer aetiology. Few dietary components have been convincingly linked to cancer outcomes. Red meat consumption has been fairly consistently related to colorectal cancer incidence, and alcohol consumption seems to increase the risk of a number of cancers. Biologically, nutrients could have anticarcinogenic and carcinogenic effects based on their possible influence on oxidation, methylation, DNA repair and other capacities—possibly affecting initiation, promotion, and progression of cancer. Thus far, however, these theoretical properties of nutrition have failed to translate into detectable effects.

The observed lack of association between diet and cancer could have a number of explanations. It is possible that diet plays only a minor role in cancer prevention. Alternatively, if a modest association exists, measurement error in dietary intake may conceal it. A true reduction or increase in cancer risk of 10–30% may be impossible to detect. Furthermore, insufficient variation in diet among the study population may not permit meaningful comparisons. An important difference, however, in the aetiology of heart disease and type 2 diabetes and that of cancer is the long latency in the development of tumours. Initial malignant transformations and clinically manifest cancer may be separated by several decades. For dietary factors to act in this lengthy process, long-term diet and, possibly, nutrition during early periods of life may be relevant.

Where do we go from here? Hopefully towards accurate methods of assessment and analyses of nutritional data, towards identifying the role of diet at various times in life, and towards systematically studying populations with large variations in diet. Statistical models of diet—disease relations have focused on the role of individual foods and nutrients. Foods and nutrients, however, are not consumed in isolation. Our diet consists of a variety of foods and nutrients that are consumed in varying amounts according to individual preferences. Interactions of food constituents in their impact on health and disease are likely. Recent attempts to incorporate dietary patterns into our analytical models have explored the possibilities that factor analysis, principal component analysis, cluster analysis, and diet scores have to offer. While identifying patterns or scores that relate to health is relevant for public health recommendations, they are less relevant for understanding underlying mechanisms. Revealing possible gene—diet interactions may provide new insights into the effects of nutrition, which might allow targeted dietary interventions. Moreover, Mendelian randomization may prove more powerful and allow detection of the main effect of a genotype, which mimics the influence of the dietary factor.

Nutritional epidemiology has focused on the role of diet during adulthood; few studies have considered early life diet. Chronic diseases may well originate in childhood and nutrition during these early periods may have long-lasting consequences. Tissues may be particularly susceptible to the influence of nutrients during periods of growth, the effect of diet may be cumulative, and the long-term impact may only translate into disease decades later. There is a need to examine diets at various times in life and with long follow-up, especially for studies of cancer.

It is possible that the aforementioned lack of variation in diet in the populations studied presents a crucial obstacle in identifying the true role of diet in health and disease. Most participants in epidemiological studies follow a diet without major restrictions. Migrant studies have taught us that environmental factors are major contributors to most chronic diseases, independent of the genetic background of the population. Cancer rates change dramatically in populations migrating from countries of sparse nutrition to those of more affluence. Though other environmental factors probably play an important role, the influence of dietary changes is likely. Moreover, countries experiencing changes in dietary trends also see differences in chronic disease rates; in Japan, where diet has changed from one based mostly on plants and fish to a more Westernized diet, cancer rates are on the rise.

Dietary regimens more extreme than vegetarianism or high fruit, vegetable, and fibre consumption have been explored in Europe. The potential therapeutic effect of nutrition on chronic disease was described a century ago. Patients with severe gastrointestinal diseases and rheumatoid arthritis recovered after interventions consisting largely of raw fruit, berries, vegetables (salad and roots), nuts, and freshly ground whole grains. Although these observations were case series rather than the results of comparisons within properly conducted observational studies, this work provides valuable clues about the role of diet. The results from population-based observational studies have not provided the relevant data on whether a more restricted diet consisting of fresh, ‘living’, and whole foods including freshly ground whole grains, plant proteins, and a large variety of organic and/or biodynamically grown raw fruits and vegetables, as for example practised among the anthroposophic community, might have a profound effect on cancer incidence. The potential beneficial effect of such living raw plant foods is not explained by the caloric energy it provides (which is chaotic heat) but rather its ‘ordered’ energy which, according to the laws of physics, can store information and therefore promote healing. Well-designed epidemiological studies among populations following such extreme diets are warranted and may provide invaluable insights.
Measuring dietary intake in large populations remains a challenge. In an attempt to reduce the misclassification inherent in diet assessment, measurement error correction models have been developed but are seldom used.\textsuperscript{19–21} Biomarkers of nutrient intake represent the optimal standard for calibration of questionnaire-based diet assessment methods, as the errors of the two methods are uncorrelated and therefore a true reduction of the questionnaire errors should be possible. Unfortunately, biological markers are currently not available for most nutrients, but much hope is held for their development.

Another issue of concern in nutritional epidemiology is confounding. Individuals who try to eat a healthy diet are likely to lead a healthy lifestyle in general. It is probably not possible to measure all important markers of a healthy lifestyle sufficiently to eliminate confounding. The inability to distinguish the effect of diet from that of other lifestyle factors may pose a threat to the validity of diet—disease associations observed in epidemiologic studies.

In the meantime, most observations made in nutritional epidemiology would not surprise your mother. There are a few exceptions. The identification of transfatty acids in (partially) hydrogenated oils and vegetable shortening and their hazardous exceptions. The identification of transfatty acids in (partially) epidemiology would not surprise your mother. There are a few epidemiologic studies.

In the meantime, most observations made in nutritional epidemiology would not surprise your mother. There are a few exceptions. The identification of transfatty acids in (partially) hydrogenated oils and vegetable shortening and their hazardous effect on health has been one of the most important findings in nutritional research.\textsuperscript{22} Furthermore, the distinction between ‘good’ and ‘bad’ fats is a significant contribution to shaping the optimal diet.\textsuperscript{23} Mother, however, told you a long time ago that refined carbohydrates are bad for you and whole grains are the way to go. At least my mother did.

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