REVIEW ARTICLE

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Diets

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CME

Food consumption provides essential and nonessential nutrients in the human body and thereby promotes growth and health. Individual food choice and the potential modification of eating habits are complex issues, influenced by the availability and acceptability of foods.[1] The availability of foods depends on physical, political, and economic factors. From the myriad foods that are available or potentially available for consumption, the selection is based on socioeconomic, cultural, and individual factors. Individual foods are parts of diets; diets are characterized by nutrient content, clustering of foods, and temporal consumption patterns. The plethora of diets continually expands, and some diets have been extensively investigated.

We review the underlying rationale for and constituents of the most widely recognized, scientifically explored, and broadly promoted diets (Fig. 1). We do not review diets for specific nutritional or metabolic deficiencies or many of the constructed dietary indexes. This review is not intended to detail the clinical efficacy of each diet presented, although we briefly outline some of the well-known potential effects on health and the underlying mechanisms. Even though most (but not all) of the dietary modifications have been driven by the desire to control body weight, we consider important health effects independently of adiposity.

PLANT-BASED DIETS

MEDITERRANEAN DIET

Scientific research on the dietary patterns adopted by people in the Mediterranean region and the potential health effects of these patterns started after the Second World War, led by two scientists based in the United States. Leland Allbaugh, the field director of a survey on the island of Crete that was funded by the Rockefeller Foundation, described the diet of Cretan people as "surprisingly good" and "extremely well adapted to their natural and economic resources as well as their needs."[2] This diet consisted of olives, cereal grains, pulses (edible seeds from legumes), fruits (the typical after-dinner dessert), vegetables, and herbs, together with limited quantities of goat meat, milk, game, and fish. Bread (whole-grain, made of barley, wheat, or both) had a predominant role at each meal, and olive oil accounted for a relatively large proportion of energy intake.

The second scientific investigation that endorsed the health-related attributes of the Mediterranean diet is the Seven Countries Study, led by Ancel Keys.[3] The original design of the study included a comparison of diets and lifestyles among seven countries that was based on data from one or more cohorts of men in each country. Rates of death from any cause and death from coronary heart disease were lower in the cohorts for which olive oil was the main dietary fat than in the northern European and U.S. cohorts.[4]

Nowadays, the term Mediterranean diet is used to describe a dietary pattern

characterized by the predominance of plant foods (fruits, vegetables, cereals with as little processing as possible, pulses, nuts, and seeds), with moderate amounts of dairy products, mostly fermented (e.g., cheese and yogurt); low-to-moderate amounts of fish and poultry; low amounts of red meat; and usually wine along with the meal.[5] This diet has been the most extensively investigated, representing a potential dietary modification of great interest for many health outcomes.

An umbrella review of meta-analyses of observational studies and randomized clinical trials, with data from more than 12,800,000 participants, suggested that the evidence is robust for a protective association between adherence to the Mediterranean diet and the following health outcomes (of 37 examined): death from any cause, cardiovascular diseases, coronary heart disease, myocardial infarction, cancer, neurodegenerative diseases, and diabetes.[6] The beneficial effects of the Mediterranean diet may be mediated through multiple mechanisms, including reductions of blood lipids and inflammatory and oxidative stress markers, improvement in insulin sensitivity, enhancement of endothelial and antithrombotic function, and even a reduction in cerebral neurodegenerative changes.[7,8]

VEGETARIAN DIETS

Vegetarian diets have been adopted since antiquity for ethical or philosophical reasons and as part of religious commitments. Since the last decades of the 20th century, however, increasing attention has been given to the associated health effects of vegetarian diets, as well as the ecologic benefits (lower greenhouse gas emissions and less water and land use).[9] Nowadays, vegetarianism may comprise a range of eating behaviors characterized by various attitudes, perceptions, motives, and also social and health dimensions. A vegetarian diet can be defined as any dietary pattern that excludes meat, meat-derived foods, and to varying extents, other animal products, whereas plant-based is a broader term, used to characterize dietary patterns that rely mostly on foods of nonanimal origin but do not exclude foods of animal origin. The Mediterranean diet is an example of the latter type. Fruits, vegetables, grains, nuts, seeds, and legumes or pulses constitute an important part of vegetarian and plant-based diets.

A vegan diet is a strict form of a vegetarian diet, consisting of only plant foods and excluding all foods and beverages that are wholly or partly derived from animals. In the lacto-vegetarian diet, dairy products are part of the dietary regimen,

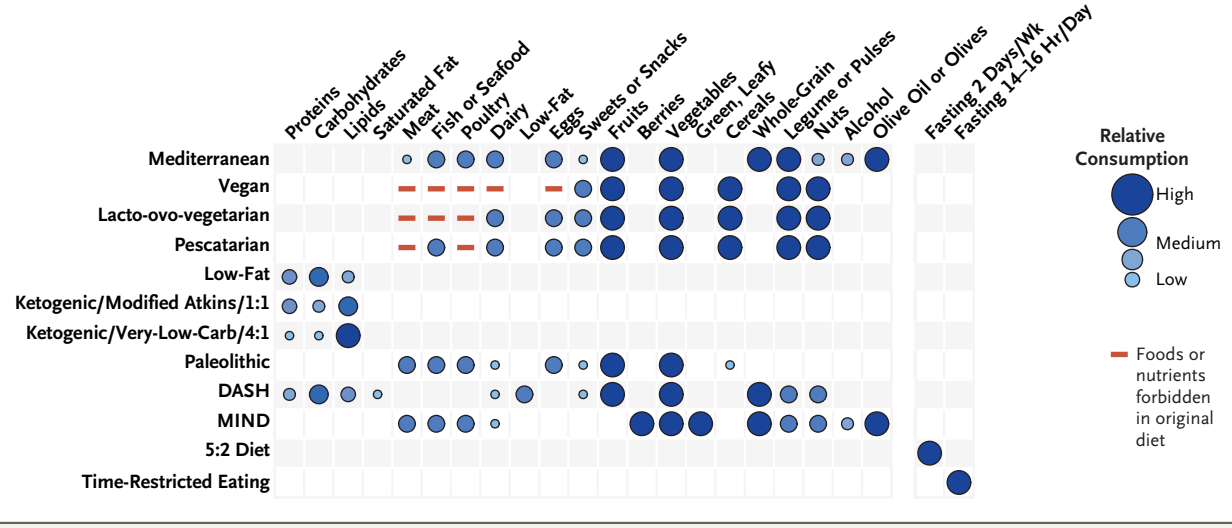

Figure 1. Relative Consumption of Foods and Nutrients and Temporal Patterns of Consumption Associated with Common Diets.

Data are based on the original or most widely accepted definition of each diet shown. Circle size and color intensity indicate relative consumption. Empty cells indicate that the nutrients or foods are not included in the original diet definition. Carb denotes carbohydrate, DASH Dietary Approaches to Stop Hypertension, and MIND Mediterranean–DASH Intervention for Neurodegenerative Delay.

and in the ovo-vegetarian diet, eggs can be consumed; in the lacto-ovo-vegetarian diet, the most common version of the vegetarian diet, both dairy products and eggs are allowed. The pescatarian diet allows fish and shellfish, as well as dairy products and eggs. Finally, there are several versions of flexible dietary patterns, classified under the broad umbrella term flexitarian diets, which are basically vegetarian diets that include some animal products, with varying amounts and combinations.

Given the multitude and multidimensionality of vegetarian dietary patterns, singling out a specific biologic mechanism is quite challenging. Influences on multiple pathways have been invoked, including metabolic, inflammatory, and neurotransmitter pathways; gut microbiota; and genome instability.[10,11] Greater adherence to vegetarian diets has been linked to a reduced risk of cardiovascular diseases, ischemic heart disease and death from ischemic heart disease, dyslipidemia, diabetes, certain types of cancer, and potentially, death from any cause.[12-15] Associations between adherence to vegetarian diets and body composition, anthropometric markers, and body weight–related measures have been debated.

The more restrictive the diet, the higher the risk of various nutrient deficiencies.[16] Vegans are particularly susceptible to vitamin B_{12} deficiency, since vitamin B_{12} is present only in foods of animal origin, and lower intakes of other nutrients (including vitamin B_2, niacin, iodine, zinc, calcium, potassium, and selenium) have also been reported. Nutritional supplementation or intermittent consumption of animal protein in low-to-moderate amounts (the flexitarian approach) may mitigate potential adverse health effects.

LOW-FAT DIETS

Because lipids and carbohydrates are the two macronutrients that make the greatest contribution to total energy intake in modern diets, a balance of these macronutrients is the goal of several dietary modifications for successful weight management and other health outcomes. Low-fat diets for weight loss were already in place before they were promoted by the medical community to reduce the risk of cardiovascular disease.[17] During the 1980s, dietary fat was blamed for coronary heart disease and obesity. Low-fat diets, low-fat products, and the ideology of low fat became increasingly popular.

Although no definition is universal, when lipids contribute less than 30% of total energy intake, the diet is considered to be low in fat. In very-low-fat diets, 15% or less of total energy intake is derived from lipids (e.g., a 2000-kcal diet plan would include <33 g of lipids), leaving approximately 10 to 15% from proteins and 70% or more from carbohydrates.[18] The Ornish diet is a type of very-low-fat vegetarian diet in which lipids contribute 10% to daily calories (ratio of polyunsaturated to saturated fats, >1) and in which persons otherwise eat as desired.[19] The nutrient adequacy of low-fat and very-low-fat diets is highly dependent on individual food choices. Adherence to these diets may be challenging, since not only many foods of animal origin but also vegetable oils and oily plant foods (e.g., nuts and avocados) must be restricted. Supplementation with fortified products may be considered in such cases.[20]

Low-fat diets have been evaluated in several well-designed studies and dietary interventions,[21] including the Women's Health Initiative Dietary Modification Trial.[22] The results of this trial provided evidence of lower mortality from breast cancer among women who were advised to follow a low-fat diet (20% of calories from lipids) than among those who followed their usual diet, but the difference was small. Low-fat interventions appear to lead to weight loss, as compared with the usual diet, but may be less effective than low-carbohydrate or other diets.[23,24] In addition, low-fat diets may have a beneficial effect on various cardiometabolic factors, including blood lipids (particularly low-density lipoprotein [LDL] cholesterol, but with a controversial, lowering effect on high-density lipoprotein [HDL] cholesterol) and blood pressure, with reduced risks of myocardial infarction, diabetes, and death from any cause.[23,25-27] However, the type of fat consumed may also matter. The literature on the biologic mechanisms linking various fatty acids with cardiovascular disease and total lipid intake with obesity is extensive, and proposed mechanisms for the associations of low-fat diets with cancer have included immune alterations, antiinflammatory changes, and fatty acid–related reactive oxygen species production.[28]

CARBOHYDRATE-RESTRICTED DIETS

ATKINS, KETOGENIC, AND LOW-CARBOHYDRATE DIETS

Since the end of the 19th century, there have been medical reports on the potential health effects of diets with low–to–very-low carbohydrate content and no restrictions on lipids, proteins, and total energy intake. The initial therapeutic focus was on weight reduction and on the management of drug-resistant epilepsy. However, the widest promotion of these dietary patterns that induce the production of ketone bodies came after the publication of *Dr. Atkins' Diet Revolution* in 1972. Despite the popularity of these diets, several concerns were raised. The Council on Foods and Nutrition of the American Medical Association criticized the scientific evidence behind this approach and the potentially harmful health effects, mainly on the cardiovascular system.[29]

However, in the 2000s, some randomized controlled trials showed that participants who were advised to follow diets with the lowest carbohydrate content (i.e., versions of the Atkins diet) had greater weight loss and greater improvements in some risk factors for coronary heart disease than those assigned to diets with higher carbohydrate content.[30-33] Although the superiority of this dietary modification was not found to persist in all studies at the follow-up or maintenance phase and although adherence was variable, the scientific community subsequently began to explore the clinical potential of this diet more thoroughly.

The term ketogenic is used to describe a variety of diets. For most persons, consumption of only 20 to 50 g of carbohydrates per day leads to the presence of measurable ketones in the urine. These diets are referred to as very-low-carbohydrate ketogenic diets.[34] Another classification, used mostly in the management of drug-resistant epilepsy, is based on the ratio of dietary lipids to the sum of dietary proteins and carbohydrates.[35] In the classic or most strict version, this ratio is 4:1 (diets in which <5% of energy is derived from carbohydrates), whereas in the most relaxed option, the ratio is 1:1 (the modified Atkins diet, with approximately 10% of energy from carbohydrates), with several options in between.

Diets containing higher amounts of carbohydrates (50 to 150 g per day) are still considered to be low in carbohydrates, as compared with the usual consumption, but these diets may not induce the metabolic changes of the very-low-carbohydrate diets. In practical terms, any diet in which carbohydrates contribute less than 40 to 45% of total energy intake, a percentage that is assumed to represent the average carbohydrate consumption, can be classified as low in carbohydrates. Several popular diets may fall into this category. In the Zone diet, 30% of calories are from protein, 30% are from lipids, and 40% are from carbohydrates, and every meal should conform to a protein-to-carbohydrate ratio of 0.75.[36] The Zone diet, along with the South Beach diet and other low-carbohydrate diets, promotes the consumption of complex carbohydrates, with the aim of reducing postprandial serum insulin concentrations.[37]

Diets that restrict carbohydrates concomitantly induce metabolic changes, to a greater or lesser extent, that are similar to those seen during a starvation state (e.g., changes in plasma levels of free fatty acids, insulin, glucose, and ketone bodies).[38] Since a decrease in one particular macronutrient is always accompanied by a parallel increase in another macronutrient, it is important to evaluate these diets by taking into account not only the low carbohydrate content but also the high content of lipids, protein, or both.

Evidence from long-term studies (i.e., >6 months) suggests that diets that are very low or low in carbohydrates result in weight loss that is equivalent to — not better than — that achieved with other diets that have a higher carbohydrate content.[39] On the other hand, randomized controlled trials have shown that low-carbohydrate ketogenic diets effectively reduce cardiovascular risk factors (levels of blood glucose, glycated hemoglobin, and certain but not all blood lipids), especially in patients with overweight or obesity and type 2 diabetes.[40,41] Ketogenic diets have been reported to significantly reduce body weight and fat mass in patients with cancer.[42] Interest is growing in the potential effects of these diets on schizophrenia and mood disorders, as well as the role of these diets in relation to cognitive function, Alzheimer's disease, and other dementias.[43,44]

The anticonvulsant effect of the ketogenic diet occurs through a series of potential mechanisms that stabilize synaptic function and increase resis-

tance to seizures. Such mechanisms are not fully understood but include central nervous system carbohydrate reduction and glycolysis inhibition, changes in neuronal excitability by ATP-sensitive potassium channels through alterations in mitochondrial function, inhibition of the mammalian target of rapamycin (mTOR) pathway, and inhibition of glutamatergic excitatory synaptic transmission.[45] Thus, low-carbohydrate ketogenic diets seem to reduce the frequency of seizures in children with drug-resistant epilepsy.[46] Benefits in seizure control appear in the short-to-medium term and seem to be similar to the benefits of current antiepileptic drugs.[47] Some efficacy in seizure reduction, albeit not as great, has been shown with less restrictive forms of the ketogenic diet.[46,47] Ketogenic diets may also reduce the frequency of seizures in adults with drug-resistant epilepsy, although the evidence is uncertain,[47] and some promising results have been reported in adults with super-refractory status epilepticus.[48] The most commonly reported adverse clinical effects of the ketogenic diets include gastrointestinal symptoms, such as constipation, and dyslipidemia (potentially related to animal sources of protein, which are often rich in saturated fatty acids and fat).[48,49]

LOW-GLYCEMIC-INDEX DIET

The glycemic index, a classification system that measures (on a scale from 1 to 100) the degree to which a particular food increases blood glucose levels, supplements the information about macronutrient composition.[50,51] The value of the glycemic index of a food or a meal depends not only on the nature of the carbohydrates included but also on other food and nonfood factors that affect nutrient digestibility or insulin secretion. In general, nonstarchy vegetables, fruits, legumes, and whole-grain cereals induce low glycemic responses and are part of a low-glycemic-index diet. Meat, fish, poultry, eggs, and most dairy products also have a very low glycemic index. Low-glycemic-index diets may be a tool in the management of diabetes, as well as related cardiometabolic conditions and diseases, particularly in the context of glucose dysregulation.[52,53]

PALEOLITHIC DIET

No universal dietary regimen was adopted by all humans during the Stone Age. However, as indicated by studies using isotopes, the basic foods in the diet of hunter-gatherers were uncultivated plants (fruits, roots, and vegetables), some wild game, fish, and sometimes, honey.[54] This diet was very high in fiber and contained varying amounts of fats, and protein was predominantly from animal sources. Most carbohydrates were derived from vegetables and fruits, with little contribution from cereal grains and none from sugar-containing foods or dairy products. The Paleolithic diet (or Paleo diet) has become a popular diet in the media. Several definitions of this diet have been used in the scientific and nonscientific literature, with lists of the foods that should be included (vegetables, fruits, lean meat, fish, nuts, and eggs) and excluded (grains or cereals, dairy products, legumes, added sugar and salt, and refined fats).[55] The Paleolithic diet is generally considered to be a low-carbohydrate diet, but in some versions of it, carbohydrates account for up to 45% of total daily energy intake.[56]

It has been postulated that the scarcity of high-glycemic-index and processed foods in the Paleolithic diet may beneficially affect insulin resistance and inflammation mechanisms.[57] This diet has been associated with improvements in insulin resistance and diabetes, dyslipidemia, hypertension, and inflammation,[57,58] as well as body composition and weight-related measures.[57,59] The evidence regarding the clinical efficacy of the Paleolithic diet is not as extensive as the evidence for other diets,[60] and any benefit is a focus of investigation.

DASH DIET

In the early 1990s, a multicenter, randomized clinical trial, Dietary Approaches to Stop Hypertension (DASH), was conducted to test the effect of dietary patterns on blood-pressure control.[61] Participants assigned to the trial diet for 8 weeks had greater reductions in blood pressure (by 5.5 mm Hg systolic and by 3.0 mm Hg diastolic, on average) than participants assigned to a control diet. On the basis of this evidence, the trial diet, called the DASH diet, was identified as an effective strategy for preventing and treating hypertension. The diet is rich in fruits and vegetables (five and four servings per day, respectively) and low-fat dairy products (two servings per day), and it contains low amounts of saturated lipids and cholesterol and relatively low total lipid levels.

With this diet, potassium, magnesium, and calcium levels are close to the 75th percentile of consumption in the U.S. population, and the diet includes high amounts of fiber and proteins. Basic and clinical research has linked alterations in these and other nutrients in the DASH diet to multiple physiological mechanisms affecting blood-pressure control, glucose tolerance, inflammation, oxidative stress, fat absorption, and adipogenesis.[62]

Since the original report, the DASH diet has been studied in relation to several disorders, in addition to hypertension. Greater adherence to this diet has been associated with a significant reduction in all-cause mortality,[63] and results from multiple observational studies suggested associations with reductions in the incidence of cancer and cancer-related mortality.[63] An umbrella review of meta-analyses showed that on the basis of prospective cohort data for a total population of approximately 950,000 participants, greater adherence to the DASH diet was associated with a decreased incidence of cardiovascular disease, coronary heart disease, stroke, and metabolic diseases such as diabetes.[64] The controlled trials showed decreases in diastolic and systolic blood pressure and in several metabolic measures, including insulin and glycated hemoglobin levels and total and LDL cholesterol levels, as well as reductions in body weight.[64] Modifications or improvements of the DASH diet have also been proposed, such as the DASH-sodium diet,[65] combining the DASH diet with low sodium intake, and the OmniHeart diet,[66] in which a partial replacement of carbohydrates with protein (about half from plant sources) or with unsaturated fatty acids (predominantly monounsaturated) is advised.

MIND DIET

MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) is a dietary pattern that was conceived to address the needs of a specific health outcome, cognitive function. Built on the findings of previous research on nutrition and cognition or dementia, MIND combines features of the Mediterranean and DASH diets.[67] The emphasis is on consumption of plant foods (whole grains, vegetables, beans, and nuts), with a unique focus on berries and green, leafy vegetables. The diet restricts consumption of red meat, as well as other foods with high total and saturated lipid content (fast and fried foods, cheese, butter and margarine, and pastries and sweets), and olive oil is the primary oil in the diet. Consumption of fish more than once a week and poultry more than twice a week is recommended. MIND has shown some potential benefits with respect to cognitive outcomes[68] and is being actively investigated in randomized clinical trials.[69]

TIME-RESTRICTED DIETS

Fasting (i.e., no ingestion of food or caloric beverages for periods ranging from 12 hours to a few weeks) has been practiced for centuries. Many religions recommend periods of fasting for believers (e.g., Muslim Ramadan) as a mark of devotion, self-restriction, and denial of physical needs, as well as an opportunity for introspection. Clinical investigations have largely focused on fasting for the long-term effects on aging, metabolic dysregulation, and energy balance. Fasting is distinct from caloric restriction, in which energy intake is reduced by a certain percentage, usually 20 to 40%, but meal frequency is maintained.

Intermittent fasting has emerged as a less demanding alternative to continuous fasting. It is an umbrella term describing various regimens that include alternating periods of fasting or restrictive eating and periods of normal eating or eating as desired.[70] The approaches used so far can be categorized into two major types. For the first type, the period of reference is the week. In alternate-day fasting, fasting is practiced every other day, with each fasting day followed by a day of unrestricted food intake, whereas in alternate-day modified fasting, a very-low-calorie diet is alternated with eating as desired. Fasting may be practiced for 2 consecutive or nonconsecutive days, with normal eating for the remaining 5 days (the 5:2 diet). Other approaches include consecutive days of restrictive eating (a very-low-calorie diet for 5 days) followed by periods of unrestricted food intake (for at least 10 days). In the second type of intermittent fasting, time-restricted eating, the day is the period of reference, and eating takes place only during a specific period during the day (usually a period of 8 or 10 hours).

When eating is modified to accommodate intermittent fasting, a metabolic switch in fuel source use takes place, from glucose to fatty acids and ketone bodies, with subsequently greater efficiency in energy production,[71,72] as well as multiple effects on cell and organ functions, including increased resistance to stress.[72] Evidence supporting the long-term effects and clinical benefits of intermittent fasting as compared with continuous energy restriction is scarce and debatable.[73] However, some preliminary studies in humans and animals have found intermittent fasting to be related to improvements in a wide range of health conditions, disorders, and indicators of cardiovascular health, such as glucose regulation and diabetes, body composition indexes, abdominal fat and obesity, dyslipidemia, hypertension, and inflammation.[70,72,74,75] Because intermittent fasting is thought to have positive effects on energy metabolism, reduce the growth potential of cancer cells, and increase the susceptibility of cancer cells to treatment,[72] the clinical effects of intermittent fasting on cancer initiation and progression are of interest.[76] Similarly, because of the preclinical evidence of the effects of intermittent fasting on neurodegenerative processes and other brain biologic pathways,[72] recent research focuses on the possible effects on neuropsychiatric disorders.[77]

CONCLUSIONS

From a medical research perspective, a focus on the elucidation of efficacy and the biologic mechanisms linking specific diets with various health outcomes is justifiable. An important requirement for such investigations is agreement on the definition of each diet. However, the great variation in the diets that have been investigated makes standardization and evaluation difficult tasks. Additional challenges are the relatively limited evidence from randomized clinical trials, the reliance on single-blind dietary interventions, variable degrees of adherence, and other inherent limitations of this research, including dietary measurement errors, potential confounding factors, and the magnitude of the effect size, all of which have been widely discussed.[78,79] Evidence is also limited for comparisons of one potentially healthy diet with another potentially healthy diet, although a recent investigation attempted such comparisons mostly between constructed dietary indexes.[80]

Diets have been developed in different historical and cultural frameworks and for different populations and groups of patients, which poses difficulties for clinical translation into everyday practice. Although health effects and transferability of diets have been shown for some ethnic groups and locations around the world, adaptation to other cultures and underrepresented groups can be challenging. Recent advances with regard to nutrient biomarkers, imaging, and other diagnostic techniques, as well as our understanding of the microbiome and food exposome, the interaction of these factors with the genome, and multi-omics approaches, might enable the construction of individualized profiles and a more personalized application of diets for small groups or individuals.[81] Potential adherence should also be taken into account. Adherence may decrease over time, and higher discontinuation rates have been recorded for more restrictive dietary patterns.[32]

Although many diets have been developed with the initial aim of controlling body weight, dietary composition also has important health effects that are independent of the effects on adiposity. An overall inspection of the literature suggests that plant-based diets with a moderate lipid content, characterized by the consumption of vegetables, fruits, whole-grain cereals, legumes or pulses, nuts, and unsaturated fats, with low-to-moderate amounts of poultry and seafood and low quantities of red meat and sugar, may offer substantial health benefits. The Mediterranean diet may be an option, at least for some population groups.

Educating health professionals about diets and the potential effects of these diets on diseases is imperative. Advice on healthy eating should be incorporated into clinical practice and taught in medical curricula, and health care professionals should propose variations of plant-based diets by considering individual preferences, cost, affordability, and cultural issues.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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