REVIEW ARTICLE

NUTRITION IN MEDICINE

C. Corey Hardin, M.D., Ph.D., Editor

Guidance on Energy and Macronutrients across the Life Span

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OOR NUTRITION IS A MAJOR RISK FACTOR FOR AND A LEADING PREVENTable cause of chronic disease in the United States.¹ Suboptimal diets contribute to one in five deaths worldwide.² "Food is medicine" interventions are being increasingly studied as a means of preventing and treating multiple chronic diseases.³.⁴ Unlike traditionally approved medicines for which molecular targets are well established, dietary intake comprises a large variety of food ingredients, and their functions are spread out over a lifetime. Providing recommendations to patients, specifically those with chronic diseases, on what and how much to eat is thus more complex than most health recommendations. Here we present an overview of contemporary nutritional concepts, with a specific focus on energy and macronutrients.

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HISTORICAL DEVELOPMENT

EVOLUTION OF NUTRITION SCIENCE

More than 2000 years ago, Greek philosophers and physicians recognized that food was needed to replace inexorable losses of body material, that those requirements varied during the stages of life, and that food, along with air, was needed to fuel "innate" body heat.⁵ During the chemical revolution, which began at the end of the 18th century,⁵ Antoine Lavoisier and his collaborators laid the foundations for the modern understanding of metabolism by showing that body heat results from an oxygen-requiring combustive process (Fig. 1).⁶ In the first half of the 19th century, Gerardus Johannes Mulder and Jöns Jacob Berzelius identified and named protein,⁵ Michel Eugène Chevreul and others consolidated concepts related to lipids and fat,⁷ and multiple scientists identified sugars and starch as carbohydrates.⁵ Today we recognize that proteins, fats, and carbohydrates are the major macronutrients serving as metabolic fuels and that they participate in many other vital functions.

By the early 20th century, it was clear that food components beyond macronutrients were required for maintaining optimum health. The 13 currently recognized water- and fat-soluble vitamins were identified between 1912 and 1948.^{8,9} There are also 21 essential minerals, classified as macrominerals (e.g., calcium; daily requirement, ≥100 mg) and microminerals (e.g., iodine; daily requirement, <100 mg). These additional nutrients — namely, vitamins and minerals — are collectively referred to as micronutrients.

The Great Depression led to widespread malnutrition, and the United States entered World War II with a paucity of nutritional relief programs. In 1940, the National Defense Advisory Commission requested that the National Research Council of the National Academy of Sciences assist with examining issues related

to poor nutrition in the U.S. population. In 1943, the National Research Council published the first Recommended Dietary Allowances (RDAs) for energy, protein, and eight vitamins and minerals, with the goal of providing standards to prevent nutrient deficiencies.¹⁰ Multiple RDA updates followed over the next four decades, with the last update, in 1989, including recommendations for 25 vitamins and minerals in addition to energy and protein.11 The RDAs were derived by first estimating the average daily nutrient intake needed to meet the requirements for half the healthy persons in a particular sex and life-stage group. This value is referred to as the Estimated Average Requirement. The RDA was then set at 2 standard deviations above the Estimated Average Requirement, with the aim of meeting most nutrient requirements (97.5%) for healthy persons. 11 In the case of insufficient data to establish this value, an adequate intake level, based on animal or observational studies. is used.

In 1994, the RDAs were reassessed and subsequently revised as Dietary Reference Intakes. Dietary Reference Intakes are a broad set of evidence-based nutrient reference intakes, including RDAs, Tolerable Upper Intake Levels to avoid toxic effects, and an Acceptable Macronutrient Distribution Range, which represent the range of intakes for each energy source associated with a reduced risk of chronic disease while providing adequate intakes of essential nutrients.12,13 The Dietary Reference Intakes were published between 1997 and 2003, with revisions for calcium and vitamin D in 2011,14 sodium and potassium in 2019,15 and energy in 2023.16 They were expanded in 2019, beginning with sodium, to include a Chronic Disease Risk Reduction Intake value, which represents the relationship between a nutrient and the risk of chronic disease.15 For example, for persons 14 years of age or older, reducing intake of sodium to the Chronic Disease Risk Reduction Intake level of 2300 mg per day or lower is associated

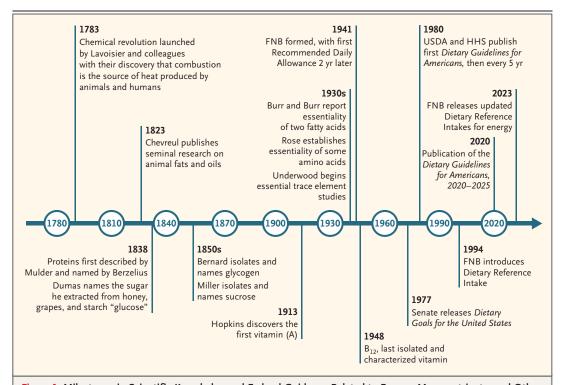


Figure 1. Milestones in Scientific Knowledge and Federal Guidance Related to Energy, Macronutrients, and Other Essential Nutrients.

FNB denotes Food and Nutrition Board, HHS Department of Health and Human Services, and USDA U.S. Department of Agriculture.

with a decreased risk of hypertension and cardiovascular disease.

In the 1970s, federal attention began to focus on emerging chronic diseases. The Senate Select Committee on Nutrition and Human Needs prepared and released Dietary Goals for the United States in 1977.^{17,18} The recommendations in the report were later expanded to become Dietary Guidelines for Americans. First published by the Departments of Agriculture and Health and Human Services in 1980 and now published every 5 years, these guidelines represent a shift from an early-20th century focus on nutrient adequacy to the effect of diet on overall health and chronic disease risk.^{17,19} The science of nutrition continues to evolve, now moving to define underlying nutrient-sensing mechanisms, macronutrient circadian20 and hedonic21 effects, and algorithms based on artificial intelligence that predict food and dietary pattern responses at the individual level.22

ENERGY AND MACRONUTRIENTS

ENERGY

In the late 19th century, Max Rubner evaluated heat production and other forms of energy loss in a dog maintained at a stable weight while inside a calorimeter.6 The energy served as food to the dog (17,349 kcal) matched the dog's total energy losses (17,406 kcal), validating the first law of thermodynamics in a living organism.23 Wilbur Atwater soon extended Rubner's studies. confirming that the first law of thermodynamics applies in humans.6 Atwater also derived "metabolizable" energy values for carbohydrate, fat, and protein, at 4, 9, and 4 kcal per gram, respectively, by adjusting the gross energy value of each macronutrient for chemical energy losses in feces and urine. 6,24 Still in widespread use today, these Atwater values assume an average "apparent" digestibility of each macronutrient and apparent energy losses as urinary nitrogenous end products of protein metabolism. The values may not be accurate for individual foods. For example, almonds in the human diet produce 4.6 kcal per gram, which is substantially less than the predicted value of 6 kcal per gram based on their macronutrient composition.^{25,26}

Rubner and Atwater's experiments show that an animal or human will remain at fixed weight, reflecting energy equilibrium, when energy in food intake balances energy losses in heat, feces, urine, and skin. The current Dietary Reference Intakes for energy are based on the doubly labeled water method of indirect calorimetry, which quantifies total energy expenditure over a period of 1 to 2 weeks in people living in their natural environments. A simplified model of macronutrient conversion to body substance and heat is shown in Figure 2.

The Dietary Reference Intake for energy is the Estimated Energy Requirement, defined as the predicted average energy intake required for maintaining energy balance in persons, according to age, sex, physical activity level, and life stage. The four physical activity levels — inactive, low active, active, and very active - range from energy expended for minimal independent living to that required for vigorous activities. Energy predictions are further refined for pregnant and breast-feeding persons. Calorie intake levels can be estimated with the use of an online calculator.31 Wearable sensors and mobile apps are providing a new opportunity to objectively evaluate food intake and activity at the individual and population levels.32

PROTEIN

Proteins, synthesized from amino acids, are the major structural and functional components of the human body. Nine of the 20 amino acids found in human proteins are indispensable (essential); omitting any one of them from the diet leads to physical signs and a negative wholebody protein balance.33 Six amino acids are recognized as conditionally indispensable, meaning that sufficient amounts cannot be synthesized during periods of rapid growth and severe metabolic stress.11 The remaining 5 amino acids are dispensable (nonessential); they can be synthesized in vivo to meet the needs of the body. In the 1930s, Rudolf Schoenheimer and his colleagues showed that biomolecules in the body such as proteins are in a dynamic state of continual turnover that requires replacement through the diet to maintain most body functions and health.34

Animal sources of protein contain all 9 indispensable amino acids, whereas plant proteins are usually deficient in 1 or more indispensable amino acids. A digestible amino acid score is used to

digestibility-adjusted indispensable amino acid requirements for a preschool-age child.35 Cow's milk, beef, and eggs have the highest score, at a value of approximately 1; rice has a value of approximately 0.5. Soy protein, with a score of approximately 0.9, is a beneficial plant source of amino acids. Vegetarians and vegans can maintain adequate high-quality protein intake by eating a

grade protein sources, with a reference set at the variety of plant-based foods, including legumes, grains, soy products, nuts, and seeds.36

> Individual amino acid requirements are mainly established by means of isotopic tracer methods.37 Protein requirements are estimated with the use of nitrogen-balance methods, which monitor nitrogen losses in feces, urine, and skin according to variations in protein intake.³⁸ An inadequate intake of total protein or any indis-

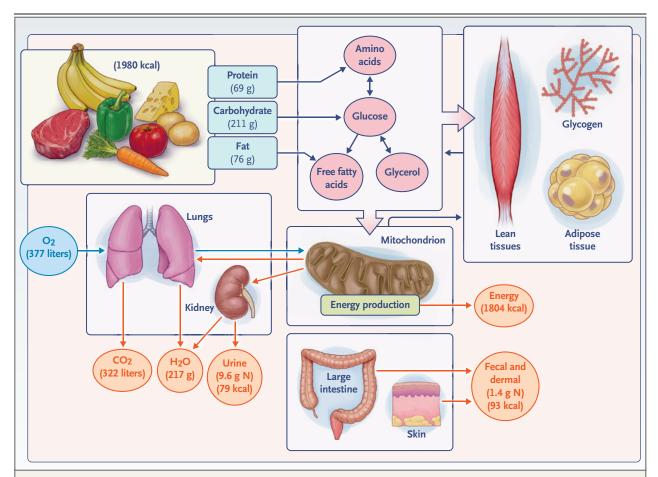


Figure 2. Dietary Macronutrient Pathways for Preserving Energy Balance and Maintaining Weight and Body Composition in Healthy

After digestion and absorption, the three main macronutrients — protein, carbohydrate, and fat — release their respective metabolically active substrates: amino acids, glucose, and free fatty acids or glycerol. These substrates, which for some pathways can be interconverted, have two main potential fates: replacement of lean tissue proteins, adipose tissue triglycerides, and glycogen catabolized during postingestive periods and provision of the necessary energy to fuel these processes and other biochemical reactions, including those producing the energy needed for physical activities. The energy-producing reactions consume oxygen and release carbon dioxide, water, and heat. Not all ingested macronutrient energy is available for metabolic processes. Average net digestive losses on mixed diets are 8%, 5%, and 2% for protein, fat, and carbohydrate, respectively; urea and other nitrogenous end-products of protein metabolism excreted in urine account for an additional 1.25 kcal per gram of protein.24 The classic Atwater values for protein, fat, and carbohydrate — 4, 9, and 4 kcal per gram — account for these fecal and urinary energy losses.²⁴ Estimates of macronutrient intakes, shown in parentheses, are based on averages reported by women in the United States who were 20 years of age or older in the prepandemic period from 2017 until March 2020^{27,28}; the remaining values were derived from previous studies.^{29,30}

Life Stage	Protein		Fat		Carbohydrates		Total Fiber	Water		
	RDA	AMDR	RDA	AMDR	RDA	AMDR	RDA	Overall	Males	Females
	g/kg/day	%	g/kg/day	%	g/day	%	g/1000 kcal/day		liters/day	,
0 to 6 mo	1.52	ND	31		60	ND	ND	0.7		
7 mo to <1 yr	1.2	ND	30		95	ND	ND	0.8		
≥1 to 3 yr	1.05	5–20	ND	30–40	130	45–65	14	1.3		
4 to 8 yr	0.95	10-30	ND	25-35	130	45–65	14	1.7		
9 to 13 yr	0.95	10-30	ND	25-35	130	45–65	14		2.4	2.1
14 to 18 yr	0.85	10-30	ND	25-35	130	45–65	14		3.3	2.3
≥19 yr	0.80	10-35	ND	20-35	130	45–65	14		3.7	2.7
Pregnancy	1.1	10–35	ND	20–35	175	45–65	14			3.0
Lactation	1.3	10-35	ND	20-35	210	45–65	14			3.8

^{*} Values shown in bold are Recommended Daily Allowances (RDAs), and all other values are Adequate Intake levels. Carbohydrates include sugars and starches. Total fiber is the combination of dietary fiber and functional fiber. For healthy breast-fed infants, the adequate intake level for water is the mean intake; for infants 7–12 months of age, water is assumed to be from breast milk and complementary foods and beverages. Water for other life-stage groups includes total water contained in food, beverages, and drinking water. A higher total water intake will be required for persons who are physically active or exposed to hot environments. The full set of Dietary Reference Intake macronutrient, cholesterol, and fiber tables are available from the Institute of Medicine. AMDR denotes Acceptable Macronutrient Distribution Range, and ND not determined.

pensable amino acid leads to adaptations in protein metabolism that can impair infant brain development, immune competence, and many other physiological and metabolic functions. Inadequate intake of energy from fat and carbohydrates can also lead to a negative nitrogen balance. In contrast, excess amino acids that are present during periods of high protein intake can be deaminated to form α -keto acids, which can then be oxidized for energy or converted to glucose or fat.³⁹

Healthy young adults can maintain a neutral nitrogen balance with protein intakes of 0.55 to 0.6 g per kilogram of body weight per day. The RDA for protein, 0.8 g per kilogram per day, includes a safety margin above this level for men and women over the age of 18 years (Table 1). The protein requirements for infants and children are higher to promote healthy growth. The requirements for protein also increase during pregnancy and lactation. There may be subgroups of persons for whom higher intakes of protein are beneficial, such as athletes, community-dwelling older adults, and people with obesity who are dieting for weight loss. Although the tolerable upper limit of protein intake is 3.5 g per

kilogram per day in adults on the basis of ureaproduction estimates and small-scale experimental studies, prolonged intake levels above 2 g per kilogram per day should be avoided because of multiple adverse health effects. Levels of protein intake below approximately 0.4 to 0.5 g per kilogram per day in adults lead to muscle atrophy and functional impairments. The Acceptable Macronutrient Distribution Range for protein, expressed as a percentage of total energy intake, is 10 to 35% for all persons over the age of 3 years.

About 6% of Americans 1 year of age or older in 2015–2018 had low protein intake, which was more prevalent in some subgroups (e.g., persons ≥71 years of age and Hispanic Black Americans). Increasing protein intake is not straightforward; foods containing protein often include other macronutrients and micronutrients. Protein foods are typically consumed as mixed dishes (e.g., sandwiches and casseroles) that are high in saturated fat and sodium. Persons who consume only plant-based foods may need to pay special attention not only to protein quality but also to the inclusion of vitamins B_{12} and D, calcium, iron, zinc, and iodine. In the same subgroups of the same subgroups of the same subgroups of the same subgroups.

FAT

Fat that is present in the human body is almost entirely in the form of triglycerides that have a glycerol backbone and three attached fatty acids. Saturated fatty acids have no double bonds, are derived from animal sources, and typically are solid at room temperature. Unsaturated fatty acids have double bonds and include two geometric isomers, cis with both hydrogen atoms bonded to carbon atoms on the same side where the double bond exists, and trans with the two hydrogen atoms on opposite sides. Cis unsaturated fatty acids can have one double bond (monounsaturated) or more than one double bond (polyunsaturated), are derived from plant sources, and are liquid at room temperature.

The early–20th century view of fat was that triglycerides serve as a compact dietary energy source and carrier of lipid-soluble vitamins.⁴⁸ In 1929, George and Mildred Burr discovered that two fatty acids, linoleic and α -linolenic, were required to facilitate growth and prevent symptomatic deficiency in a rodent model.⁴⁹ These respective n–6 and n–3 essential polyunsaturated fatty acids were later found to be precursors to a wide range of bioactive lipids, contributing to multiple functions.⁵⁰

In addition to linoleic acid, arachidonic acid, an n-6 polyunsaturated fatty acid, can become conditionally essential when synthesis from linoleic acid through desaturation and chain elongation is limited. Arachidonic acid is the precursor to a number of eicosanoids, including the prostaglandins, thromboxanes, and leukotrienes, which participate in autocrine, paracrine, and occasional endocrine functions that have widespread physiological actions.⁵¹ The cardiovascular effects of n-6 polyunsaturated fatty acids continue to be debated.^{52,53} Corn, safflower, and soybean oils, nuts, and seeds are good sources of n-6 fatty acids.

The n–3 essential polyunsaturated fatty acid, α -linolenic acid, is the precursor to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two n–3 polyunsaturated fatty acids that play important roles in the synthesis of inflammatory mediators, intracellular signaling and gene expression, and the structure of cell membranes. Higher levels of EPA and DHA are associated with a lower risk of cardiovascular disease, although the strength of these effects continue

to be investigated.⁵⁴ Of the commonly used plant oils, flaxseed, soybean, and canola oils are good sources of α -linolenic acid. Fatty fish (e.g., salmon and herring) and fish oils are high in EPA and DHA. Humans have a low capacity to convert α -linolenic acid to EPA and DHA.

Deficiencies of one or both essential fatty acids are rare, since they and their downstream products are present in ample amounts in the American diet and are stored in body fat to be released during lipolysis.⁵⁵ The n–6 and n–3 fatty acids compete for the same desaturase enzymes that moderate the synthesis rates of arachidonic acid, EPA, and DHA. Adequate intake levels for the essential polyunsaturated fatty acids are set according to life stage.³⁸

Monounsaturated fatty acids serve as components of cell membranes — notably, myelin in nerve tissue. ⁵⁶ Oleic acid is the main monounsaturated fatty acid present in food and tissues. Food sources include olive, canola, peanut, and sesame oils and fat from animal products.

Saturated fatty acids such as stearic and palmitic acids are nonessential and are derived primarily from animal-based food sources such as full-fat dairy products, fatty meats, and tropical oils (coconut and palm kernel oils). These fatty acids raise total and low-density lipoprotein cholesterol levels and increase the risk of cardiovascular disease.⁵⁷ High saturated fatty acid intake activates acute and chronic inflammatory responses through toll-like receptor 4, an essential modulator of innate immunity, and may explain its relationship with multiple diet-related diseases.⁶⁰⁻⁶³

Trans fatty acids are unsaturated fatty acids present in the diet that are derived from ruminant meats or dairy and through conversion of liquid to semisolid or solid fats by the industrial process of partial hydrogenation. Dietary trans fats have been found to be positively associated with an increase in total and low-density lipoprotein cholesterol levels and an increased risk of cardiovascular disease.⁶⁴ U.S. food companies were required to remove partially hydrogenated oils from products by 2018, resulting in a dramatic decrease in industrial trans-fat content in the food supply.

Cholesterol, a nonessential dietary lipid, plays a key role in cell membrane fluidity and is a precursor for steroid hormone, bile acid, and vitamin

Table 2. Energy and Macronutrient Contents of the Typical U.S. Diet and Healthy USDA Food Patterns.									
Energy or Macronutrient	Typical U.S. Diet, 2017–2020*	USDA Healthy Food Patterns†							
		U.S. Style	Mediterranean	Vegetarian					
Calories — kcal	2144	2003	1998	1999					
Protein — g (%)	81.0 (15.5)	91 (17.9)	89 (17.4)	71 (13.8)					
Carbohydrate — g (%)	244 (46.6)	256 (50.3)	259 (50.8)	274 (53.3)					
Total fat — g (%)	88.2 (37.9)	72 (31.8)	72 (31.8)	75 (32.8)					
Fatty acids — g (%)									
Saturated	28.6 (12.3)	18.7 (8.3)	18.0 (7.9)	18.6 (8.1)					
Monounsaturated	30.1 (12.9)	26.2 (11.6)	26.0 (11.5)	26.9 (11.8)					
Polyunsaturated‡	20.7 (8.9)	22.5 (9.9)	22.6 (10.0)	24.5 (10.7)					
Linoleic acid, 18:2, n-6	18.31 (7.9)	19.6 (8.7)	19.5 (8.6)	21.9 (9.6)					
lpha-Linolenic acid, 18:3, n–3	1.93 (0.8)	2.3 (1.0)	2.3 (1.0)	2.6 (1.1)					
Total dietary fiber (g)	16.6	31	31	35					

^{*} Values are mean nutrient intakes from food and beverages consumed per person, 20 years of age or older, during the prepandemic period from 2017 until March 2020.^{27,28} Data represent 24-hour recall, collected by trained observers. Percentages of dietary energy intake were calculated by summing calories from protein, carbohydrate, and fat; alcohol intake in the typical U.S. diet (10.6 g) was not included.68

cholesterol in the pathogenesis of cardiovascular the United States reported consuming less than disease has varied over time, in part because of the complexity in separating the independent effects of cholesterol from the effects of other dietary fats and carbohydrates. 65,66 Adhering to the saturated fat guidelines and maintaining a healthy diet that emphasizes fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean proteins, nuts, seeds, and vegetable oils will result in dietary cholesterol intakes below levels thought to increase the risk of cardiovascular disease.66

All cells except for erythrocytes and cells in the central nervous system can oxidize long-chain fatty acids liberated from dietary triglycerides for energy. Adequate intake levels for total fat are set for infants (0 to 12 months old), but there is no RDA or adequate intake recommended for older persons. The Acceptable Macronutrient Distribution Range for fat is 20 to 40% of energy intake across life stages (Table 1).41,67

Dietary Guidelines for Americans, 2020-2025, recommends that less than 10% of daily calorie intake come from saturated fat, beginning at 2

D biosynthesis. The recognized role of dietary years of age. 67 Less than one fourth of people in the recommended 10% of calories as saturated fat in the 2015–2018 period.⁴⁶ In the period from 2017 until March 2020, persons who were 20 years of age or older had a mean saturated fat intake of 12%27 and a total dietary fat intake of 38%, which exceeds the 35% upper threshold of the Acceptable Macronutrient Distribution Range in this age group (Table 2). These high saturated and total dietary fat levels in the typical U.S. adult diet could be lowered by adopting healthy dietary patterns such as those recommended by the Department of Agriculture and the Department of Health and Human Services, which have less saturated fat (8%) and total dietary fat (32%) and greater amounts of n-6 and n-3 polyunsaturated fatty acids (Table 2).69 Saturated fat should be replaced with polyunsaturated or monounsaturated fat, not refined carbohydrates and sugars, as part of an effort to maintain healthy food patterns.70 Replacing frying with steaming or boiling when cooking, trimming visible fat from meat, eating reduced-fat dairy foods and lean meats, and reducing consumption

[†] Data for healthy food patterns, designed to meet the nutritional needs of children (≥9 years of age) and adults, are adapted from the Department of Agriculture, 2015.69

[‡] Acceptable Macronutrient Distribution Ranges for n−6 and n−3 polyunsaturated fatty acids are 5–10% and 0.6–1.2% of dietary energy intake, respectively.

of desserts and sweet snacks can also lower saturated fat intake.⁷¹

Although there is broad support for limiting saturated fat intake, discussions continue regarding the nature of specific dietary sources of saturated fats that vary in chemical properties and possible atherogenic effects.⁷²,⁵⁷ The cardiometabolic effects of saturated fatty acids are moderated to some extent by the chemical interactions between the nutrient and nonnutrient components of a given food, the so-called food matrix.58,59 High intakes of saturated fatty acids from cheese, for example, may have less of a lowdensity lipoprotein-cholesterol raising effect than similar amounts of saturated fatty acids from butter. 59,60 Questions surrounding food sources of saturated fat and their relationship to cardiovascular disease risk are under examination by the Dietary Guidelines for Americans, 2025–2030 Advisory Committee.⁷³

CARBOHYDRATES

The human diet includes two main forms of digestible carbohydrate, sugars and starches, both of which are macronutrients that function to provide cellular energy. Sugars, mostly sucrose, are naturally present in fruits, whereas lactose, a disaccharide, is found in dairy products. Starches are polysaccharides produced by all green plants, and common dietary sources include potatoes, rice, corn, and wheat.⁷⁴ Sugars that are added to foods during processing include sugar, dextrose, brown sugar, high-fructose corn syrup, cane syrup, and honey.⁶⁷ A high intake of added sugars is associated with excess energy, low-quality diets, weight gain, and obesity.^{75,76}

Under normal conditions, erythrocytes and, to a lesser extent, neurons in the human brain rely solely on glucose as an energy source. The requirements for carbohydrates across life stages, beginning at the age of 1 year, were derived from the average minimum brain oxidation of glucose (Table 1). The Acceptable Macronutrient Distribution Range for carbohydrates is 45 to 65% of energy for all persons 1 year of age and older. The Dietary Guidelines for Americans, 2020–2025, recommends avoiding added sugars before the age of 2 years and limiting added sugar to less than 10% of calorie intake per day starting at 2 years of age. The he period from 2013 through 2016, the mean consumption of added

sugars by Americans 1 year of age or older was 266 kcal per day, or 13% of dietary energy intake. The guidance level of 10% was exceeded by more than 70% of children and adolescents 5 to 18 years of age. Among adults, more than 50% exceeded the recommendation. Sugar-sweetened beverages, not including coffee and tea with added sugar, account for almost one fourth of added sugars in the diet of Americans 2 years of age or older.⁴⁶

Fibers are naturally occurring, edible, nondigestible components of plant carbohydrates and lignin, an organic polymer that is abundant in plant cell walls. The term functional fiber refers to isolated, extracted, or synthetic, nondigestible carbohydrates with proven beneficial health effects.41 Total fiber intake represents the sum of dietary and functional fiber intake. Higher intakes of total dietary fiber are associated with laxation and improved glycemic control.⁷⁷ Randomized trials have shown that the highest fiber intakes are associated with lower body weight, serum cholesterol levels, and systolic blood pressure, and observational studies have shown that persons with high fiber intakes have a 15 to 30% decrease in the incidence of some common noncommunicable diseases and associated mortality.77,78 The gut microbiota produces short-chain fatty acids from dietary fiber through anaerobic fermentation in the colon, a beneficial metabolic process in the context of diseases such as type 2 diabetes.62 Whole grains, fruits, and vegetables are nutrient-dense sources of dietary fiber and provide other essential micronutrients.

Life-stage guidelines for dietary fiber beginning at the age of 1 year account for the protective effects of fiber on the risk of cardiovascular disease (Table 1). The mean consumption of dietary fiber by Americans 20 years of age or older was 17 g per day in the 2017–2020 period (Table 2), about half that recommended on the basis of the adequate intake level (Table 1)⁴¹ and much lower than the optimum intake of 25 to 29 g per day, which is associated with risk reductions for a range of health outcomes.⁷⁸ Among Americans 1 year of age or older, 94% do not meet the adequate intake levels for dietary fiber at their life stage.⁴⁶

Early nutrition guidelines focused on total carbohydrates in the diet and their classification into simple and complex forms, a taxonomy now

Table 3. Recommendations for Patients and Caregivers on Healthy Eating Patterns Consistent with Energy and Macronutrient Guidelines.

Establish calorie requirements.

Calorie intake levels based on the patient's sex, age, weight, height, physical activity level, and pregnancy or lactation status can be estimated with an online calculator (https://www.nal.usda.gov/human-nutrition-and-food-safety/ dri-calculator).

Modifications may be needed for patients with underlying health conditions. The calculator also gives intake recommendations for other macronutrients, total fiber, fatty acids, cholesterol, and water.

Choose healthy food patterns.

The overarching nutritional goal is for people to enjoy eating foods that maintain their health across all life stages and minimize the risks of chronic diseases.

Healthy food intake patterns consistent with macronutrient Dietary Reference Intakes should be recommended for patients >1 year of age.

The core elements of healthy food patterns include vegetables of all types, fruits (especially whole fruits), grains (at least half of which are whole grains), dairy (e.g., fat-free or low-fat milk, yogurt, and cheese), protein foods (e.g., lean meats and eggs, seafood, beans, and nuts), and oils (e.g., plant and seafood oils).62

Healthy food intake patterns associated with relatively low all-cause mortality are also low in red and processed meat, high-fat dairy, and refined carbohydrates or sweets.81

- •Examples of healthy meal patterns are available from the USDA (https://www.fns.usda.gov/usda-food-patterns). MyPlate, published by the USDA, presents a useful visualization for initiating discussions with patients that includes the five food groups (fruits, vegetables, grains, proteins foods, and dairy), along with healthy recipes and their energy and macronutrient content (https://www.myplate.gov).
- •The Acceptable Macronutrient Distribution Ranges for adults are 10 to 35%, 20 to 35%, and 45 to 65% of calories for protein, fat, and carbohydrate, respectively. Available evidence is limited or insufficient with regard to disease prevention effects of dietary carbohydrate levels below the Acceptable Macronutrient Distribution Range. 46
- •The Healthy Eating Index assesses a diet's overall quality, independent of quantity, by aligning with the Dietary Guidelines for Americans, 2020–2025,⁶⁷ and includes two sections, one for infants and toddlers (birth to 23 months of age), and one for persons 2 years of age or older.⁸²
- •The Dietary Guidelines for Americans, 2020–2025, addressed the question of alcoholic beverages as part of healthy food patterns.⁶⁷ Alcoholic beverages can contribute to total daily calorie intake (ethanol is 7 kcal/g). The dietary guidelines state that drinking less is better for health than drinking more, adults of legal drinking age can choose to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women, and some adults should not drink alcohol, such as women who are pregnant. 62

Focus on these key points.

Meet macronutrient needs with nutrient-dense foods and beverages that provide health-promoting components that have no or little added sugars and saturated fat.

Keep saturated fat intake at <10% of total calorie intake starting at 2 years of age.

Keep added sugar intake at <10% of total calorie intake starting at 2 years of age and avoid foods and beverages with added sugars for children who are <2 years of age.

Maintain healthy fiber and water intakes according to the Dietary Reference Intakes.

Use Nutrition Facts labels to monitor calorie and macronutrient contents of purchased foods^{66,73,83,84}; calories and macronutrients (protein, total carbohydrate, total fat), trans fat, saturated fat, cholesterol, dietary fiber, and added sugars per serving and per container can be used to choose foods and to compare ingredients across products; labels also include % Daily Values based on reference intakes set for specific groups related to the product's intended market.

being reconsidered. Increasing evidence supports the observation that foods containing natural sugars and added sugars have different metathe risk of several noncommunicable diseases.^{78,79} The quality of carbohydrate sources is related to the type of carbohydrate, its digestibility, and the amount of fiber. The quantity and quality of dietary carbohydrates are now recognized as independent determinants of diseases such as type 2 diabetes.80

FROM MACRONUTRIENTS TO HEALTHY FOOD PATTERNS

bolic effects, with added sugars associated with Varying energy requirements and variable needs for the three main macronutrients and multiple micronutrients, across 10 life stage groups, and for special populations such as pregnant or lactating persons contribute to the complexity of recommending healthy dietary patterns to patients with widely varying financial resources, personal preferences, cultural backgrounds, and ethnic food traditions. Key energy and macronutrient recommendations in the context of healthy food patterns are summarized in Table 3. *Dietary Guidelines for Americans*, 2020–2025, is an excellent source of expanded nutritional recommendations according to life stage, from birth to older adulthood.⁶⁷ Patients with diet-related chronic conditions such as obesity, cardiovascular disease, or type 2 diabetes can specifically benefit from these guidelines to reduce symptoms and coexisting conditions. Consultation with a registered dietitian or nutritionist should be considered for patients with complex nutritional requirements.

CONCLUSIONS

The amount and pattern of foods people eat are major determinants of growth and health maintenance throughout life. Macronutrients fuel and sustain these processes. Recognizing their subtle effects is important for providing effective care for all patients and, notably, the increasing number of patients with diseases that have nutritional components as key contributors to their pathophysiology.

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REFERENCES

- 1. Chronic health conditions: federal strategy needed to coordinate diet-related efforts. Washington, DC: Government Accountability Office, 2021. (Publication no. GAO-21-593) (https://www.gao.gov/products/gao-21-593).
- **2.** GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393:1958-72.
- 3. Downer S, Berkowitz SA, Harlan TS, Olstad DL, Mozaffarian D. Food is medicine: actions to integrate food and nutrition into healthcare. BMI 2020;369:m2482.
- **4.** Mozaffarian D, Blanck HM, Garfield KM, Wassung A, Petersen R. A food is medicine approach to achieve nutrition security and improve health. Nat Med 2022:28:2238-40.
- 5. Guggenheim KY, Wolinsky I. Nutrition and nutritional diseases: the evolution of concepts. Lexington, MA: Collamore Press, 1981.
- **6.** Heymsfield SB, Bourgeois B, Thomas DM. Assessment of human energy exchange: historical overview. Eur J Clin Nutr 2017;71:294-300.
- 7. McNamara JR, Warnick GR, Cooper GR. A brief history of lipid and lipoprotein measurements and their contribution to clinical chemistry. Clin Chim Acta 2006;369:158-67.
- 8. Scott JM, Molloy AM. The discovery of vitamin B(12). Ann Nutr Metab 2012;61: 239-45.
- 9. Semba RD. The discovery of the vitamins. Int J Vitam Nutr Res 2012;82:310-5.
 10. Murphy SP, Yates AA, Atkinson SA, Barr SI, Dwyer J. History of nutrition: the long road leading to the Dietary Reference Intakes for the United States and Canada. Adv Nutr 2016:7:157-68.
- 11. National Research Council. Recommended dietary allowances. 10th ed.

- Washington, DC: National Academies Press, 1989.
- 12. Institute of Medicine. How should the recommended dietary allowances be revised? Washington, DC: National Academies Press, 1994.
- **13.** Institute of Medicine. Dietary reference intakes: the essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006.
- **14.** Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press, 2011.
- **15.** National Academies of Sciences, Engineering, and Medicine. Dietary reference intakes for sodium and potassium. Washington, DC: National Academies Press. 2019.
- **16.** National Academies of Sciences, Engineering, and Medicine. Dietary reference intakes for energy. Washington, DC: National Academies Press, 2023.
- 17. Department of Agriculture. History of the Dietary Guidelines. 2020 (https://www.dietaryguidelines.gov/about-dietary-guidelines/history-dietary-guidelines).
- **18.** U.S. Senate Select Committee on Nutrition and Human Needs. Dietary goals for the United States. 2nd ed. Washington, DC: Government Printing Office, December 1977.
- **19.** Schneeman BO. Evolution of dietary guidelines. J Am Diet Assoc 2003;103: Suppl 2:S5-S9.
- **20.** Mihaylova MM, Chaix A, Delibegovic M, et al. When a calorie is not just a calorie: diet quality and timing as mediators of metabolism and healthy aging. Cell Metab 2023;35:1114-31.
- **21.** James Stubbs R, Horgan G, Robinson E, Hopkins M, Dakin C, Finlayson G. Diet composition and energy intake in humans. Philos Trans R Soc Lond B Biol Sci 2023; 378:20220449.

- 22. National Institutes of Health. Nutrition for Precision Health, powered by the All of Us Research Program (https://commonfund.nih.gov/nutritionforprecisionhealth).
- **23.** Jackson DC. Academic genealogy and direct calorimetry: a personal account. Adv Physiol Educ 2011;35:120-7.
- 24. Merrill AL, Watt BK. Energy value of foods: basis and derivation. Agriculture handbook no. 74. Washington, DC: Government Printing Office, 1955.
- **25.** Novotny JA, Gebauer SK, Baer DJ. Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. Am J Clin Nutr 2012;96:296-301.
- **26.** Department of Agriculture. FoodData central (https://fdc.nal.usda.gov/).
- 27. Department of Agriculture. Food Surveys Research Group: Beltsville, MD. 2021 (https://www.ars.usda.gov/northeast-area/beltsville-mbhnrc/beltsville-human-nutrition-research-center/food-surveys-research-group/).
- 28. Agricultural Research Service. Nutrient intakes from food and beverages: mean amounts consumed per individual, by gender and age. What we eat in America, NHANES 2017–March 2020 prepandemic. Washington, DC: Department of Agriculture, 2022 (https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1720/tables_1-56_2017-March%202020.pdf).
- **29.** Jéquier E, Acheson K, Schutz Y. Assessment of energy expenditure and fuel utilization in man. Annu Rev Nutr 1987;7: 187-208
- **30.** Morrison SD. A method for the calculation of metabolic water. J Physiol 1953; 122:399-402.
- **31.** USDA National Agricultural Library. DRI calculator for healthcare professionals (https://www.nal.usda.gov/human-nutrition-and-food-safety/dri-calculator).

- **32.** Berciano S, Figueiredo J, Brisbois TD, et al. Precision nutrition: maintaining scientific integrity while realizing market potential. Front Nutr 2022;9:979665.
- **33.** Rose WC. Nutrition classics: Federation Proceedings 8(2)546-52, June 1949: amino acid requirements of man. Nutr Rev 1976;34:307-9.
- **34.** Schoenheimer R, Ratner S, Rittenberg D. The process of continuous deamination and reamination of amino acids in the proteins of normal animals. Science 1939;89:272-3.
- **35.** Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser 2007;935:1-265.
- 36. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian dietsa review. Nutrients 2019;11:2661.
- **37.** Hudson JL, Baum JI, Diaz EC, Børsheim E. Dietary protein requirements in children: methods for consideration. Nutrients 2021:13:13.
- **38.** Protein and amino acids. In: Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press, 2005:589-768.
- **39.** Bender DA. The metabolism of "surplus" amino acids. Br J Nutr 2012;108: Suppl 2:S113-S121.
- **40.** Garibotto G, Picciotto D, Saio M, Esposito P, Verzola D. Muscle protein turnover and low-protein diets in patients with chronic kidney disease. Nephrol Dial Transplant 2020;35:741-51.
- **41.** Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press, 2005.
- **42.** Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr 2008;87:150-5.
- **43.** Houston DK, Tooze JA, Garcia K, et al. Protein intake and mobility limitation in community-dwelling older adults: the Health ABC Study. J Am Geriatr Soc 2017; 65:1705-11.
- **44.** Ogilvie AR, Schlussel Y, Sukumar D, Meng L, Shapses SA. Higher protein intake during caloric restriction improves diet quality and attenuates loss of lean body mass. Obesity (Silver Spring) 2022;30:1411-9.
- **45.** Wu G. Dietary protein intake and human health. Food Funct 2016;7:1251-65.
- **46.** Agricultural Research Service. Scientific report of the 2020 Dietary Guidelines Advisory Committee. Washington, DC: Department of Agriculture, 2020 (https://www.dietaryguidelines.gov/2020 -advisory-committee-report).

- **47.** Craig WJ, Mangels AR, Fresán U, et al. The safe and effective use of plant-based diets with guidelines for health professionals. Nutrients 2021;13:4144.
- **48.** Flatt JP. Conversion of carbohydrate to fat in adipose tissue: an energy-yielding and, therefore, self-limiting process. J Lipid Res 1970;11:131-43.
- **49.** Spector AA, Kim H-Y. Discovery of essential fatty acids. J Lipid Res 2015;56:11-21. **50.** Spector AA, Kim H-Y. Emergence of omega-3 fatty acids in biomedical research. Prostaglandins Leukot Essent Fatty Acids 2019;140:47-50.
- **51.** Dyall SC, Balas L, Bazan NG, et al. Polyunsaturated fatty acids and fatty acidderived lipid mediators: recent advances in the understanding of their biosynthesis, structures, and functions. Prog Lipid Res 2022;86:101165.
- **52.** DiNicolantonio JJ, O'Keefe JH. Omega-6 vegetable oils as a driver of coronary heart disease: the oxidized linoleic acid hypothesis. Open Heart 2018;5(2):e000898.
- **53.** Marklund M, Wu JHY, Imamura F, et al. Biomarkers of dietary omega-6 fatty acids and incident cardiovascular disease and mortality. Circulation 2019;139:2422-36.
- **54.** Farukhi ZM, Mora S, Manson JE. Marine omega-3 fatty acids and cardiovascular disease prevention: seeking clearer water. Mayo Clin Proc 2021;96:277-9.
- **55.** Mogensen KM. Essential fatty acid deficiency. Pract Gastro 2017;41:37-44 (https://practicalgastro.com/2017/06/01/essential-fatty-acid-deficiency/).
- **56.** Martínez M, Mougan I. Fatty acid composition of human brain phospholipids during normal development. J Neurochem 1998;71:2528-33.
- **57.** Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136(3):e1-e23.
- **58.** Aguilera JM. The food matrix: implications in processing, nutrition and health. Crit Rev Food Sci Nutr 2019;59: 3612-29.
- **59.** Lamarche B. Yet another study stirring the debate on saturated fat. Am J Clin Nutr 2022;116:1466-7.
- **60.** Brassard D, Tessier-Grenier M, Allaire J, et al. Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. Am J Clin Nutr 2017;105:800-9.
- **61.** Fritsche KL. The science of fatty acids and inflammation. Adv Nutr 2015;6:293S-301S.
- **62.** Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016; 165:1332-45.
- **63.** Wang Y, Qian Y, Fang Q, et al. Saturated palmitic acid induces myocardial inflam-

- matory injuries through direct binding to TLR4 accessory protein MD2. Nat Commun 2017;8:13997.
- **64.** Oteng A-B, Kersten S. Mechanisms of action of trans fatty acids. Adv Nutr 2020; 11:697-708.
- **65.** Lichtenstein AH. Dietary fat and cardiovascular disease: ebb and flow over the last half century. Adv Nutr 2019;10:Suppl 4:S332-S339.
- **66.** Carson JAS, Lichtenstein AH, Anderson CAM, et al. Dietary cholesterol and cardiovascular risk: a science advisory from the American Heart Association. Circulation 2020;141(3):e39-e53.
- **67.** Department of Agriculture. Dietary guidelines for Americans, 2020–2025. 9th ed. 2020 (https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf).
- Robert Star V. Rehm CD, Rogers G, et al. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999-2016. JAMA 2019;322:1178-87.

 69. USDA Food and Nutrition Service. USDA dietary patterns. 2015 (https://www
- USDA dietary patterns. 2015 (https://www.fns.usda.gov/cnpp/usda-dietary-patterns).
- **70.** Kris-Etherton PM, Krauss RM. Public health guidelines should recommend reducing saturated fat consumption as much as possible: YES. Am J Clin Nutr 2020;112:13-8.
- 71. World Health Organization. Healthy diet. April 29, 2020 (https://www.who.int/news-room/fact-sheets/detail/healthy-diet).
 72. Astrup A, Magkos F, Bier DM, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. J Am
- Coll Cardiol 2020;76:844-57.

 73. Hoelscher DM, Anderson C, Booth S, et al. Food sources of saturated fat and risk of cardiovascular disease: a systematic review protocol. Alexandria, VA: USDA Center for Nutrition Policy and Promotion 2023 (https://nesr.usda.gov/sites/default/files/2024-02/2025-DGAC-Protocol-Food-sources-saturated-fat-Cardiovascular
- -disease.pdf).
 74. Schulz R, Slavin J. Defining carbohydrate quality for human health and environmental sustainability. Adv Nutr 2021; 12:1108-21.
- **75.** Bailey RL, Fulgoni VL, Cowan AE, Gaine PC. Sources of added sugars in young children, adolescents, and adults with low and high intakes of added sugars. Nutrients 2018;10:102.
- **76.** Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr 2006;84:274-88.
- 77. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 1999;69:30-42.

- 78. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 2019;393:434-45.
- 79. Tan D, Drewnowski A, Lê K-A. New metrics of dietary carbohydrate quality. Curr Opin Clin Nutr Metab Care 2023;26:
- 80. Sluijs I, van der Schouw YT, van der A DL, et al. Carbohydrate quantity and quality and risk of type 2 diabetes in the Euro-
- pean Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study. Am J Clin Nutr 2010;92:905-11.
- 81. English LK, Ard JD, Bailey RL, et al. Evaluation of dietary patterns and allcause mortality: a systematic review. JAMA Netw Open 2021;4(8):e2122277.
- 82. Pannucci TE, Lerman JL, Herrick KA, et al. Development of the Healthy Eating Index-Toddlers-2020. J Acad Nutr Diet 2023;123:1289-97.
- 83. Food and Drug Administration. Food

labeling: revision of the nutrition and supplement facts labels: final rule. Fed Regist 2016;81(103):33742-999 (https://www .federalregister.gov/documents/2016/05/27/ 2016-11867/food-labeling-revision-of-the -nutrition-and-supplement-facts-labels). 84. Food and Drug Administration. The new nutrition facts label: what's in it for you? 2022 (https://www.fda.gov/food/nutrition

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-nutrition-facts-label).

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