REVIEW

Dietary fat: From foe to friend?

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For decades, dietary advice was based on the premise that high intakes of fat cause obesity, diabetes, heart disease, and possibly cancer. Recently, evidence for the adverse metabolic effects of processed carbohydrate has led to a resurgence in interest in lower-carbohydrate and ketogenic diets with high fat content. However, some argue that the relative quantity of dietary fat and carbohydrate has little relevance to health and that focus should instead be placed on which particular fat or carbohydrate sources are consumed. This review, by nutrition scientists with widely varying perspectives, summarizes existing evidence to identify areas of broad consensus amid ongoing controversy regarding macronutrients and chronic disease.

A report by the U.S. Senate Select Committee on Nutrition and Human Needs in 1977 called on Americans to reduce consumption of total and saturated fat, increase carbohydrate intake, and lower calorie intake, among other dietary goals (*1*). This report, by elected members of Congress with little scientific training, was written against a backdrop of growing public concern about diet-related chronic disease, precipitated in part by attention surrounding President Eisenhower's heart attack in 1955.

Even then, the recommendations were hotly debated. The American Medical Association stated that "The evidence for assuming benefits to be derived from the adoption of such universal dietary goals as set forth in the report is not conclusive … [with] potential for harmful effects." Indeed, the lack of scientific consensus was reflected in the voluminous, 869-page "Supplemental Views" published contemporaneously by the committee. Nonetheless, reduction in fat consumption soon became a central principle of dietary guidelines from the U.S. government and virtually all nutrition- and health-related professional organizations. [Note that modern approaches to the study of diet-related chronic diseases were at that time in their infancy; previously, nutritional science was focused on individual nutrients for the prevention of deficiency diseases (*2*).]

The Surgeon General's Report on Nutrition and Health in 1988 identified reduction of fat consumption as the "primary dietary priority," with sugar consumption only a secondary concern for children at risk for dental caries (*3*). The 1992 Food Guide Pyramid of the U.S. Department of Agriculture advised eating 6 to 11 daily servings of starchy foods such as bread, cereal, rice, and pasta while limiting all fats and oils. To facilitate this goal, the U.S. Healthy People 2000 report of the Department of Health and Human Services called on the food industry to market thousands of new "processed food products that are reduced in fat and saturated fat" (*4*). This intensive focus on reducing dietary fat was driven by a prevailing belief that carbohydrates—all carbohydrates, including highly processed grains and sugar—were innocuous and possibly protective against weight gain, cancer, and cardiovascular disease through multiple mechanisms (*5*).

As a result, the proportion of fat in the U.S. diet decreased from about 42% in the 1970s to about 34% of total calories today (somewhat greater than the stated goal of <30%) and the proportion of dietary carbohydrates increased substantially (*6*). During this time, rates of obesity and diabetes increased greatly, contributing to the first nationwide decrease in life expectancy since the flu pandemic 100 years ago (*7*). These trends could be causally connected or unrelated.

If causal, how could some traditional societies, such as that of Okinawa, enjoy relative freedom from chronic disease and long lifespan when they consume a low-fat diet (*8*)? In Mexico, Brazil, and China, rates of obesity and diet-related chronic diseases have also increased without similar government dietary guidance to individuals and food manufacturers. Moreover, many other aspects of the American diet changed in the past 40 years, including increased portion sizes, greater consumption of foods away from home, and more extreme food processing. At the same time, labor-saving technology and the digital age have led to declines in occupational and recreational physical activity, and budget shortfalls in schools have led to curtailments in physical education classes, recess time, and after-school recreation opportunities.

Despite a lack of clear evidence specifically relating fat consumption (as a proportion of total energy intake) to the epidemics of diet-related disease—and a lack of high-quality, long-term trials focused on macronutrients in general—the pendulum has recently swung in the opposite direction, with rising consumer popularity of low-carbohydrate, high-fat diets. Among the current top-10 best-selling weight loss books on Amazon.com, four promote a ketogenic diet with energy intake derived mainly from fat. In support of higher fat intake, several meta-analyses found slightly greater weight loss on high-fat rather than low-fat diets (*9*, *10*), and preliminary data suggest the potential for excellent control of diabetes through carbohydrate restriction (*11*, *12*). But versions of low-carbohydrate, high-fat diets have been around at least as early as the 1800s, with no clear evidence of superiority for long-term obesity treatment at present. And regardless of body weight, high intakes of fat—especially from red meat and dairy products—might increase risk for heart disease or cancer.

Perhaps both high-carbohydrate, low-fat and low-carbohydrate, high-fat diets have benefit for different populations or for different clinical outcomes, and the critical issue is to identify the optimal macronutrient ratio for an individual. Or perhaps the focus on macronutrient quantity has been a distraction, and qualitative aspects (the particular sources of fat or carbohydrate) and overall eating patterns are more important.

To explore these issues, we have joined together as scientists with a diversity of expertise, perspectives, and prior research focus. Our aim is not to assemble a premature consensus among the like-minded, but rather to identify areas of general agreement and delineate a research agenda to address long-standing controversies.

The case for a low-fat, high-carbohydrate diet

Physiologic mechanisms

Among many societies worldwide, carbohydrate is the primary source of energy, providing 50% or more of daily energy, with lesser amounts from both fat and more expensive and scarce protein. Population-level or ecological studies comparing global chronic disease rates show that less developed countries have lower rates of cardiovascular disease, obesity, and cancer than more Westernized countries. When individuals move from countries with low chronic disease rates to Westernized countries, their incidence of chronic diseases approaches that of their new country within one to two generations. This rapid shift in chronic disease rates spurred thinking that environmental exposures, such as adoption of a higher-fat Western diet, may be causally related to disease risk patterns. [A low-fat diet typically contains <30% energy as fat, and a very-low-fat diet ≤20%, versus 32 to 36% in the United States (*6*).]

Humans ingest complex food mixtures that include macronutrients (fat, carbohydrate, and protein) and alcohol as energy sources. Macronutrients have highly regulated yet integrated metabolic interactions. One consideration for judging optimal macronutrient intake is the relative efficiency of substrate oxidation and interconversion. Humans preferentially oxidize carbohydrate over fat, a process that helps to maintain blood glucose within homeostatically controlled ranges. Further, carbohydrate consumption acutely increases carbohydrate oxidation, with only a quantitatively small increase in de novo lipogenesis under typical conditions (*13*–*16*). Humans have limited storage capacity for carbohydrate but also

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have extensive adipose stores, thus favoring fat deposition with excess fat intake (*17*, *18*). Fat is also highly palatable and may have a weak effect on satiation, potentially leading to passive overconsumption (*18*). This excess intake, if not coupled with increased energy expenditure, results in weight gain. This effect may be enhanced because, by weight, fat provides more than twice as much energy (9 kcal/g) as carbohydrate or protein (4 kcal/g). Conversely, diets rich in whole grains, which are low in fat and have a relatively low glycemic load, promote satiety and reduce overconsumption, possibly by increasing concentrations of glucagon-like peptide–1 after eating (*19*). Of 29 diets with varying macronutrient composition tested in mice, only high-fat diets, but not high-carbohydrate diets, led to overconsumption and weight gain (*20*). Of particular interest, the high-fat diets increased expression of three serotonin receptors and both dopamine and opioid signaling pathways, components of the reward system in the hypothalamus.

Fat and specific fatty acids also have adverse metabolic effects independent of calorie content. High-fat diets up-regulate inflammatory mediators including tumor necrosis factor–α (TNF-α), interleukins (IL-1β, IL-6) (*21*), complement (*22*), and Toll-like receptors (*23*) in human and animal studies. In contrast, lower-fat diets reduce amounts of these and other inflammatory cytokines, as well as activity of the transcription factor NF-κB (*24*). Palmitic and stearic acids (abundant in animal foods) influence the structure and function of mitochondrial membranes, such that an increase in these saturated fatty acids leads to impaired membrane function (*25*). High-fat diets may also promote unfavorable epigenetic profiles. For example, excess saturated fat changes DNA methylation patterns in adipose tissue (*26*) and skeletal muscle, and alters histone acetylation (*27*, *28*). When acetyl–coenzyme A concentrations are high, such as under conditions of low glucose, histone acetylation increases according to in vitro human and animal studies (*28*).

High-fat diets also stimulate hepatic bile acid synthesis, which, after conversion into secondary bile acids in the colon, may promote tumorigenesis (*29*–*31*). Among Africans consuming a diet high in minimally processed carbohydrates, gut microbial communities were dominated by butyrate-producing bacteria, whereas genetically similar African Americans consuming a high-fat diet had a less healthful gut microbiome with high secondary bile acid production (*31*). Fat-stimulated production of bile acids was also unfavorably associated with inflammation and proliferation in colonic biopsy samples (*29*–*31*). Conversely, high-carbohydrate diets containing whole grains and other high-fiber foods provide the preferred fuel for colonic bacteria, with less secondary bile acid production and greater production of butyrate and other short-chain fatty acids that lower inflammation, decrease cellular proliferation, and enhance expression of genes with antineoplastic properties. Low-fat diets may also decrease serum estradiol and increase sex hormone–binding globulin (*32*, *33*) and may reduce other breast cancer risk factors such as mammographic density (*34*), although the persistence of these effects remains unclear.

Taken together, these multiple physiologic mechanisms suggest that higher dietary fat may be harmful for health. However, it is critically important to consider carbohydrate quality when fat intake is lowered. Refined grains provide negligible nutrition and their high glycemic load causes unhealthful spikes in postprandial glucose and insulin, promoting hunger, inflammation, insulin resistance, and dyslipidemia. However, with a lower-fat diet containing high-fiber, low-glycemic carbohydrates such as minimally processed grains, legumes, and nonstarchy fruits and vegetables, these measures improve. Whole plant foods are also rich sources of micronutrients, antioxidants, and phytochemicals with beneficial health effects.

Obesity and diabetes

Low-fat diets may favorably influence body weight and adiposity. In the Women's Health Initiative Dietary Modification Trial (WHI-DM), the low-fat intervention (20% energy as fat, as part of a healthy eating pattern) was associated with significant, small reductions in body weight, total fat mass, and percent body fat as measured by dual x-ray absorptiometry (*35*). Another randomized controlled trial (RCT) in postmenopausal women tested a lower-fat, higher-carbohydrate diet (20% and 65% energy, respectively), a lower-carbohydrate, higher-fat diet (45% and 35% energy, respectively), and a walnut-rich higher-fat, lower-carbohydrate diet (18%, 35%, and 45% energy, respectively) for weight loss. All three diets led to weight loss at 12 months, with slightly higher weight loss in the lower-fat diet group (*33*). A meta-analysis of dietary intervention trials showed that low-fat diets were effective for weight loss under ad libitum conditions (*36*); however, this was published prior to recent carbohydrate-restricted diet studies.

Although obesity has a dominant role in the development of diabetes, clinical trial evidence suggests benefit for low-fat eating patterns in risk reduction and disease management. The Diabetes Prevention Program (DPP) was an RCT of 3234 adults at risk for diabetes (*37*). DPP's primary goal was to compare the effect of at least 7% reduction in body weight achieved by following a low-calorie, low-fat diet and increasing physical activity, with that of the drug metformin or a placebo. Rates of diabetes incidence were reduced by 58% in the lifestyle intervention group and by 31% in those taking metformin, although the effects of dietary composition cannot be fully disentangled from weight loss and other factors. Numerous other trials and observational studies support the use of high-fiber whole grains and fiber supplements for diabetes prevention and control. A recent meta-analysis found that fiber, typically consumed in greater amounts in low-fat, high-carbohydrate diets, improved measures of glycemia and weight (*38*).

Cardiovascular disease

The effects of dietary macronutrient composition on cardiovascular disease (CVD) risk have been a subject of debate for more than 40 years. Ecological studies and controlled feeding trials supported associations of higher-fat diets with CVD or its biomarkers of risk. However, definitive trials have not been conducted that explicitly test this "diet-heart hypothesis." WHI-DM was not designed to test CVD endpoints; even so, participants in the low-fat group had significantly lower low-density lipoprotein (LDL) cholesterol and metabolic syndrome scores and no unfavorable changes to high-density lipoprotein (HDL) cholesterol or triglycerides relative to those of controls (*39*). Although the overall results of WHI-DM were negative for CVD, follow-up showed that women without baseline hypertension had a 30% reduced CVD risk, whereas

Box 1. Current controversies.

1. Do diets with various carbohydrate-to-fat proportions affect body composition (ratio of fat to lean tissue) independently of energy intake? Do they affect energy expenditure independently of body weight?

2. Do ketogenic diets provide metabolic benefits beyond those of moderate carbohydrate restriction? Can they help with prevention or treatment of cardiometabolic disease?

3. What are the optimal amounts of specific fatty acids (saturated, monounsaturated, polyunsaturated) in the context of a very-low-carbohydrate diet?

4. What is the relative importance for cardiovascular disease of the amounts of LDL cholesterol, HDL cholesterol, and triglycerides in the blood, or of lipoprotein particle size, for persons on diets with distinct fat-to-carbohydrate ratios? Are other biomarkers of equivalent or greater importance?

5. What are the effects of dietary fat amount and quality across the lifespan on risk of neurodegenerative, pulmonary, and other diseases that have not been well studied?

6. What are the long-term efficacies of diets with different carbohydrate-to-fat proportions in chronic disease prevention and treatment under optimal intervention conditions (designed to maximize dietary compliance)?

7. What behavioral and environmental interventions can maximize long-term dietary compliance?

8. What individual genetic and phenotypic factors predict long-term beneficial outcomes on diets with various fat-to-carbohydrate compositions? Can this knowledge inform personalized nutrition, with translation to prevention and treatment?

9. How does variation in the carbohydrate-to-fat ratio and in sources of dietary fat affect the affordability and environmental sustainability of diets?

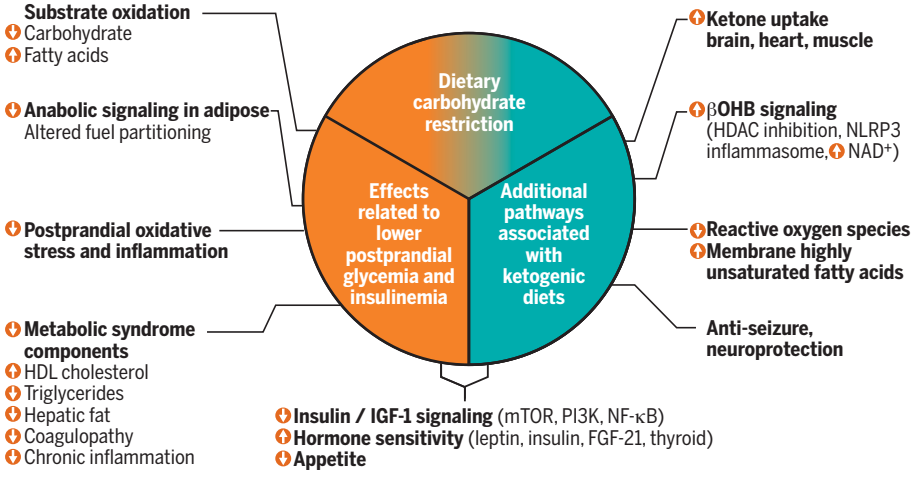

Fig. 1. Pleiotropic effects of low-carbohydrate, high-fat diets. Ketogenic diets (aqua) may enhance these effects and act through additional mechanisms. Abbreviations: βOHB, β-hydroxybutyrate; HDAC, histone deacetylase; NAD^+, nicotinamide adenine dinucleotide; mTOR, mechanistic target of rapamycin.

those with baseline hypertension or prior CVD had no benefit or increased CVD risk; these findings suggest that a low-fat diet might have a greater effect on prevention than treatment (*40*).

In a meta-analysis of RCTs, addition of at least 3 g of oat β-glucan per day reduced total and LDL cholesterol without unfavorable effects on triglycerides or HDL cholesterol (*41*), highlighting the benefits of a low-fat, grain-based diet. In another meta-analysis of examined RCTs, low-fat diets lowered LDL cholesterol, a major CVD risk factor, whereas low-carbohydrate diets lowered triglycerides (*42*).

Cancer

Cancer includes more than 100 disease types and subtypes, precluding a comprehensive assessment of potential diet effects here, but several major trials provide useful evidence. In the low-fat diet arm of WHI-DM, there was no significant effect on total breast cancer incidence, but estrogen receptor–positive, progesterone receptor–negative cancers were significantly reduced by 36% over a mean of 8.1 years of follow-up (*32*). Among women who had higher baseline fat intake (>36.8% of energy), overall risk of breast cancer was significantly reduced by 22% over a median of 11.5 years. For these women, total and breast cancer deaths were reduced by 22% and 14%, respectively. However, a low-fat, high-carbohydrate intervention conducted in high-risk women had no significant effect on incidence of invasive breast cancer in another study with a mean 10-year follow-up (*43*). Breast cancer patients in the Women's Intervention Nutrition Study randomly assigned to the low-fat diet group had a statistically significant 24% reduced risk of cancer relapse relative to controls over a median of 5 years (*44*). In another randomized trial among breast cancer patients with very low risk of recurrence, a low-fat, plant-based diet had no effect on recurrence or mortality (*45*).

Specific types of fats may influence prostate cancer risk, possibly as a result of effects on cell signaling and other cancer-related pathways. In the Prostate Cancer Prevention Trial and the Selenium and Vitamin E Cancer Prevention Trial, higher blood measures of omega-3 (N-3) fatty acids, particularly docosahexaenoic acid (DHA), were associated with increased risks of both total and high-grade prostate cancer (*46*, *47*). These findings are consistent with a study in which prostate cancer patients were randomly assigned to flaxseed supplements [a rich source of the N-3 fat α-linolenic acid (ALA)] or placebo (*48*). The supplement led to increased tumor proliferation and higher prostate-specific antigen (PSA) at prostatectomy. However, the clinical implications remain unknown; research is needed to determine whether specific fatty acids should be reduced in people at risk for specific cancers.

The case for a low-carbohydrate, high-fat diet

Carbohydrate-restricted diets vary in macronutrient composition, but the defining feature is that contributions to total energy are reduced for carbohydrate and increased for fat (≥40% of energy) relative to conventional diets. Emerging evidence suggests that a ketogenic diet—a special type of low-carbohydrate diet with fat typically ≥70% of energy—may have unique therapeutic effects beyond those of less restrictive regimens.

Physiological mechanism

Conventional lifestyle recommendations and existing drug treatments have failed to stem the twin epidemics of obesity and type 2 diabetes. Nearly three-fourths of U.S. adults are overweight or obese, and half have prediabetes or diabetes, despite a 40-year focus on reducing dietary fat. The most salient change in macronutrient intake over this period has been a marked increase in processed starches and added sugars, which suggests that they may have a role in the public health crisis of diet-related chronic disease (*49*).

As dietary carbohydrate is replaced by fat, postprandial spikes in the blood concentrations of glucose and insulin decrease, glucagon secretion increases, and metabolism shifts to a greater reliance on fat oxidation (Fig. 1). These metabolic and hormonal responses are associated with attenuated oxidative stress and inflammatory responses after eating (*50*, *51*), reduced hormone resistance [to insulin, leptin, fibroblast growth factor–21 (FGF-21), and thyroxine] (*52*, *53*), and improvements in many features of metabolic syndrome (*54*–*56*)—effects that increase throughout the range of carbohydrate restriction. Additional mechanisms arise as carbohydrate is restricted to a point that results in nutritional ketosis, in which serum concentrations of β-hydroxybutyrate increase from <0.1 mM to 0.5 to 5 mM. This normal physiological state differs from diabetic ketoacidosis, in which β-hydroxybutyrate concentrations exceed 10 mM. Ketones, an alternative fuel used by the brain (*57*) and heart, affect metabolic efficiency and a panoply of signaling functions, producing beneficial changes in gene expression, inflammation, oxidative stress, and possibly health span (*58*, *59*).

From a pathophysiological perspective, low-carbohydrate, high-fat diets may directly target underlying metabolic dysfunction in insulin resistance and type 2 diabetes, characterized by defects in the body's ability to oxidize ingested carbohydrate. With insulin resistance, dietary carbohydrate is diverted at increased rates into hepatic de novo lipogenesis, resulting in increased hepatic triglyceride synthesis and abnormal concentrations of lipids in the blood (*60*). From a historical perspective, some aboriginal hunting and fishing cultures (e.g., Inuit of the Arctic and First Nations groups in Canada) survived for millennia with little available dietary carbohydrate. In fact, mild ketosis was the "normal" metabolic state for many cultures before the advent of agriculture (i.e., for all but the last 1% or less of the existence of humans as a species). When these ethnic groups underwent a transition from their low-carbohydrate and high-fat traditional diets, the prevalence of obesity and type 2 diabetes increased markedly, although changes in other lifestyle factors may have also had a role.

Obesity, type 2 diabetes, and cardiovascular disease

The most recent systematic reviews and meta-analyses have concluded that carbohydrate-restricted diets tend to outperform low-fat diets for short- to medium-term weight loss, especially in trials that involved a ketogenic diet (*9*, *10*, *54*, *61*). Whereas individuals with insulin sensitivity seem to respond similarly to low-fat or low-carbohydrate diets, those with insulin resistance, glucose intolerance, or insulin hypersecretion may lose more weight on a low-carbohydrate, high-fat diet (*62*, *63*). The lower insulin concentrations and accelerated rates of adipose tissue lipolysis and ketogenesis may provide more stable metabolic fuel availability,

especially for the brain, resulting in greater satiety during weight loss; potential effects on energy expenditure remain a subject of investigation (*63*).

Metabolic syndrome—including central adiposity, high circulating concentrations of triglycerides, low levels of HDL cholesterol, high blood pressure, glucose intolerance, fatty liver, and chronic inflammation—comprises a constellation of clinical risk factors associated with insulin resistance that predispose to diabetes and CVD. Reduction in dietary carbohydrate may improve these markers more effectively than do low-fat diets (*54*–*56*, *64*). In an 8-week trial of patients with type 2 diabetes in Italy, a diet high in total (42% of energy) and monounsaturated (MUFA) fat decreased liver fat significantly more than did a low-fat (28% of energy), high-fiber diet (*65*). In a 2-year trial conducted at a worksite in Israel, participants in the low-carbohydrate diet group (fat approximately 40% of energy) lost more weight and experienced greater improvements in HDL cholesterol and triglycerides than did those in the low-fat diet group (fat approximately 30% of energy) (*66*). With restriction of carbohydrate to ketogenic levels (<50 g/day), individuals with metabolic syndrome lost more weight, total fat, and abdominal fat than did those consuming a low-fat (24% of energy), calorie-restricted diet (*56*). The ketogenic diet also significantly decreased serum triglycerides, increased HDL cholesterol concentration, lowered inflammatory markers, and reduced concentrations of circulating saturated fatty acids (*50*), consistent with metabolic benefits seen in other studies (*67*).

Carbohydrate restriction in general, and specifically a ketogenic diet, may provide exceptional benefits in the setting of diabetes, essentially a disease of carbohydrate intolerance. Historically, ketogenic diets were the treatment of choice for diabetes, but the discovery of insulin in the early 1920s allowed for control of acute symptoms on higher-carbohydrate diets. By the 1980s, low-fat diets with up to 60% energy from carbohydrate had become the standard of care, although current recommendations emphasize individualizing macronutrient composition. However, despite modern insulin analogs and glucose monitoring technologies, management of diabetes remains suboptimal. In a recent survey, 316 children and adults with type 1 diabetes following a low-carbohydrate, high-fat diet for a mean of >2 years reported exceptional glycemic control, low rates of complications, and excellent metabolic health markers (*12*). Among 262 participants with type 2 diabetes assigned to a ketogenic diet with intensive telemedicine support, 83% completed the 1-year intervention; in this group, weight was reduced by 12%, hemoglobin A1c (HbA1c, a measure of long-term average glucose concentration) was reduced by 1.3%, and a majority had HbA1c levels of <6.5% (i.e., below the diagnostic threshold for diabetes) while taking no medications other than metformin (*11*).

Low-carbohydrate diets are typically (but not necessarily) high in saturated fat. As discussed below, saturated fat is directly associated with cardiovascular and total mortality in the general population (although this relation has been a subject of controversy, related in part to the nature of the substituted calories) (*68*, *69*). However, with the higher rates of fatty acid oxidation and decreased de novo lipogenesis on a ketogenic diet, blood concentrations of saturated fatty acids and palmitoleic acid (a marker of de novo lipogenesis) may decrease (*50*, *55*, *56*), suggesting a lower risk of diabetes and CVD. Furthermore, any effects of increased LDL cholesterol (a risk marker for CVD that occurs in about half of individuals on a ketogenic diet) need to be considered together with improvements in triglycerides, HDL cholesterol, inflammatory markers, and other features of metabolic syndrome. However, there are no long-term studies tracking CVD outcomes.

Box 2. Points of consensus.

1. With a focus on nutrient quality, good health and low chronic disease risk can be achieved for many people on diets with a broad range of carbohydrate-to-fat ratios.

2. Replacement of saturated fat with naturally occurring unsaturated fats provides health benefits for the general population. Industrially produced trans fats are harmful and should be eliminated. The metabolism of saturated fat may differ on carbohydrate-restricted diets, an issue that requires study.

3. Replacement of highly processed carbohydrates (including refined grains, potato products, and free sugars) with unprocessed carbohydrates (nonstarchy vegetables, whole fruits, legumes, and whole or minimally processed grains) provides health benefits.

4. Biological factors appear to influence responses to diets of differing macronutrient composition. People with relatively normal insulin sensitivity and β cell function may do well on diets with a wide range of carbohydrate-to-fat ratios; those with insulin resistance, hypersecretion of insulin, or glucose intolerance may benefit from a lower-carbohydrate, higher-fat diet.

5. A ketogenic diet may confer particular metabolic benefits for some people with abnormal carbohydrate metabolism, a possibility that requires long-term study.

6. Well-formulated low-carbohydrate, high-fat diets do not require high intakes of protein or animal products. Reduced carbohydrate consumption can be achieved by substituting grains, starchy vegetables, and sugars with nonhydrogenated plant oils, nuts, seeds, avocado, and other high-fat plant foods.

7. There is broad agreement regarding the fundamental components of a healthful diet that can serve to inform policy, clinical management, and individual dietary choice. Nonetheless, important questions relevant to the epidemics of diet-related chronic disease remain. Greater investment in nutrition research should assume a high priority.

Cancer

Certain cancer cells rely on glycolysis for energy metabolism. By decreasing glucose flux into tumor cells, a ketogenic diet could target the defective mitochondrial oxidative phosphorylation specific to some cancers. Carbohydrate restriction might also help to prevent or treat cancer by lowering oxidative stress, inflammation, and cellular signaling involving anabolic hormones such as insulin (which is thought to mediate in part the association between obesity and cancer risk) (*70*, *71*). Preclinical data involving various models appear promising, including the use of a ketogenic diet to enhance the effectiveness of phosphoinositide 3-kinase (PI3K) inhibitors in cancer treatment (*72*). However, clinical reports are largely limited to small case series, with no high-quality RCTs.

Clinical translation

Moderately low-carbohydrate diets entail relatively simple changes in diet, focused primarily on substituting high-fat foods for processed carbohydrates while allowing several daily servings of whole fruits, legumes, and minimally processed grains. A ketogenic diet may include various nutrient-dense whole foods such as nonstarchy vegetables, nuts, eggs, cheese, butter/cream, fish, meats, oils, and select fruits. Proper formulation of a ketogenic diet entails restriction of carbohydrate, adequate but not high intake of protein, and sufficient sodium to offset the natriuretic effect of ketosis and reduced insulinemia. Recent data among motivated patients suggest the possibility of good compliance and improved quality of life through 1 year (*11*), although safety has not been fully assessed in long-term trials.

The case for dietary fat quality

At one time, dietary fat, primarily triglycerides, was considered simply a source of energy. However, the fatty acids in triglycerides can vary in chain length, number and position of double bonds, and whether the double bonds are in cis or trans configuration. These features profoundly affect the biological function of fatty acids, and thus their effects on heath, in complex, incompletely understood ways.

The position of double bonds, described by the number of carbons from the noncarboxyl end of the fatty acid to the first double bond, has particular importance. Two families of polyunsaturated fatty acids (PUFAs), the N-3 and N-6 fatty acids, are essential because they cannot be synthesized by humans. Both are critical components of every human cell membrane and are precursors of eicosanoid hormones that mediate inflammation, thrombosis, immunity, and insulin resistance. An increase in N-3 fatty acid intake alters expression of more than 6000 genes, underscoring this biological complexity (*73*).

A vast literature based on controlled feeding studies with physiologic endpoints, long-term epidemiologic studies, and randomized trials with clinical outcomes has documented that the type of dietary fat strongly influences human health independent of total fat intake. N-6 and N-3 fatty acids provide benefit at intakes above minimum levels to prevent essential fatty acid deficiency, and nonessential dietary fatty acids also have important metabolic effects.

Obesity and diabetes

Whereas the literature on total fat intake is extensive, little is known about the effects of specific types of fat on weight control and body composition. In a 7-week controlled overfeeding study, saturated fat increased hepatic and visceral fat storage relative to polyunsaturated fat (*74*). In a large cohort analysis (*75*), increases in the intakes of trans and saturated fat were positively associated with weight gain when compared isocalorically with carbohydrate, but intakes of MUFA and PUFAs did not influence weight. To our knowledge, no RCTs lasting 1 year or longer have compared the effects of different types of fat on body weight.

Consistent with the effects of trans fat on multiple components of metabolic syndrome (see below), higher intake was associated with risk of type 2 diabetes in a large cohort study with repeated measures of diet (*76*). In a 10-week randomized trial, consumption of PUFA reduced biomarkers of insulin resistance relative to consumption of saturated fat (*77*). In a large cohort study, the ratio of polyunsaturated to saturated fat intake was inversely associated with risk of type 2 diabetes (*76*), and relative blood levels of linoleic acid, which reflect intake, were inversely associated with risk of type 2 diabetes in a pooled analysis of 20 cohort studies (*78*).

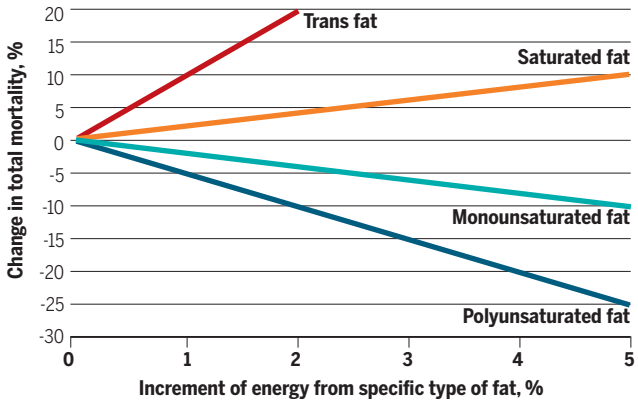

Fig. 2. Relation between increasing intakes of trans, saturated, unsaturated, monounsaturated, and polyunsaturated fatty acid (compared isocalorically with carbohydrate) in relation to total mortality. Data are based on 126,233 men and women followed for up to 32 years, with assessments every 4 years, as described in Wang *et al*. (*94*). The strong inverse association with polyunsaturated fatty acids was primarily due to N-6 polyunsaturated fatty acids; associations with N-3 polyunsaturated fatty acids were weaker.

Cardiovascular disease

Early evidence on dietary fats and CVD was based on comparisons of incidence and mortality rates across geographical areas, and on knowledge of the effects of dietary fats on blood cholesterol levels. In the Seven Countries Study (*79*), per capita intake of saturated fat, but not total fat, was strongly correlated with rates of CVD; although potentially confounded by other variables, this provided a strong incentive to understand the major geographical variation in CVD rates. In controlled feeding studies lasting several weeks, compared isocalorically to carbohydrate, saturated fat increased blood cholesterol concentrations, whereas PUFA reduced them (*80*, *81*). Thus, from the 1960s, dietary advice to reduce CVD emphasized replacing saturated fat with PUFAs, primarily N-6, and consumption of N-6 PUFA in the United States increased from approximately 3% to 7% of energy. Concurrently, age-adjusted coronary heart disease mortality decreased by about 75%, although lower rates of tobacco use and other prevention efforts (e.g., statins) contributed to this secular trend.

In subsequent epidemiologic studies, blood lipid subfractions predicted CVD better than did total cholesterol; higher amounts of LDL cholesterol and triglycerides are associated with higher risk, whereas higher amounts of HDL cholesterol predict lower risk (*82*). In further controlled feeding studies, replacement of saturated fat with carbohydrates reduced both LDL cholesterol and HDL cholesterol and increased blood concentrations of triglyceride during fasting, suggesting little or potentially adverse effects on risk of CVD. Replacement of monounsaturated or polyunsaturated fat with carbohydrate increased LDL cholesterol and had minimal effects on HDL cholesterol or triglycerides.

Consistent with the controlled feeding studies of blood lipids, in several randomized trials with CVD as the outcome, replacement of saturated fat with PUFA reduced the risk of CVD, whereas replacement with carbohydrate did not (*83*); however, these studies were small, short-term, and had other limitations (e.g., a lack of emphasis on carbohydrate quality). Long-term prospective cohort studies are also consistent with these findings: When compared isocalorically with saturated fat, N-6 PUFAs—but not typical carbohydrates in Western diets—are associated with lower risk of CVD (*84*–*86*). Controlled for other types of fat, MUFAs are also inversely associated with risk. This inverse association with PUFA is linear up to about 8% of energy, beyond which data are sparse. These epidemiologic studies also highlight the importance of carbohydrate quality; relative to saturated fat, whole grains are associated with lower CVD risk (*87*).

By the 1990s, the distinction between N-6 and N-3 PUFAs and between cis and trans isomers gained widespread recognition. In animals, N-3 fatty acids protect against cardiac arrhythmias, and in epidemiologic studies, intakes of N-3 fatty acids [DHA or eicosapentaenoic acid (EPA) from fish and ALA from plant sources] are inversely but nonlinearly associated with risk of sudden cardiac death (*88*). Specifically, risk decreases with intakes up to about 250 mg/day (equivalent to one or two servings of fish per week) but then plateaus. The inconsistent effects of supplements seen in these RCTs may relate to the variability in intakes within and among populations (intakes among some individuals in the United States and mean intakes in many countries remain very low) (*89*). At high dosage, fish oil supplements may reduce the risk of cardiovascular events such as heart attack and stroke among people with hypertriglyceridemia, according to preliminary data from a large trial (*90*)—a possibility that warrants further study.

The main N-6 PUFA in diets, linoleic acid, can be elongated and desaturated to form eicosanoids that are prothrombotic and proinflammatory. In addition, linoleic acid may competitively inhibit biosynthetic pathways shared by the N-3 fatty acid ALA in the formation of antithrombotic and anti-inflammatory eicosanoids. For these reasons, some have concluded that higher N-6 fatty acid intake should be minimized to prevent CVD and other diseases associated with chronic inflammation. However, this reasoning disregards evidence that N-6 PUFA intermediates in these pathways, such as arachidonic acid, are highly regulated (*91*). Although very high intakes of N-6 PUFA increase inflammatory measures in some animal models, this effect has not been convincingly demonstrated in humans (*92*); higher intake of linoleic acid in humans may actually have anti-inflammatory effects (*93*). Moreover, the ratio of N-6 to N-3 fatty acids has not been associated with risk of CVD, consistent with both being beneficial (*94*). Nonetheless, special effects in subgroups or at very low intakes of carbohydrate cannot be ruled out.

The process of partial hydrogenation, which creates trans isomers from the natural cis double bonds of fatty acids, was widely used to create margarine and vegetable shortening with favorable commercial properties (solidity at room temperature, long shelf life). This industrial process altered the structure and function of linoleic acid and ALA, the dominant fatty acids in many widely used oils, resulting in major health impacts. Trans fat has uniquely adverse effects on LDL, LDL particle size, HDL, triglycerides, and inflammatory factors (*95*). In multiple large-cohort studies, intake of trans fat is directly associated with risk of coronary heart disease and other chronic illnesses. Through regulations, education, and food labeling, trans fat was largely eliminated from the food supply in the United States and some European

FIGURE 2 REPRINTED WITH PERMISSION OF THE AMERICAN MEDICAL ASSOCIATION

countries. However, intake remains high in some parts of the world.

Cancer

Mechanistic studies have suggested that both N-6 and N-3 fatty acids could either increase or reduce cancer risk (*46–48*), and some animal studies have suggested that intakes of PUFA beyond the range of typical human diets might increase risks. In human studies, consumption of these fatty acids and other specific types of fat during midlife do not have consistent relationships to risks of various cancers, according to biomarkers of intake and assessments of diet (*96*). Higher intake of fat from animal sources, but not vegetable sources, during early adult life was associated with higher risk of breast cancer, which may reflect the type of fat or nonlipid factors (*97*). Because of long latencies and windows of vulnerability for carcinogenic influences, further studies of specific types of fat across the lifespan are desirable.

Other outcomes

Adequate intake of both N-6 and N-3 fatty acids in utero and during early life is critical for neurological development because these fatty acids constitute much of the lipid in the central nervous system. Low consumption of fish, the primary source of DHA and EPA, during pregnancy is associated with lower cognitive function and preterm birth (*98*, *99*). In later life, lower consumption of N-3 fatty acids and higher consumption of trans fats have been associated with greater risk of dementia (*100*).

In a recent prospective study, 126,233 men and women were followed for up to 32 years, with diet assessed every 4 years (*94*). Compared isocalorically to carbohydrate intake, intake of trans fat was strongly associated with higher mortality. Intakes of MUFA and N-3 PUFA were weakly associated with lower mortality, and intake of N-6 PUFA was strongly associated with lower mortality (Fig. 2). Because of reductions in saturated and trans fats over the study period, total fat intake was inversely associated with mortality.

Conclusion

The optimal proportion of carbohydrate to fat in the diet for obesity treatment and chronic disease prevention has been a topic of debate for decades, often generating more heat than light (*101*). Of course, any meaningful assessment of a diet's impact on health must extend far beyond macronutrient quantity, to include the myriad qualitative aspects of food and food combinations that influence hormonal response, gene expression, and metabolic pathways. Further complicating this issue is the likelihood that inherent or acquired biological differences among individuals or populations, especially related to glucose homeostasis, affect response to specific diets.

Unfortunately, the national nutrition research agenda has not been adequate to address important areas of controversy (Box 1). Currently, the United States invests a fraction of a cent on nutrition research for each dollar spent on treatment of diet-related chronic disease. All too often, scientific results in this field have been ambiguous: Macronutrient feeding studies have been too short and too small to distinguish transient from chronic effects; many behavioral trials have lacked the intensity to produce meaningful differences between dietary treatment groups; and observational studies can be affected by confounding, inability to distinguish cause and effect, and other methodological problems. Furthermore, despite promising preliminary data, few major studies of a ketogenic diet in the treatment of diabetes have been conducted. Additional questions related to sustainability for the individual (whether people can realistically remain on prescribed diets) and for the environment (the impacts of specific dietary patterns on natural resources and climate change) require more study. Given the enormous human and economic toll of diet-related disease, high-quality research into key controversies should be given priority.

The incomplete nature of research notwithstanding, data from multiple lines of investigation have led to important areas of consensus (Box 2). Current evidence indicates that no specific carbohydrate-to-fat ratio in the diet is best for the general population. Nor do all diets, and calorie sources, have similar metabolic effects in everyone. With attention to diet quality—and specifically a focus on reducing processed foods, including sugar and refined grains—many people do relatively well with substantial variation in macronutrient composition (*102*). For the rapidly rising proportion of the population with severe metabolic dysfunction or diabetes, a more specific dietary prescription may be needed.

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ACKNOWLEDGMENTS

Funding: D.S.L. was supported in part by a career award from the National Institute of Diabetes and Digestive and Kidney Diseases (K24DK082730). **Competing interests:** D.S.L., W.C.W., and J.S.V. received royalties for books about obesity and nutrition that include recommendations on dietary fat. J.S.V. is a founder, stockholder, and consultant for VirtaHealth Corp. and a member of the advisory boards for Atkins Nutritionals Inc., UCAN Co., and Axcess Global.

10.1126/science.aau2096