THE BENEFITS OF PLANT-BASED NUTRITION

AMERICAN COLLEGE OF Lifestyle Medicine

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DIET QUALITY

Key Points for Practitioners

- Typical dietary patterns of US adults are of poor quality, with underconsumption of calcium, magnesium, potassium, iron, vitamins A, C, D, E, choline, and fiber,[14] as well as overconsumption of added sugars, saturated fat, and sodium.[14]
- Whole food diets that are either predominantly plant-based or entirely plant-based are naturally higher in most underconsumed nutrients and lower in overconsumed nutrients.
- A high-quality dietary pattern is more likely to be achieved by choosing primarily plant foods and paying attention to specific important details—these include supplementation with vitamin B12, vitamin D in the case of inadequate sunlight exposure, and consuming sea vegetables and/or iodized salt.
- Adequate protein intakes are easily achieved eating a whole food, entirely plant-based diet.
- If patients express interest in trying a whole food, plant-based diet of some kind, it is helpful to share educational and support resources with them.

ABSTRACT | Poor diet quality is a growing problem and driver of poor health and chronic disease. Globally, we are facing a "double burden" of undernutrition due to insufficient consumption of energy and/or nutrients, as well as poor nutrition due to overconsumption of calorie-dense, nutrient-poor foods. Plant-based diets can address poor diet quality by providing essential macronutrients and micronutrients with intact fiber that helps to regulate the consumption and absorption of food. This paper reviews the essential nutrients needed for optimal health and the ability of plant-based diets to adequately meet recommendations.

Diet Quality in Context

Though variation exists with respect to the definition,[1,2] diet quality refers to the ability of the overall dietary pattern to supply energy and all essential nutrients from food to allow for growth, healing, physical activity, and optimal health at all stages of life, according to standardized dietary metrics.[2] A new global, multidimensional definition considers nutritional, sociocultural, food safety, and sensory features.[1] It is generally agreed that a diet founded on minimally processed whole foods while limiting or avoiding refined foods with added sugars, fats, and salt, and processed animal foods provide the healthiest dietary pattern for most individuals. The most frequent components of diet quality metrics include vegetables, fruits, grains, roots, tubers, as well as certain nutrients such as added sugar and saturated fat.[2] Mixed dishes such as burgers, pizza, and salty or sweet snacks contain added sugars, sodium, and saturated fats, which are associated with poor health outcomes.[3]

Poor diet quality is a leading and preventable cause of poor health and chronic disease. Globally, we are facing a "double burden" of conventional malnutrition from insufficient calories or nutrients (both macro and micronutrients) as well as poor nutrition due to overconsumption. Modern malnutrition is marked by excess calories and consumption of sugar, fat, and salt, often leading to

obesity, type 2 diabetes, cardiovascular diseases, and cancer.[2,4] In the US, poor diet quality is driving chronic disease as six in ten Americans live with at least one chronic disease.[5] Globally, improved living standards and increased food availability have shifted the problem from obtaining adequate energy to eating well for health and disease prevention in an environment of excess.[1]

The overall dietary pattern influences human health and disease and directly affects quality of life throughout the lifespan.[6] Current food trends towards a Western-style diet of animal and processed foods, including excess calories, added sweeteners, saturated fats, coupled with the underconsumption of whole grains, legumes, fruit, and vegetables, contribute to the rising levels of chronic conditions and obesity.[7] Food systems to support diet quality have the potential to nurture human health and address disease conditions. Harvard's seminal 2020 EAT-Lancet Commission on Food, Planet and Health states that "unhealthy diets pose a greater risk to morbidity and mortality than does unsafe sex, and alcohol, drug, and tobacco use combined."[7] Thus, as the U.N. Sustainable Development Goals do, public health efforts need to address the double burden of malnutrition and excess.[2] Lifestyle medicine nutritional prescriptions hold the potential to steer individuals towards higher-quality dietary patterns.

Figure 1 Alkerwi, 2014 illustrates diet quality as a holistic field of overlapping interest from a public health perspective.[1]

Measuring Diet Quality

Assessment of diet quality is essential to developing effective strategies and public policies to address malnutrition and achieve global nutrition safety. A clear example of this can be found in the U.N. Sustainable Development Goals.[2] Measuring diet quality must depend on reliable dietary metrics developed to capture diet components, such as quality, adequacy, and diversity.[2] A recent systematic review has identified nineteen dietary metrics that have been validated against health outcomes and are widely used to address maternal and child health (MCH) and non-communicable diseases (NCD).[2] While the dietary metrics varied significantly, the MCH metrics generally focused on a few key foods (grains, fruits, vegetables, dairy products, meat, and fish), while the NCD metrics had a more diverse mix of foods and nutrients. Only four metrics (Mediterranean Diet Score, Alternative Healthy Eating Index, Healthy Eating Index, and Dietary Approaches to Stop Hypertension) had convincing evidence of protective associations, mainly for all-cause mortality, cardiovascular diseases, type 2 diabetes, total cancer, and cancer mortality.[2]

Defining Nutritional Terminology in the Context of Diet Quality

A variety of terms exist that are relevant to diet quality:

Adequacy: The term "adequacy" refers to ensuring that enough of a particular food or nutrient is consumed to maintain health.

Moderation: The principle of moderation reflects the need to restrict intake to prevent harmful effects on health1 and, thus, limit selected foods that contribute to excess risk for disease.[8]

Dietary Reference Intakes (DRIs): The National Academies of Sciences, Engineering, and Medicine (NASEM) define the Dietary Reference Intakes (DRIs) as a set of standards and recommendations to address adequacy and moderation.[9] The DRIs include the following components:

1. **Estimated Average Requirement (EAR):** The mean required level of consumption. At this level, 50% of the population will receive more than their individual needs, and 50% will receive less than their individual needs.

2. **Recommended Dietary Allowance (RDA):** Two standard deviations above the EAR, this recommended intake level will meet the needs of ~97–98% of individuals.
3. **Adequate Intake (AI)** is established when evidence is insufficient to develop an RDA and is set at the population average intake, which is assumed to ensure nutritional adequacy.
4. **Tolerable Upper Intake Level (UL):** Highest average daily nutrient intake level likely to pose no risk of adverse health effects.
5. **Chronic Disease Risk Reduction Level (CDRR):** The lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction (used only for sodium).[10]

Undernutrition denotes insufficient energy intake and nutrients to meet an individual's needs to maintain good health, whereas malnutrition includes both undernutrition and overnutrition. Undernutrition is synonymous with malnutrition in much of the literature.[11]

Overnutrition: Refers to excess intake of macronutrients and micronutrients. Poor diet was previously associated with undernutrition but is now more associated with excess intake of calories, saturated fat, and sodium.

Malnutrition: Assessing malnutrition remains unclear as few widely used and validated metrics can define the double burden of MCH and NCDs.[2] Traditionally, it is defined as "insufficient caloric or other nutrient intake leading to insufficient physical growth (stunting), rapid weight loss, or failure to gain weight (wasting), cognitive impairment, exacerbation of anemia and blindness, or weakening of the immune system resulting in the increased risk of infectious diseases and mortality."[12] Regarding chronic disease, malnutrition considers excess consumption of fat, sugar, salt, and calories.[2,4] Recently, both are frequently coexisting with poor diet quality within individuals and populations.[2] The World Health Organization defines malnutrition to include undernutrition (wasting, stunting, underweight), inadequate vitamins or minerals, overweight, obesity, and resultant diet-related, chronic diseases.[13]

Underconsumed and overconsumed nutrients are nutrients or foods whereby five percent or more of Americans or a population subgroup fail to sufficiently consume to achieve recommended intakes, according to the USDA Dietary Guidelines Advisory Committee Report.[14] These include calcium, magnesium, potassium, iron; vitamins A, C, D, E; and choline, and fiber.[14] Four of these (calcium, potassium, vitamin D, and fiber) are considered Nutrients of Public Health Concern because their low intakes are associated with health concerns.[14] Overconsumed nutrients include added sugars, saturated fat, and sodium.[14] Nutrients of concern are included on U.S. food labels.

Children's Nutrition

Though there is a scarcity of research on children and plant-based diets, most studies do not indicate any detrimental effects of vegetarian or vegan diets on children, with some pointing towards multiple health benefits, such as lower risk for obesity, cardiovascular disease and diabetes.[15] Parents of vegetarian and vegan children are advised to pay close attention to critical nutrients, including protein, iron, calcium, vitamins D and B12, and omega 3 fatty acids.[16–19]

Physical development between vegetarian and omnivore children was similar, and both groups met reference values for protein and energy. Iron intakes in both groups were 60–70% of the reference intake.[20,21] The Dietary Guidelines for Americans now include children under two years old with suggestions that human milk is provided exclusively for the first six months of life and only human milk (not plant or cow's milk) for the first 12 months. Early exposure (in the first year) to highly allergenic foods is now suggested, including peanuts, egg, cow's milk products, tree nuts, milk, seafood, and soy.[22]

American children overconsume added sugar, which may be contributing to the current obesity epidemic.[23] American children also regularly consume fast food, which results in higher total energy and reduces diet quality.[24] Dietary patterns should include potassium-rich foods, alternatives to red and processed meat, whole grains, and avoidance of solid fats and sweetened beverages.[14]

Benefits of Plant-Based Diets for Diet Quality

Though previously associated with undernutrition, poor diet is now often correlated with excess calories, saturated fats, trans fats, added sugars, and sodium.[25–27] Overall, nutrition from plant-based diets is typically of higher quality than omnivorous diets, as assessed by the Alternative Healthy Eating Index (AHEI).[28] A whole food plant-based (WFPB) diet is one made up of predominantly unprocessed fruits, vegetables, whole grains legumes, nuts and seeds, and excludes animal foods, with certain selective supplementation of vitamins B12. Sometimes D. Intentionally planned, WFPB diets provide sufficient nutrient intakes for all stages of life and can be therapeutic for chronic disease and overall health and healing.[29] The plant-based dietary pattern protects against overconsumption of nutrients that lead to obesity and disease,[30] particularly animal protein, saturated fat,[31] trans-fats, cholesterol simple sugars,[32] and sodium.[33,34]

Adequacy of Plant-Based Dietary Patterns

The following sections discuss achieving appropriate intakes of specific nutrients from food and certain necessary supplements in the context of a whole food, predominantly plant-based dietary pattern. Deficiencies can be dangerous but are also preventable through nutrition. Adequate intake is necessary, but supplementation may lead to excess and may be harmful to some people.[35]

Macronutrients

All macronutrients (protein, carbohydrate, and fat) are present in whole plant foods in varying proportions. No individual food is equivalent to a particular macronutrient.

Protein

Though protein is typically associated with animal foods in the U.S., predominantly plant-based and entirely plant-based diets easily meet or exceed recommended protein intake.[29] The RDA for protein is .8 grams per kg of body weight or 10–11% of calories taken in. For instance, to calculate requirements for a person weighing 150 pounds (68.2kg), multiply 0.8 (g protein) by 68.2 (kg). This equates to ~55 g protein daily. Each gram contains 4 calories: 55 grams of protein multiplied by 4 (calories per gram) = 220 calories, which is 11% of calories in a 2,000 calorie/day dietary pattern for most individuals. Some populations, including the elderly, some athletes, and those healing from diseases, may need higher amounts. Older adults may need 1.0 to 1.3 grams per kg of body weight per day.[36] Protein intakes in the American diet are typically higher than this amount, and failing to meet this RDA is unlikely except in cases of energy malnutrition (insufficient calories).

In the body, proteins are broken down by enzymes into their amino acid building blocks and built into proteins as needed.[37] The nine essential amino acids (leucine, isoleucine, methionine, phenylalanine, histidine, tryptophan, valine, threonine, and lysine) are synthesized only by plants. They must be obtained from food or supplements to build all other amino acids (alanine, β-alanine, asparagine) and peptides.[38] With sufficient caloric intake, adequate levels of essential amino acids are supplied throughout the course of a day to meet requirements.[29] Regular intake of legumes also provide other essential nutrients, as well.[29] Though all whole plant foods have protein, rich sources include soy products, legumes, nuts and seeds.[39] Whole grains are a source of proteins, with sprouted grains having increased protein content.[40]

Fat

Those consuming a plant-based diet are more likely to achieve a healthy fat intake than most omnivorous diets. Fat requirements are very low, and plant foods are able to supply all essential fat requirements. The AIs for linoleic acid (LA, an omega-6 fatty acid) is only 12 grams per day for adult women under 70 years and 17 grams for men under 51 or 14 grams for those 51–70 years. AI for alpha-linolenic acid (ALA, an omega-3 fatty acid) is 1.6 grams/day for adult males and 1.1 grams for adult females.[41]

Fatty acids serve many vital roles, including the facilitation of normal metabolism, absorbing fat-soluble vitamins, producing hormones and other essential compounds, and controlling inflammation.[42] Both omega-3 (n-3) and omega-6 (n-6) fatty acids are needed. Most individuals consume much more n-6 polyunsaturated fat than

n-3, largely from vegetable oils (found in most processed foods) and also meat, poultry, fish, and eggs. Dietary intakes of ALA, the precursor to n-3 fatty acids eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) include cold-water fish and seafood. Flaxseed, soybeans, walnuts, and leafy green vegetables are also good sources.[39] A tablespoon of flaxseed has 3 grams of fat with 2.35 grams ALA.

Humans convert both essential fatty acids to longer-chain fatty acids using the same desaturation enzymes. The n-3 fatty acid (ALA) is converted to DHA and EPA, and the n-6 (LA) is converted to arachidonic acid (AA). N-3 and n-6 compete for the same desaturation enzymes, and a high intake of LA appears to interfere with the desaturation and elongation of ALA.[43]

The ratio between n-6 and n-3 fatty acids may be important, and a ratio of 1:1 to 2:1 is consistent with evolutionary aspects of diet as well as neurodevelopment and genetics.[44] Their balance may be an important determinant in brain development and decreasing the risk for cardiovascular disease, hypertension, cancer, diabetes, arthritis, and other autoimmune and possibly neurodegenerative diseases.[44]

Plant-based eaters generally have lower blood levels of EPA and DHA, and these nutrients may be virtually absent in vegans.[45] Those with higher needs or reduced conversion ability may receive some benefits from supplementation.5 Though deficiency in dietary fat is rare if sufficient calories are consumed, some conditions may put patients at risk, including eating disorders, large bowel obstruction, or metabolic disorders. Whole food sources of healthy fats include nuts, seeds, avocados, and olives.[46] Half an avocado contains roughly 11 grams of fat, one ounce of almonds or sunflower seeds has 14 grams, a handful of olives (5) has roughly 2 grams of fat, and 1 cup of plain tofu has 11.86 grams of fat.[47] However, whole grains, legumes, and vegetables also contain varying fat levels; given such low requirements, unrefined whole plant foods easily supply sufficient quantities.

Refer to the Saturated Fat section under "Overconsumed Nutrients" for more information on saturated fat and health risks.

Carbohydrate

Whole foods with unrefined, complex carbohydrate from legumes, vegetables, whole grains, and fruits are the best options for health and caloric needs and are associated with positive health outcomes.[48] The RDA of carbohydrates for children and adults is 130 grams per day.[41] A diet based on whole, unrefined plant foods is likely to be relatively higher in carbohydrate as a percent of total calories than typical American dietary patterns.

Refined carbohydrates such as white bread, added sugars, and polished rice or corn are associated with negative health outcomes, including overweight, obesity, metabolic disorders,[49] heart disease,[50] and type 2 diabetes[51] and should be discouraged.[48] Found in processed food, refined carbohydrates make up the bulk of carbohydrates consumed by Americans.[52,53]

Nutrients of Public Health Concern

The following sections describe plant food sources of specific nutrients and background information on each nutrient.

Calcium is found in many plant foods. Though cow's milk is often touted as the best source, our bodies may absorb calcium from plant foods at a higher rate. The RDA for calcium is 1,000 mg/day for most adults and 1,200 mg/day for women over 50.[41] Dairy foods have a 30% bioavailability, whereas some plant foods, though they contain less calcium, have a higher absorption rate.[54,55] For example, bok choy contains 160mg of calcium per 1 cup but has a bioavailability of 50%, thus 80 mg is absorbed.[55] Even though totally plant-based diets theoretically contain enough calcium to meet RDAs, nearly half of all Americans do not meet the EAR for calcium.

Plant sources of calcium are adequate to meet needs. For example, calcium-set tofu has the same calcium availability as cow's milk.[56] Plant-based sources of calcium include bok choy, broccoli, Brussels sprouts, kale, collard greens, tofu, winter squash, and almonds.[55,57] Foods high in calcium include tofu prepared with calcium sulfate, soybeans, enriched cornmeal, and fortified plant milks, as well as dairy products. Vegetables, particularly those low in oxalates, are good sources of calcium (greens such as spinach, kale, or collard greens).[47]

Potassium is easily found in many plant foods and is needed for blood pressure regulation and bone health; thus, lower intake is associated with cardiovascular, renal, and bone health risks.[58,59] The AI for adults 19–70 is 2,600 mg/day for women and 3,400 mg/day for men.[41] Lower intake of fruits and vegetables in the Western diet has led to decreased potassium intake.[60,61] The regulative effect of potassium on acid-base balance is one hypothesis for its effects on bone health and the prevention of osteoporosis. Further, dietary potassium may reduce kidney stones and slow the progression of kidney disease from renal vascular, tubular, and glomerular damage. It may also help to suppress renal inflammation.[60] Potassium's hypertensive effects include the decrease in intravascular volume. Though there is an established relationship between potassium and chronic disease, it is difficult to establish a proven lowest level of intake to prevent disease, and, thus, there is yet to be a specific potassium CDRR.[62] There is an association between white vegetable consumption and decreased risk of stroke.[58] Potatoes are the highest sources.[58] Other foods rich in potassium include yams, avocado, and most varieties of beans.[47] Fruit and vegetable sources include banana, beet greens, apricots, and dates,[63–65] as well as nuts, green vegetables, yogurt, chickpeas, and tuna.[63,65,66]

Dietary fiber is found exclusively in plant foods. The AI for fiber is 14 g per 1,000 calories per day,3 which translates to 25 g per day for women <50 yrs and 21 g for those >50 yrs. For men, it is 38 g <50 yrs and 30 g for >50 yrs.[41] On average, American adults consume half the recommended amount of fiber.[67] A predominantly plant-based diet rich in whole foods allows for plenty of fiber in the diet.[29] Foods high in fiber include black beans, split peas, lentils, avocado, raspberries, dried figs, flaxseeds, oatmeal, and whole wheat pasta. Other fiber-rich foods include blueberries, strawberries and other fruit, winter squashes, brown rice, whole-grain bread, popcorn, mushrooms, almonds or peanuts, and sunflower or sesame seeds.[47] Though it does not contribute to our energy needs, fiber is essential to gut health and immune function and helps control pathogens, as well as being a protective factor for many chronic diseases.

Vitamin D, or calcitriol, is an exception to the list of nutrients provided completely by plant food sources in that it is a fat-soluble steroid hormone produced endogenously from sun exposure. It can be consumed from some foods, as well as provided by fortified foods or supplements.[68] The RDA for vitamin D is 15 mcg/600IU up to 70 years old and 20 mcg/800 IU above 70 years.[3,68]

Sunlight is a better source of vitamin D than dietary sources as ultraviolet (UV) B radiation transforms the precursor of vitamin D in the skin into vitamin D3. Usually, adequate vitamin D levels can be synthesized internally if large areas of the body, including the face, arms, legs, back, or chest, are exposed to direct sunlight between the hours of 10am–3pm; without sunscreen for five to 30 minutes at least two days a week. Those with darker skin pigmentation require more extended amounts of time in the sun.[68,69] Supplemental sources of vitamin D may be required to meet needs in the cases of insufficient synthesis, including for those on a plant-predominant diet, and especially in winter seasons or for individuals who have limited exposure to the outdoors.[70] Foods high in vitamin D include fortified milks, both dairy and non-dairy, fortified juice, fortified cereals,[3,63] salmon, or high fat fish,[3,63] and mushrooms treated with ultraviolet light.[71] Vitamin D may be provided by eggs as well as mushrooms that are treated with or exposed to ultraviolet light, as well.[72]

The importance of vitamin D is indicated by the predominance of vitamin D receptors throughout the body. The two primary forms, D2 (ergocalciferol) and D3 (cholecalciferol), only differ in their side-chain structures. The small intestine absorbs both forms. As a vitamin, it regulates body calcium levels, phosphorus, and bone mineralization, and controls cellular proliferation and differentiation. Vitamin D also regulates gene expression in specific tissue[73] and protects against oxidative stress from its antioxidant properties.

It is assumed that most people do not make enough D from sun exposure due to indoor living. Deficiency can result in brittle bones, rickets, osteomalacia,[73] and/or osteoporosis.[74] Symptoms of low vitamin D include fatigue, bone, joint, or muscle pain, and anxiety. In addition, studies suggest that low vitamin D levels can be linked to diabetes and insulin resistance, high blood pressure, multiple sclerosis, and possibly some cancers.[73,75]

Overconsumed Nutrients

Added Sugar: Excess intake of added sugars is associated with weight gain, excess body weight and obesity, type 2 diabetes, high serum triglycerides, higher cholesterol, high blood pressure and hypertension; stroke; coronary heart disease, cancers, and dental caries.[52] The recommendation in the 2020 Dietary Guidelines for Americans is to limit added sugar intake to no more than 10% of calories.[3] A whole food diet that avoids refined grains and prepared foods is naturally low in added sugars. Naturally occurring sugar in whole food, such as fruits, is not associated with adverse health effects. On the contrary, foods with naturally occurring sugars have consistently been found to be protective against disease and are not associated with harmful health outcomes.[76]

Sodium: The ubiquitous intake of processed foods has led to an excess in sodium intake. The CDRR is <2,300 mg/day. Most adults in the U.S. consume more than 3,400 mg each day.[77] Though the body needs very small amounts of sodium to function, evidence points to an association with excess salt consumed and elevated blood pressure levels, a major risk factor for cardiovascular disease.[78] The food groups that are highest in salt are generally those that are commercially prepared. Almost 50% of dietary salt intake comes from mixed dishes defined by the USDA Dietary Guidelines as: "burgers, sandwiches, and tacos; rice, pasta, and grain dishes; pizza; meat, poultry, and seafood dishes; and soups."[26] Limiting consumption of commercially processed foods is an important strategy to reduce excess sodium intake. Focusing on whole foods and preparing meals at home naturally avoid excess sodium consumption.

Saturated Fat: The 2020–2025 USDA dietary guidelines have, again, called for Americans to cut their saturated fat intake to under 10%,[3] and the American Heart Association recommends a dietary pattern that achieves 5%-6% of calories from saturated fat,[79] which is naturally achieved by eating an entirely plant-based diet.[80] Current U.S. intake is 11%.[3] Because they are found primarily in animal foods, plant-based diets are naturally low in saturated fats, which are associated with risk of cardiovascular disease and diabetes.[80–82] Saturated fats have been shown to increase LDL-C,[83] a known causal factor in atherosclerosis,[84] through the development of lipoproteins that promote foam cell formation, part of the fatty streak phase of atherosclerosis. These deposits in the arterial wall initiate an inflammatory response.[85] Further, in epidemiologic and metabolic studies, saturated fat has been associated with insulin resistance and oxidative stress.[86–88] Research has found that individuals eating vegetarian-type dietary patterns have lower saturated fat and cholesterol intakes, and unsaturated fat intake appears to be relatively similar between plant-based and non-plant-based eaters.[45,89,90]

Other Nutrients of Interest

Vitamin B12 or cobalamin is a group of complex molecules with a single cobalt atom at their center. B12 is one of the eight B vitamins making up the water-soluble vitamins, which are absorbed easily into the bloodstream. The RDA for vitamin B12 is 2.4 mcg/day, which is easily consumed through fortified foods or supplementation.[3,41,68,91]

Vitamin B12 is made by microorganisms found in the soil and water, as well as produced by microorganisms in the intestines of animals. Vitamin B12 is stored in the liver and muscle tissue, so it is naturally found in animal foods and not plant foods. The amount made in the intestines is not adequately absorbed, so it is recommended that people consume B12 in food or supplementation. Though essential, humans need very small amounts of vitamin B12 to achieve adequate intake (2 to 3 milligrams a day). Because the body can store cobalamin for up to three years, it can take several years for deficiency to present.[91]

Vegetarians and the elderly have a high risk of vitamin B12 deficiency due to low consumption, as well as lower absorption.[92] Other factors unrelated to age or diet may influence B12 absorption, including intestinal damage and acidity levels (lack of hydrochloric acid in the stomach and increased acidity in the small intestine).[93] Medications such as proton pump inhibitors and H2 blockers prescribed for GI disorders like GERD can inhibit absorption. Pancreatic insufficiencies of intrinsic factor (IF) production, which is required for the transportation and absorption of vitamin B12, will also result in lower uptake of B12.[94] Acidification of the small intestine, parasites, or bacterial growth in the gut can

inhibit absorption, as well.[93] Plant-based eaters have lower average circulating concentrations of vitamin B12 and a higher risk for elevated homocysteine levels and developing clinical symptoms related to B12 deficiency, including unusual fatigue, tingling in the fingers or toes, poor cognition, poor digestion, and failure to thrive in small children.[95,96] Thus, there is a need for supplementation for those eating an entirely plant-based diet (no animal foods at all) for several years, as well as for older adults.

Magnesium is needed for many chemical reactions in the body as well as for neuromuscular connections. The RDA for magnesium is 310 mg for females <30 yrs and 320 mg for >30 yrs, and 400 mg for males <30 yrs and 420 mg for >31 yrs.[41] Most people obtain enough from diet, though green leafy vegetables, whole grains, nuts, and fish are good sources.[97] Other sources of magnesium include tofu, potatoes, yogurt, and meat, or tuna.[47]

Vitamin A is vital for cell reproduction and differentiation, immune function, and good vision. It comes from two sources: plant sources provide carotenoids, and animal sources provide retinol. The RDA is 700 µg /day for adult women and 900 µg/day for adult men.[41] Because it can be toxic in high supplemental doses, there is a UL of 3,000 µg/day for adults.[98] Foods high in retinol (the vitamin A1 found in food and supplements) include cooked sweet potato or spinach, raw carrots, cantaloupe, or butternut squash. Beef liver is very high in vitamin A. Other foods containing vitamin A include dairy, plant milks, and fortified cereals.

Vitamin C or L-ascorbic acid is required to turn fat into energy and make collagen. It is needed to create certain neurotransmitters and is involved in protein metabolism.[99] The RDA for vitamin C is 75 mg for adult women and 90 mg for adult men.[41] Foods high in vitamin C include bok choy, parsley, daikon radish, broccoli, cantaloupe, Brussels sprouts, pineapple, cabbage, cauliflower, mustard greens, papaya, green peas, kale, tomatoes, strawberries, turnip greens, orange, guava, kiwi, mango, and red pepper. Other sources include spinach, most other leafy green vegetables, including collard greens, celery, and fruits, including cherries, pears, and canned peaches.[47]

Vitamin E refers to a collection of fat-soluble compounds with distinctive antioxidant properties. They protect cells from the damaging effects of unstable free radicals that can damage cells and can contribute to cardiovascular disease and certain cancers.[100] The RDA for vitamin E is 15 mg/day for adults.[41] Foods high in vitamin E include sunflower seeds, almonds and hazelnuts, sunflower and safflower oils, and trout. Other foods containing vitamin E include peanut and olive oils, corn oil, and peanut butter.[47]

Iodine is an essential component of the two thyroid hormones, thyroxine and triiodothyronine, which regulate many biochemical functions, including protein synthesis and enzyme activity.[101] It is a trace element found in soil and the sea and, thus, obtained from plants and sea vegetables.[102] The RDA for iodine is 150 µg/day for adults and more for pregnant and lactating women,[97] with a UL of 1,100 µg/day.[3,103] Levels above 2 mg/day can impair hormone function and stimulate acne.[104] Iodine is also in meat and dairy, as animals eat food grown in soil. Though essential, its only known function is as a component of thyroid hormones. These hormones regulate cell growth and activity, particularly important to the nervous and skeletal system development.[105]

Dietary iodine sources can vary widely in the U.S.,[106] and iodine intake among plant-based eaters can be low for those who do not consume sea vegetables or iodized salt; supplementation may be needed.[106] Iodine deficiency was common in the early 20th century, with goiter being epidemic. Deficiency can also impair mental development and promote cognitive impairment.[107] In the U.S., iodization of salt began in the 1920's. By the 1970's, the U.S. population had excessive iodine intake, sometimes leading to hyperthyroidism or autoimmune thyroiditis.[107] High iodine intake is more common now than deficiency and can occur from excessive dairy intake. Iodine is used as a sterilizer for milking machinery and teats and as a supplement in dairy cow feed. Iodine is also used as dough conditioners in baked goods. Deficiency is found in areas where the soil is deficient, e.g., from glacial runoff or flooded plains. A majority (75%) of the sodium consumed in the U.S. is not iodized, particularly coming from processed foods. Sea vegetables are considered a good source. Skins of tubers, such as potatoes, have iodine, as well.[104,105]

Iron is needed to build hemoglobin for red blood cells to carry oxygen from lungs to body tissue. It is vital

to muscle function and ATP energy production and as a cofactor for several enzyme systems. The RDA for iron is 18 mg/day for adult women under the age of 51 and 8 mg/day for older women, as well as all adult men,[3] though RDAs for vegetarians are 1.8 times higher than for meat-eaters, as heme iron from meat is more bioavailable than nonheme iron from plant-based foods, and meat, poultry, and seafood increase the absorption of nonheme iron.[108] Iron deficiency is one of the most common nutritional deficiencies, particularly in women and children. Low levels can lead to anemia, though not necessarily due to poor diet. Blood loss from ulcers, colitis, diverticulosis, heavy menstrual bleeding (menorrhagia), and microscopic bleeding is associated with anemia.[109,110] Though vegetarians generally consume as much iron as non-vegetarians, their iron stores are typically lower, which may be advantageous unless suffering from malnutrition. Excess circulating ferritin, the protein that contains iron, has been associated with a higher risk of developing metabolic syndrome,[111] heart disease, cancer, and premature aging.[108] Heme iron found in meat is more readily absorbable than non-heme iron, found in plant foods, which is more tightly regulated by the body. Because iron is a pro-oxidant, excess iron can increase free radical production that can damage tissues. Polyphenols in coffee and tea can reduce iron absorption, while vitamin C can increase absorption. Iron is plentiful in legumes, grains and beans, and fruits and vegetables. Cow's milk has very little iron and may inhibit absorption.[112] Iron deficiency is not typically found among vegetarian populations; however, vegetarian women have been shown to have a higher prevalence of anemia (Hb <120 g/L),[113–115] and absorption of iron in the context of mixed diets is typically more influenced by iron status than by the type of iron (heme vs. non-heme).[116]

Zinc is a mineral and is found in the soil and sea. Like most minerals (calcium being the exception), the body only needs small amounts, which easily accumulate. It competes for transporters with other minerals, so absorption is affected by the balance of other minerals (iron, manganese, nickel, calcium, and phosphate). The RDA for zinc is 8 mg for adult women and 11 mg for adult men.[41] Zinc is involved in many functions, including brain cell communication, hemoglobin activity, male reproductive cell function, night vision, immunity, and wound healing.[104,105] Its absorption is partly dependent on the supply of vitamin B6, and, like any nutrient, environmental variables can affect it, particularly oral contraception or hormone replacement use and heavy metal (mercury, lead, and cadmium) interference.[104] Further, zinc (as well as copper and iron) is found to be present in the beta-amyloid plaques formed in the brains of Alzheimer's patients. Studies indicate that it may encourage these proteins to clump together into plaques. So it may be that these metals work together in this disease, encouraging plaque. Dietary sources of zinc include legumes, seeds, nuts, wheat and corn, soy products, as well as animal food sources.[105,117]

Choline, a water-soluble vitamin, is now recognized as an essential nutrient needing established dietary reference values. The AI for choline is 425 mg for adult women and 550 mg for adult men, with a UL of 3,500 mg.[41] Choline is important for the nervous system as the precursor to the neurotransmitter acetylcholine. It is also involved in cell structure, lipid transport, and cognitive development during pregnancy.[57] The requirements for choline have partly been informed by studies in women and men who developed liver damage upon becoming deficient.[118,119] Choline is found predominantly in animal foods, though there are several plant-based sources with lower amounts, including beans, tofu, green vegetables, potatoes, nuts, seeds, whole grains, and fruits.[47] High choline intake is associated with increased risk of cardiovascular disease from the production of TMAO by gut microbiota[120] and prostate cancer.[121] Egg, broccoli, and chickpeas are good sources of choline.[47]

Nutrient Intakes of US Adults

Table 1 displays mean nutrient intakes from US adults, using the What We Eat in America data (National Health and Nutrition Examination 2015–2018) for men and women in comparison to mean intakes among strict vegetarians (completely plant-based /vegan) in the 7th Day Adventist cohort. Striking contrasts are visible for both macro and micronutrients, as well as certain similarities, such as the % protein intake. The mean nutrient intakes of the strict vegetarian group demonstrate the feasibility of plant-based diets to provide adequate nutrient intake.

Table 1 Actual nutrient intakes of US adults and strict vegetarians in the 7th Day Adventist cohort

Nutrient	Actual Intakes of US Adult Men (>19 yrs) (mean)[a,122]	Actual Intakes of US Adult Women (>19 yrs) (mean)[a,122]	Actual Intakes of 7th Day Adventist Strict Vegetarians (mean)[b,123]
Energy (kcal)	2460	1825	1894
Fat (g)	99	75	66
Total fat (% energy)	36	37	30
Saturated fat (% energy)	12	12	6
MUFA (% energy)	13	13	13
PUFA (% energy)	8	9	10
Unsat:sat fat ratio	1.8	1.8	4.3
Cholesterol (mg)	352	258	NR[c]
Carbohydrate (g)	281	215	309
CHO (% energy)	46	47	62
Total sugars (g)	119	95	112
Total sugars (% energy)	19	21	24
Protein (g)	96	69	72
Protein (% energy)	16	15	15
Fiber (g)	19	16	47
Micronutrients			
Dietary vitamin A activity (RAE[d])	681	612	1108[e]
Total vitamin D (calciferol, µg)	19	12	6.3
Dietary vitamin E (Alpha-Tocopherol mg)	10	9	101
Total vitamin B12 (µg)	68	127	23
Dietary folate equivalents (µg)	757	669	888
Dietary vitamin C (mg)	166	165	531
Dietary calcium (mg)	1155	1027	1156
Dietary magnesium (mg)	372	304	652
Dietary potassium (mg)	2967	2332	1371
Dietary iron (mg)	18	16	31.6
Dietary sodium (mg)	4107	2994	3531

a. Includes intakes from foods and beverages for macronutrients and vitamins A and E. Includes intakes from foods, beverages, and supplements for all other micronutrients.

b. Includes intakes from foods, beverages, and supplements

c. NR = not reported

d. RAE = retinol activity equivalents

e. Converted form of dietary beta-carotene (1 g RAE = 12 µg dietary beta-carotene) see https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/

Common Questions and Concerns

Will I get enough protein on a plant-based diet?

Meeting protein requirements happens easily on an entirely or predominantly plant-based diet if consuming enough calories. Theoretical models of the nutrient composition of WFPB diets have calculated 16% energy from protein compared to the USDA MyPlate, which was calculated at 19% protein from mixed animal and plant sources.[70] Research including the comprehensive China Study indicates consumption in excess of human requirements may promote disease.[124,125]

Will I get enough calcium and iron on a plant-based diet?

Though plant foods contain phytates that inhibit iron, zinc, and calcium absorption, the estimated intake of these minerals in theoretical nutrient compositions of whole food, plant-based diets exceeded the RDA, except for calcium in women over 50 years.[70] Unfortunately, nearly half of Americans do not even meet the EAR for calcium, despite the majority of them consuming an omnivorous diet.[122] Fruit and vegetable intake may help in absorption by shifting pH towards base. Caffeine and alcohol may inhibit absorption modestly by increasing excretion of calcium.[126]

Will I be at risk for anemia?

Anemia indicates a reduced level of red blood cells from decreased production, blood loss, or destruction of red blood cells. Iron deficiency is the most common cause of anemia, and menorrhagia is the most common cause of blood loss.[116] Iron is an essential protein of hemoglobin in red blood cells that carry oxygen in the blood and myoglobin that provides oxygen to muscles. Since iron absorption is determined by the amount present in the body (circulating and stored), and the modulation effect of both inhibitors and enhancers to absorption of dietary iron, the amount of iron absorbed varies depending on the food taken in at each meal, the composition of the overall diet, and individual iron status. When iron stores are low in the body, absorption from food is higher, and visa-versa.[116] It is important to note that meat and vitamin C from fruits and vegetables enhance the absorption of iron,[127] and that cow's milk and dairy products might inhibit absorption due to their calcium,[128] and from their protein casein.[129]

Plant-based eaters need to take in adequate amounts of vitamin C from food, as well as vitamin B12 from supplementation, in order to maintain optimal iron status. Vitamin B12 is necessary to produce new red blood cells, which carry oxygen throughout the body. The B vitamin folate is also necessary for the production of red blood cells. Sufficient intake of these nutrients has been correlated with adequate serum ferritin levels, the circulating protein that contains iron. Ferritin is what is used to measure iron stores.[115]

In some studies, vegetarians have been found to have a higher prevalence of depleted iron stores, as well as higher incidence of iron deficiency anemia, particularly in premenopausal vegetarian women.[115] Other studies have shown that serum ferritin and hematocrit levels of vegetarians were similar to non-vegetarians.[114] Helicobacter pylori infections can also leave people at risk for deficiency.[130] Healthful sources of iron include greens and legumes, and a diet including these as well as fortified grains can easily provide adequate iron. The CDC recommends that iron supplementation be individualized based on hemoglobin and hematocrit screenings, as well as medications taken.[131]

Will I get enough vitamin D on a plant-based diet?

Humans are designed to obtain most vitamin D from sunlight, and many individuals who spend most or all of their time indoors may fall short of requirements. Vitamin D is not naturally widespread in food but is mostly in animal products, particularly fish and egg yolks. Mushrooms also contain vitamin D, and if left out in the sun, they can absorb more.[132] Foods fortified with vitamin D in the United States include cow and soy milk, orange juice, and certain breakfast cereals.

Will I get enough B12 on a plant-based diet?

Supplementation will be necessary. Vitamin B12 (and possibly vitamin D) are the exception to the overriding understanding that a whole food, plant-based diet provides all nutrients needed for a health-promoting diet. This vitamin is not widely in soil or water as it once was, and therefore supplementation is advised for vegans. Animals produce it in their

lower intestines, so meat and dairy products may be sources, but nutritional deficiency can occur in plant-based populations and the elderly.[133]

Summary of Key Studies

Diet quality should be a concern for all regardless of the parameters of the specifics of an individual's diet. To examine the nutritional quality of plant-based diets, we extracted information on 13 studies examining nutrient status and overall diet quality of plant-based diets—WFPB, vegan, vegetarian, and lacto-ovo-vegetarian (LOV) diets. Studies are detailed in Appendix Table 1. Of the studies extracted,[3] were randomized controlled trials (RCTs),[134–136] one was an observational cohort study,[137] two were cross-sectional,[95,138] and three were systematic reviews and/or meta-analyses,[89,139–141] and one examined theoretically derived dietary patterns.[70] Studies examined overall dietary quality, omega-3 (n-3) fatty acid intake and levels, magnesium status, vitamin D and calcium intake, vitamin B12 and folate levels, zinc intake, and iron status.

For n-3 fatty acids, one study examined whether retroconversion of DHA to EPA was a viable method for replacing seafood intake in maintaining n-3 levels.134 The authors estimated that rates of retroconversion in vegetarians were approximately 9.4% DHA to EPA compared to just over 1% in previous studies, suggesting a significant retroconversion of DHA to EPA in humans.

In studies that examined magnesium intake in vegans,[141] it was found that vegans had higher magnesium consumption than meat-eaters and that red blood cell content of magnesium was not statistically different between groups. In addition, pregnant subjects from the same study reported fewer calf cramps on a plant-based diet compared to meat-eaters. One study examining theoretically derived diet plans found that a WFPB diet may contain 70% more magnesium compared to diet plans based on USDA MyPlate.

It is well-known that plant-based diets often lack vitamin B12, especially if individuals refrain from consuming fortified foods. One cross-sectional study found that vegans had significantly lower serum concentrations of vitamin B12 but higher folate levels compared to meat-eaters.[95] These findings highlight the necessity of plant-based individuals to supplement with vitamin B12, consume B12 fortified foods, or both.

As discussed, vitamin D is a Nutrient of Public Health Concern. Consumption and serum levels of vitamin D are lower on plant-based diets than omnivorous diets, as animal foods contain vitamin D.[135,136,138] Individuals should consider incorporating fortified sources of vitamin D into their plant-based diets in addition to meeting RDAs for calcium consumption. Multiple studies found that calcium intake was lower in individuals on plant-based diets,[70] except with one study that found an increase in calcium consumption with a tailored whole food, plant-based diet intervention.[135] Finally, zinc and iron are nutrients of interest for plant-based and non-plant-based individuals alike, as studies extracted found decreases in serum zinc and increases in zinc excretion associated with pregnancy in both groups,[140] and vegans and vegetarians were found to have lower iron intakes and iron stores in one meta-analysis.[141]

At the same time, plant-based diet interventions have consistently shown improvements in diet quality. One theoretical analysis found that WFPB diet adherence could lead to increased vitamin A activity, vitamin E, folate, vitamin C, magnesium, potassium, and iron while lowering saturated fat and added sugar consumption.[70,89,136] In terms of food components, WFPB diets could lead to more than a doubling in vegetable, legume, whole fruit and grain, and nut and seed consumption.[70,89,136] In addition, observational and intervention studies alike consistently find significant increases in dietary quality indices such as the Healthy Eating Index and Alternative Healthy Eating Index compared to baseline and individuals following control diets, including American Diabetes Association guidelines.[89,135,136]

Well-planned plant-based diets can lead to significant improvements in dietary quality and provide a framework for individuals to adjust lifestyle factors to prevent chronic conditions like obesity, hypertension, cardiovascular disease, and type II diabetes. However, these diets should be well planned to meet nutrient requirements and should be high in vegetables, fruits, whole grains, legumes, nuts and seeds, and other whole plant foods. Supplements for vitamin B12, and as needed, vitamin D, should be incorporated.

Conclusion

Though diet quality is intrinsically linked to disease etiology and health outcomes, the typical American diet lacks the micronutrients needed for optimal health. Excess energy contributes to disease epidemics, including cardiovascular diseases, metabolic diseases including diabetes, many cancers, and decreased quality of life. Whole food, plant-based diets address these problems of nutrition adequacy and excess by providing all nutrients necessary (with the possible exception of vitamins B12 and D) without excess calories and foods that promote increased risk for chronic disease.

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APPENDIX 1 Diet Quality and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Karlsen, 2019[70] **Theoretical Dietary Intake Analysis** n = 200 randomly sampled web-recruited participant responses to Adhering to Dietary Approaches for Personal Taste (ADAPT) Feasibility Survey
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Six most frequently cited diet information sources were selected, from which six 5-day meal plans were synthesized to create a representative 30-day meal plan for whole food, plant-based (WFPB) diet.
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	No exposure. Nutrient intakes from 30-day WFPB meal plans were calculated and compared to Recommended Dietary Allowances. MyPlate plans posted online were also used to create 21-day compliant meal plans.
Outcome(s) of interest and units	• Comparison of nutrient and food group intakes from WFPB diet plan compared to RDA values for Americans in nutrients of public health concern • Comparisons of food intake between isocaloric meal plans for WFPB diet and MyPlate
Key Results (Bold qualitative assessment followed by quantitative results)	**Theoretical WFPB diet nutrient levels had lower saturated fat, reduced energy consumption from added sugars, and elimination of animal protein, while increasing fiber and various micronutrient intakes compared to a MyPlate meal plan. Without supplementation, WFPB diets may fall short in vitamins D and B12. In addition, calcium consumption decreases with WFPB diets compared to MyPlate, leading to theoretical WFPB diets not meeting the RDA for calcium in men and women.** Comparing the theoretically derived WFPB meal plan to the isocaloric MyPlate meal plan, the WFPB plan had a 66%, 41% and 46% lower saturated, total, and monounsaturated fat level, along with a 21% lower polyunsaturated fatty acid intake. WFPB diet had 34% increased consumption of carbohydrate as a percentage of energy, but a 65% reduction in energy from added sugars as a percentage of daily energy intake. WFPB diets had 15% lower protein content and a 146% higher fiber content. All nutrients (after supplementation with vitamin D and B12) surpass recommended values of intake on WFPB diet except for calcium in both men and women.
Comments: Significance to clinical application	WFPB diets exceed nutrient recommended daily values for various health-promoting nutrients like fiber and many vitamins and minerals, while reducing saturated fat and added sugar consumption. Though WFPB diets exceed recommendations on many fronts, there are some caveats. It is recommended that those following WFPB-style diets supplement with vitamin D in colder climates, and vitamin B12 regularly. In addition, calcium intake tends to be lower on WFPB diets, so inclusion of calcium-fortified foods like plant milks may help fill the gap in vitamin D consumption for plant-based dieters. Otherwise, WFPB diets have the potential to greatly improve diet quality as long as the diet is balanced and adherence is maintained.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Parker, 2019[89] **Systematic Review** n = 12 studies on adult vegetarians and nonvegetarians with any study design
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 12 studies comparing vegetarian and nonvegetarian adults using *a priori* diet quality index Overall number of subjects, age, and BMI not specified
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Lacto-ovo-vegetarian (LOV), Vegan, Pesco-vegetarian, and Semi-vegetarian compared to non-vegetarian diets
Outcome(s) of interest and units	• Scores of various diet quality indices for followers of exposure diets [Healthy Eating Index (HEI), Alternative Healthy Eating Index (AHEI)] • Diet quality in adequacy component scores • Diet quality in moderation component scores • Diet quality in more- and less-restrictive diets
Key Results (Bold qualitative assessment followed by quantitative results)	**In general, it was observed that vegetarians had improved diet quality compared to nonvegetarians via various *a priori* defined dietary indices. In addition, the authors found some evidence that diet quality increased as vegetarian diet-type became more restrictive, with vegans having the highest diet quality, followed by vegetarians, followed by non-vegetarians.** Overall diet quality was significantly higher in vegetarian diets compared with nonvegetarian diets in 8 of 12 studies. In 6 studies examining self-reported vegetarian status in convenience samples, vegetarians had consistently higher diet quality compared to nonvegetarians (by 4.5-7.4% on HEI). Vegetarians also had higher diet quality with 2 nationally representative samples and 1 study from Germany. In NHANES, those who were identified as vegetarian through 24-hour food recall had significantly higher HEI (72.81 vs. 56.44, $p < 0.001$) and AHEI-2010 (49.73 vs 38.49, $p < 0.001$) scores compared to nonvegetarians. For adequacy component scores, vegetarians generally scored higher on components for total fruit, whole grains, plant, and seafood protein and lower on total protein foods compared to nonvegetarians. For moderation components, vegetarians generally consumed more refined grains, similar amounts of empty calories, and less sodium compared to non-vegetarians.
Comments: Significance to clinical application	This study shows evidence of improved diet quality among self-reported and recall-identified vegans and vegetarians compared to omnivores. These findings suggest that elimination of certain food groups from the diet may be associated with improved scores on dietary indices like the HEI and AHEI, which have been associated with improved long-term health outcomes. In addition, increased restrictiveness of diet was associated with increased dietary score. This may mean that more strict rules of adherence lead to improved adherence among dieters. The authors' findings suggest that vegan and vegetarian diets may be used to improve diet quality in the general population. However, vegan and vegetarian diets must be planned to meet nutrition requirements.

First author, year, study design (bold), name of study (if applicable), sample population	Haider, 2018[141] **Systematic Review and Meta-Analysis** n = 27 cross-sectional studies + 3 intervention studies, of adults >18 years of age without any existing iron/ferritin disorders
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Characteristics of study participants not synthesized
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian (LOV, Vegan, Semi-Vegetarian) vs. non-vegetarian control groups
Outcome(s) of interest and units	• Mean difference (MD) in iron status (serum ferritin) of vegetarians and matched omnivores

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**After controlling for high risk of bias, calculation issues with the analysis, and removing studies with iron supplementation, the authors found that various types of vegetarians had lower mean levels of ferritin compared to non-vegetarians. These results were more pronounced in men than in premenopausal women or in all women. Short term adherence to a meat-free but not vegan diet didn't show significant decreases in ferritin stores in men.** When comparing various types of vegetarian diet with non-vegetarian diet, significantly lower ferritin values were found for vegetarians in premenopausal women (-17.70 µg/L; 95% CI -29.80 to -5.60), all female groups (-13.5 µg/L; 95% CI -22.96 to -4.04), studies that combined male and female groups (-30.80 µg/L; 95% CI -47.24 to -14.35), men (-61.88 µg/L; 95% CI -85.59 to -38.17), and all studies combined (-29.71 µg/L; 95% CI -39.69, -19.73). No effect was found in studies including pre- and postmenopausal women on ferritin values. Heterogeneity was considerable in studies examining postmenopausal women, combined female groups, men, and overall analysis. After removing studies at high risk of bias and subject to supplement use, in addition to calculation issues, associations decreased in significance. Effects remained significant in men (-64.88 µg/L; 95% CI -104.80 to -24.96) and all groups combined, but ceased to be significant in premenopausal women and all female groups. Intervention diets found no significant change in ferritin after following LOV diet for 21 days, eight weeks, or twelve weeks.
Comments: Significance to clinical application	This meta-analysis reveals that much cross-sectional research on vegetarian diets and iron status is influenced by high risk of bias, low sample size, and other study issues. In addition, intervention studies found that no significant change in ferritin stores in men following meatless diets in the short-term. In terms of examining vegan and plant-based diets, this study includes primarily vegetarians that still consume some animal products, making it difficult to ascertain if there are differences in iron levels between completely vegan diets and those containing animal products.

First author, year, study design (bold), name of study (if applicable), sample population	Foster, 2015[58] **Systematic Review and Meta-Analysis** n = 6 observational studies that examined zinc intake and/or status in vegetarian compared to non-vegetarian (NV) pregnant women
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 980 pregnant women subjects from 6 observational studies (2 in USA, 3 in UK, and 1 in India) Overall age and BMI of participants not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Studies compared vegetarian women to non-vegetarian women in observational-style studies.
Outcome(s) of interest and units	• Dietary zinc intake • Zinc Biomarkers • Period of gestation • Birth weight
Key Results (Bold qualitative assessment followed by quantitative results)	**Zinc intakes were consistently lower among vegetarian groups compared to NVs across all study countries. In addition, supplemental zinc did not appear to have an effect on plasma levels of zinc. Both omnivorous and vegetarian pregnant women experienced drops in zinc levels associated with pregnancy, though functional outcomes of birth were similar across groups.** Zinc intake of pregnant vegetarians was found to be lower than non-vegetarians (NV) (-1.38 (0.35) mg/day, $p < 0.001$). After excluding low-meat (LoM) participants from vegetarians, the difference between vegetarians and NV with respect to zinc intake became (-1.53 (0.44) mg/day, $p < 0.001$). Lowest dietary zinc values were recorded in the study in India, with both vegetarian and NV groups having zinc intake below 6 mg/day. Supplemental zinc did not appear to have any effect on plasma, urinary, or hair zinc levels in pregnant vegetarian or omnivorous women. Both omnivorous and vegetarian diet groups experienced falls in zinc plasma levels associated with pregnancy, and increases in urinary zinc levels during the study. No differences were found between vegetarian populations and control groups in period of gestation and birth weight. No studies observed relationships between measures of zinc status and either outcome.
Comments: Significance to clinical application	Zinc is a common nutrient of concern for pregnant women, as there is increased zinc demand throughout pregnancy. This study found that intake of zinc for pregnant vegetarians was lower than non-vegetarians. Even more concerning, supplementary zinc did not seem to effect plasma levels for any groups in the study, suggesting increased zinc secretion with supplementation. Interestingly, no difference in outcomes was observed for gestation period and birth weight between groups. This study shows the need for women to monitor zinc status throughout pregnancy, and perhaps to increase intake of zinc-rich foods to meet increased zinc demand.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Collings, 2013[116] **Systematic Review and Meta-Analysis** n = 19 studies from the United States, Europe, and Mexico with a randomized or non-randomized controlled trial design; reporting an iron-absorption outcome, and reporting iron-status biomarkers at baseline Populations were healthy adults >18 years old.
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 19 studies, with no synthesized data on subject age or BMI
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures were various diets, including low-iron-bioavailability diet, Western diet, high-bioavailability diet, omnivorous diet, LOV diet, diet + a specific meat product, diet with low vitamin C and high phytic acid, cereal based diet + milk, typical Mexican diet, self-selected diet, and others
Outcome(s) of interest and units	• % iron absorption when one inhibitory or enhancing factor of iron absorption is present
Key Results (Bold qualitative assessment followed by quantitative results)	**Various inhibitory factors were found to have a pooled effect of decreasing iron absorption, including milk, calcium, and phytates, though these effects were not observed individually. Factors like whether iron was heme, ascorbic acid, and low serum ferritin levels were found to increase iron absorption. High-bioavailability diets also had consistent and large increases in absorption compared to low-bioavailability diets.** Various inhibitory factors were found to have a pooled effect of decreasing iron absorption, including milk, calcium, and phytates, though these effects were not observed individually. Factors like whether iron was heme, ascorbic acid, and low serum ferritin levels were found to increase iron absorption. High-bioavailability diets also had consistent and large increases in absorption compared to low-bioavailability diets. Authors found a nearly statistically significant reduction in iron absorption of 1.7% (95% CI -3.4%, 0.1%, p = 0.06) with inhibitory factors such as milk, calcium, and phytate. Ascorbic acid showed a significant increase in iron absorption of 2.4% (95% CI 0.4% to 4.4$%) in the authors' analysis, and remained significant with sensitivity analysis. The effect of meat on nonheme-iron absorption reached borderline significance, with an increase of iron absorption of 1.6% (95% CI 0.0%, 3.2%, p = 0.05). Limited data on inhibitory factors calcium, milk, and phytate showed no individual effect for any factor, though there was limited data on each, likely the cause for no significant effects. In studying absorption factors simultaneously, diets designed to have high absorption of iron had a 3.6% (95% CI 1.9%-4.3%, p < 0.0001) higher absorption rate than diets designed to have low-bioavailable iron, with the effect remaining highly statistically significant through sensitivity analysis.
Comments: Significance to clinical application	This study showed that common inhibitory factors of iron absorption and common enhancers of iron absorption behave as expected. However, iron absorption levels are largely governed by the overall diet and serum ferritin status. For example, the group that showed the highest iron absorption rates were women eating a traditional Mexican diet with low bioavailability, while consuming limeade during meals (high vitamin C). **Iron absorption is much more a factor of the entire diet and the individual, rather than any one component of the diet or individual.**

First author, year, study design (bold), name of study (if applicable), sample population	Crowe, 2011[138] **Cross-Sectional Study** European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford cohort n = 2107 white men and women meat eaters, fish eaters, vegans, and vegetarians aged 20-76 years			
Study/analysis groups, mean age, mean BMI (SD), total N, duration	<u>Meat eaters</u> n = 1388 Age = 55 (10.0) years BMI = 25.0 (4.3) kg/m^2 21% male	<u>Fish Eaters</u> n = 210 Age = 51.0 (12.0) years BMI = 23.1 (2.9) kg/m^2 14% male	<u>Vegetarians</u> n = 420 Age = 48.0 (13.0) years BMI = 23.4 (3.6) kg/m^2 22%male	<u>Vegans</u> n = 89 Age = 44.0 (14.0) years BMI = 22.3 (2.6) kg/m^2 39% male
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Participants were categorized as meat eaters, fish eaters (do not eat meat but eat fish), vegetarians (do not eat meat or fish but eat dairy products and/or eggs) and vegans (do not eat meat, fish, eggs, or dairy products). <u>Covariates:</u> Age, sex, season and year of blood collection, case-control status, BMI, smoking status, outdoor activity, vigorous exercise, current use of hormones, supplement use and interactions of age with sex, season of blood collection with year of blood collection, season of blood collection with age, season of blood collection			

Outcome(s) of interest and units	• Time of adherence on diets • Proportion of each diet group with plasma 25(OH)D < 25 nmol/l and > 75 nmol/l for risk of bone conditions and optimal ranges, respectively • Calcium Intake • Time spent outdoors (proxy for sunlight exposure)
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegans and vegetarians had consistently lower serum vitamin D levels compared to meat and fish eaters throughout all seasons. In addition, consumption of vitamin D in vegans was ¼ the level of consumption of meat eaters, with calcium consumption in vegans being ½ the consumption of all other diet groups.** Fish eaters, vegetarians, and vegans adhered to their diet for an average of 11.6, 15.5, and 9.5 years, respectively. Dietary intake of vitamin D was significantly different among diet groups, with meat eaters consuming 3.1 micrograms/day, fish eaters 2.2, vegetarians 1.2, and vegans 0.7, while calcium intake was 1026, 1019, 1019, and 557 mg for each respective group. For plasma vitamin D concentrations, in all four seasons, concentrations did not differ significantly between meat eaters and fish eaters. However, vegetarians and vegans had significantly lower plasma concentrations of 25(OH)D compared with meat eaters ($P < 0.05$). Differences in blood concentrations of vitamin D between meat eaters and vegans were 38% when concentrations were taken in winter, but only 20% in the summer. Supplement users had significantly higher plasma concentrations of 25(OH)D (78.1; 95% CI 76.3 to 80.0 nmol/l) compared with non-supplement users (66.9; 95% CI 65.1 to 68.9 nmol/l).
Comments: Significance to clinical application	This study provides expected results that vegans consume less vitamin D than meat eaters and vegetarians. This is to be expected, as primary food sources of vitamin D are animal products and fortified foods. In addition, this article suggests calcium as a nutrient of concern for vegans, as primary sources of calcium are usually dairy products in western diets. Vegans living in northern climates should have their vitamin D levels monitored regularly and supplemented if needed. In addition, vegans should focus on meeting their recommended daily intake of calcium either from fortified foods like plant milks, or from green leafy and/or cruciferous vegetables.

First author, year, study design (bold), name of study (if applicable), sample population	Gilsing, 2010[95] **Cross-Sectional study** European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford cohort n = 689 men (226 omnivores, 231 vegetarians, and 232 vegans)		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Omnivores n = 226 Age = 52.8 (10.7) years BMI = 26.1(3.7) kg/m^2	Vegetarians n = 231 Age = 46.2 (11.7) years BMI = 23.4 (3.0) kg/m^2	Vegans n = 232 Age = 42.8 (13.1) years BMI = 22.7 (3.1) kg/m^2
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Omnivores were defined as people reporting meat consumption. Vegetarians were defined as individuals who reported consuming dairy products and eggs, but no meat or fish. Vegans were defined as having no consumption of animal products. Duration of adherence to diets for each individual was reported.		
Outcome(s) of interest and units	• Concentrations of serum vitamin B12 and folate		
Key Results (Bold qualitative assessment followed by quantitative results)	**In this cross-sectional study, vegans were found to have lower levels of vitamin B12 compared to vegetarians who, in turn, had lower serum levels compared to omnivores. This led to 52% of vegans having vitamin B12 levels below biochemical deficiency, with only 18.5% of vegan participants and 19.5% of vegetarian participants using vitamin B12 supplements. Vegans and vegetarians had higher intakes and serum levels of folate, though folate deficiency was rare even in omnivores.** Mean serum B12 concentrations in vegans was 33% lower than in vegetarians and 57% lower than in omnivores, and was 35% lower in vegetarians compared with omnivores. 52% of vegans and 7% of vegetarians had B12 concentrations below deficiency levels. 21%, 17%, and 1% of vegans, vegetarians, and omnivores had B12 levels indicative of depletion. Mean concentrations of serum folate in vegans was 34% higher than in vegetarians and 88% higher than in omnivores, with <1% of omnivores being categorized with a biochemical folate deficiency. There was no significant association between length of adherence to a vegan or vegetarian diet and serum B12 concentration. There was also no association between age or education and serum B12 levels.		
Comments: Significance to clinical application	This study reinforces the fact that vegans and vegetarians should either consume vitamin B12 fortified foods, or consume vitamin B12 supplements to maintain adequate serum B12 levels. As vegan and vegetarian diets have fewer sources of vitamin B12 compared to omnivorous diets, vegans and vegetarians should be conscious of consuming an adequate amount of vitamin B12 regularly. Companies that produce fortified foods should necessarily be adding vitamin B12, especially if such foods are targeted towards vegans and vegetarians.		

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Levin, 2010[136] **Randomized Controlled Trial** n = 109 Government Employees Insurance Company (GEICO) employees who were either overweight (BMI>=25) or had Type 2 Diabetes		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Intervention n = 68 50 female, 18 male Age = 46 (10.0) years Weight = 98.7 (2.8) kg	Control n = 45 43 female, 2 male Age = 42 (10.0) years Weight = 100.1 (3.5) kg	Duration 22 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention group participated in 1 hour, weekly group support meetings and were asked to follow a low-fat vegan diet, including vegetables, fruit, grains, and legumes, with 10% energy from fat, 15% energy from protein, and 75% energy from carbohydrate. No restrictions were placed on portion sizes, energy, or carbohydrate intake. Participants took daily multivitamin to meet B12 requirements.		
Outcome(s) of interest and units	• Dietary intake as assessed through three-day diet records.		
Key Results (Bold qualitative assessment followed by quantitative results)	**Low-fat vegan diet educational intervention led to significant decreases in energy from fat, quantity of trans and saturated fats, and increases in fiber, beta-carotene, vitamin A activity, vitamin E, folate, vitamin C, iron, magnesium, and potassium. However, decreases were observed with B12 and vitamin D consumption when supplementation was excluded from the analysis.** At the end of 22 weeks, the intervention group significantly reduced reported intake of energy (intervention effect -262.5; 95% CI -469.3 to -55.7 kcal). Percent energy from fat (-15.4 %; 95% CI -18.9 to -11.9), increased energy from carbohydrate (19.6%; 95% CI 14.9 to 24.3), and decreased energy from protein (-2.0%; 95% CI -3.8 to -0.2). Intake of trans, monounsaturated and saturated fatty acids decreased along with cholesterol, while fiber intake increased with an intervention effect of an increase in 8.9 g/day (95% CI 6.2 to 11.7). Significant intervention increases were also found for total vitamin A activity, beta-carotene, vitamin E, folate, vitamin C, iron, magnesium, potassium, and sodium intakes, while vitamin B12 and vitamin D intake decreased in the intervention group.		
Comments: Significance to clinical application	This study suggests that significant improvement in diet quality was achieved through transitioning individuals to a low-fat vegan diet. Increases in various micronutrients, minerals, fiber, and higher intakes of carbohydrates were achieved, while reducing energy intake with a treatment effect of -262.5 kcal/day while not placing energy restrictions on participants. Though vitamins D and B12 may require supplementation or consumption of fortified foods, it is clear that low-fat plant-based diets can improve dietary quality and help as a weight-loss intervention for overweight individuals.		

First author, year, study design (bold), name of study (if applicable), sample population	Merrill, 2009[135] **Randomized Controlled Trial** n = 119 women from greater Rockford, Illinois metropolitan area. This study is a sub-analysis of a randomized study including 337 men and women of which 42% participated with a significant other.		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Intervention n = 69 Age = 56.0 (8.5) years BMI = 33.9 kg/m^2	Control n = 50 Age = 58.0 (9.0) years BMI = 30.8	Duration Short-term measures at 6 weeks, and long-term measures at 6 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention group underwent a health educational program (4 x 2 hour sessions/week for 4 weeks) adhering to a plant-based diet, including grocery shopping tours, cooking lessons, textbook and workbook activities, and promotion of exercise. Ideal dietary adherence involved a diet composed of whole grains, legumes, vegetables, and fresh fruits. The diet was also low in fat, animal protein, sugar, salt, very low in cholesterol, and high in fiber.		
Outcome(s) of interest and units	• Total calcium from food and supplements • Dietary intake • Weight • BMI • Parathyroid Hormone (PTH)		• Serum calcium • 25-hydroxyvitamin D • Bone Collagen Equivalents per liter (nM BCE) • N-telopeptide (NTx)—a breakdown product of type I collagen found in bone cartilage, a product of bone breakdown

Key Results (Bold qualitative assessment followed by quantitative results)	**Intervention led to increases in consumption of fruits, vegetables, grains, decreases in BMI, and decreases in protein, phosphorous, calcium from food, total calcium, vitamin D from food, total vitamin D, and meat and dairy servings per day. Intervention also led to increases in PTH secretion and NTx levels, along with decreases in vitamin D levels, though reductions in vitamin D were similar across intervention and control groups at 6 months.** After 6 months, those in the intervention group saw greater increases in steps per week and daily intake of fruit, vegetables, and grain. Intervention group participants also saw greater decreases in BMI (intervention MD -1.5; 95% CI -2.0, -1.0; control MD -0.5; 95% CI -0.8, -0.2), protein, phosphorous, calcium from food, total calcium (MD intervention -197.1 mg/day; 95% CI 315.5, -78.7; MD control 27.6; 95% CI -136.4, 191.6), vitamin D from food, total vitamin D (MD intervention -42.4; 95% CI -92.5, 7.7; MD control -6.8; 95% CI -66.1, 52.5) and meat and dairy servings per day. Change in means between baseline and 6 weeks was significant for PTH (MD intervention at 6 weeks 11.7 ng/mL; 95% CI 7.7, 15.7) between intervention and control groups. In addition, calcium levels significantly increased (MD 6 weeks 0.2; 95% CI 0.1, 0.3), and 25-hydroxyvitamin D levels decreased (MD intervention -7.5; 95% CI -9.8, -5.2) in the intervention group, though calcium remained within homeostatic range. Change in means between baseline and 6 months was significantly different between intervention and control groups for NTx (MD intervention 3.3; 95% CI -0.8, 7.7; MD control -3.0; 95% CI -7.0, 1.4).
Comments: Significance to clinical application	This study examined the effect of a plant-based lifestyle intervention on nutrients and biomarkers related to bone health. The authors found that intervention led to significantly greater intakes of healthful foods including whole grains, fruits and vegetables, but also decreases in intake of phosphorous and calcium. Increases in PTH and NTx were observed, both of which are reliable metrics of bone resorption, and correlate with decreases in 25-Hydroxyvitamin D in intervention groups but not in control groups. These findings suggest that intervention with plant-based diets may lead to decreases in calcium consumption, which, in turn, can lead to increases in markers of bone resorption, risking the loss of bone mineral density. Plant-based diets should be planned to supply adequate calcium, either through fortified foods like plant milk or an abundance of calcium-rich green vegetables.

First author, year, study design (bold), name of study (if applicable), sample population	Koebnick, 2005[142] **Observational Cohort Study (prospective)** n = 108 healthy pregnant women in their 9th-12th, 20-22nd, 36-38th gestational week habitually following a plant-based diet for > 3 years or a Western diet—from pop in Giessen, Germany			
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Lacto-Ovo-Vegetarian (LOV) n = 27 Age = 30.8 (0.9) BMI = 20.6 (0.4)	Low Meat Eaters (LME) n = 43 Age =30.6 (0.6) BMI = 21.4 (0.3)	Average Western Diet (AWD) n = 38 Age = 29.1 (0.6) BMI = 23.2 (5.3)	Duration Entire course of pregnancy from 1st to 3rd trimester
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Subjects had either habitually followed a plant-based diet for more than 3 years or followed an average Western diet. Vegetarians were divided into LOV and LMEs. Plant-based diets were defined as a consumption of raw vegetables > 100g/day, a ratio of refined grain products to whole grain products of < 0.95, and weekly consumption of <105 g/week of meat products and < 300 g/week of meat. Plant diets were subdivided into ovo–lacto vegetarians (who did not consume any meat or meat products) and low-meat eaters. Covariates: BMI, intake of magnesium from supplements, serum calcium, and serum potassium concentrations			
Outcome(s) of interest and units	• Blood samples: Magnesium, calcium, potassium • Dietary intake • Calf-muscle cramps			
Key Results (Bold qualitative assessment followed by quantitative results)	**LOVs and LMEs had higher consumptions of magnesium compared to controls, mostly attributable to higher consumption of whole grains, fruits, and vegetables. LMEs had slightly higher RBC concentrations of Mg, but differences were not significant between LOV and control groups. Calf cramps were most often reported by control participants and were significantly less frequent in LME and OLV groups in 2nd and 3rd trimesters of pregnancy.** Plant-based dieters reported an average of 8.1 (0.75) years of diet adherence. LOV and LMEs both had higher intakes of magnesium in mg/day (LOV: 527 +/- 23 vs control: 404 +/- 13 mg/day), mg/MJ (LOV: 63.9 +/- 2.1 vs. control: 44.2 +/- 0.8 mg/MJ) and in mg/kg body weight (LOV: 8.5 +/- 0.4 vs. Control: 5.8 +/- 0.3 mg/kg), all p < 0.001. LOV and LMEs had higher intakes of fiber, similar intakes of calcium, while LMEs had higher intakes of phosphorous compared to controls. Higher intakes of magnesium were attributed to plant-based dieters having higher intakes of whole grain products, vegetables, and fruits. Magnesium concentrations in RBC were slightly higher in LME but not in LOVs compared to controls. Mg excretion was highest in LOV (p = 0.023) and LMEs (p = 0.017) with controls used as the reference.			

Appendix continued

Comments: Significance to clinical application	This study demonstrates that those who had been adherent to plant-based diets for long periods of time had higher consumption of magnesium compared to those following a standard western diet. Magnesium concentrations did not differ significantly between all study groups, though frequency and prevalence of calf cramps was lower in LME and OLV groups compared to controls. These findings suggest that in well-planned plant-based diets with high consumption of whole grains, vegetables, and fruits, sufficient magnesium consumption is easily attainable. In addition, plant-based diets may lead to improved comfort during pregnancy in the form of reduced cramps. Magnesium should not be a barrier to consuming or recommending a plant-based diet for participants.

First author, year, study design (bold), name of study (if applicable), sample population	Conquer, 1997[134] **Randomized Controlled Trial** n = 20 healthy vegetarian (12) or omnivorous (8) subjects Each group was 50% female.
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Overall subject measurements n = 20 (12 vegetarian, 8 omnivore) Age = 26.8 (1.6) y BMI = 22.5 (1.2) kg/m^2 Duration 42-day intervention with 21-day washout period
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Supplementation with algae-derived triglyceride oil capsule, 9 per day, with meals, totaling 1.62 g DHA/day. Subjects followed their habitual diets. After 42 days of consuming capsules, subjects underwent a 21-day washout period.
Outcome(s) of interest and units	• Serum total phospholipid fatty acid profiles (EPA and DHA levels)
Key Results (Bold qualitative assessment followed by quantitative results)	**There is concern about the seeming lack of DHA and EPA sources on a vegetarian diet, whereas omnivorous diets derive much of their n-3 fatty acids from seafood. One source of DHA and EPA from vegan diets may be from the retroconversion of AA to DHA and, in turn, to EPA. This study found that vegetarians have lower baseline levels of DHA, but similar levels of EPA compared to omnivores. After 6 week supplementation with DHA capsules, researchers found similar rates of increases in DHA and EPA levels in serum and platelets of vegetarian and omnivorous subjects, and estimated a retroconversion rate of 9.4% DHA to EPA.** DHA levels rose by 247% in vegetarians and 240% in omnivores, while EPA increased by 122% in vegetarians and 58% in omnivores. DHA/AA acid ratio increased by 414% in vegetarians and 318% in omnivores, while the EPA/AA ratio increased by 228% in vegetarians and 94% in omnivores. For net mol % increase in DHA and EPA, DHA levels in total phospholipids of serum increased from 2.1 mol% to 7.1% in vegetarians and from 2.2% in omnivores to 7.6%. In platelets, DHA values increased from 1.1 mol% to 3.4 mol% in vegetarians and from 1.4 to 3.8 mol% in omnivores. For vegetarians, EPA levels increased by 0.7 mol% in serum and 0.3% in platelets. For omnivores, EPA levels increased from 0.4 mol% in serum and platelets. In total, the net mol% increase in EPA and DHA after 6 weeks of supplementation with DHA was 5.7% in serum and 2.6% in platelets of vegetarians, and 5.8% in serum and 3.0% in platelets of omnivores. In total, this study calculated a rate of retroconversion of DHA to EPA of 7.4-11.4% using serum values, and 12.3-13.8% based on platelet values.
Comments: Significance to clinical application	This study examines the ability for humans to convert DHA to EPA through retroconversion. As there are few sources of DHA and EPA besides microalgae in a vegetarian diet, the question of conversion of AA to DHA to EPA as a viable route to achieve healthful levels of n-3 fatty acids is of interest. This study found (in a small sample size) that retroconversion rates of DHA to EPA from DHA supplementation were approximately 9.4%, suggesting significant conversion of DHA to EPA, as compared to previous estimates of 1.4% retroconversion. This study suggests that retroconversion of DHA to EPA may be a viable source of EPA, though health benefits of n-3 fatty acid levels in vegans and vegetarians has yet to be determined. For vegans and vegetarians concerned about n-3 fatty acid intake, microalgae supplements may be recommended, as supplementation with DHA and EPA has reliably shown to increase levels in serum.

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OBESITY

Key Points for Practitioners

- Realistic expectations for any lifestyle intervention is 5–10% weight loss, based on the Diabetes Prevention Program,[37] LOOK AHEAD,[64] and other trials. There is potential for greater weight loss with a WFPB diet, but more research is needed.
- Many patients are interested in making dietary changes, and a WFPB diet can be offered as a safe and effective option for losing weight and maintaining a healthy weight, independent of increasing exercise.[45,81,82]
- The dietary patterns that seem most advantageous for weight loss and healthy weight maintenance are founded on fruits and vegetables, legumes, and whole grains, moderate or more limited amounts of nuts and seeds, and avoidance of added sugars and oils.[1]
- Advantages of plant-based diets for weight control include low or no cost of the intervention, as well as reduced risk for metabolic syndrome and other chronic diseases, and improved quality of life.[83]
- High fiber intake from whole plant foods has been associated with decreased risks of diabetes,[84] cancer,[85,86] and heart disease.[87]
- Some evidence suggests that the majority of individuals are able to eat a WFPB diet and consume appropriate levels of total energy in ad libitum conditions and maintain a healthy weight,[45,50] while a certain minority may need more structured meal plans or portion control to prevent overeating.[65,88] In a recent residential feeding study comparing a low-carbohydrate, ketogenic-style diet (n=11) with a low-fat, WFPB diet (n=10), the WFPB diet led to more significant weight loss, with an average lower ad libitum energy intake of 689 ± 73 kcal d (-1) as compared to the low-carbohydrate diet over 2 weeks ($P < 0.0001$).[89]
- Mechanisms through which plant-based diets improve weight outcomes include greater satiety and reduced energy density due to high fiber content, reduced fat, and avoidance of refined foods.[90,49]
- Some research suggests that good adherence is the most salient predictor of successful weight loss for overweight patients, over and above any particular diet. While this may be true in theory, WFPB diets pose some particular advantages for those susceptible to food addiction in that for some individuals, it may be easier to avoid refined foods entirely than to cut back on them.[65,91]
- Existing evidence on plant-based diets and healthy weight can be communicated to patients to support their ability in order to make informed decisions about their diet and course of treatment.
- If patients express interest in trying a WFPB diet of some kind, it is helpful to share educational and support resources with them.

ABSTRACT | Individuals consuming more plant-based diets have lower rates of overweight and obesity than those whose diets include or emphasize meat and refined foods.[1–4] Plant-based patterns are lower in fat and cholesterol and promote both weight loss and long-term healthy weight maintenance.[5] Fiber and water in whole plant foods promote satiety with lower caloric density more than animal-based foods, thus allowing the body to reach its natural weight setpoint without deprivation.[5,6]

Obesity is a complex disease state involving excessive adipose tissue.[7] Overweight and obesity are prominent risk factors for developing metabolic syndrome, heart disease, diabetes, and certain cancers.[8] Findings from large-scale epidemiological studies indicate that plant-based diets lead to

healthy weight maintenance and reduce both prevalence and incidence of overweight and obesity.[1] The American Medical Association designated obesity a disease in 2013.[9] As a result, the idea that obesity is caused by insufficient willpower, lack of discipline, and bad personal choices has transformed the public discourse around the condition and reframed it as a disease that increases other health complications and conditions.

Emerging research on the effects of the obesogenic food environment driven by the addictive qualities of refined sugar, salt, and fat, coupled with prevalent sedentary behavior indicates the importance of considering broader environmental conditions when addressing overweight and obesity.[10] Plant-based diets help circumnavigate the built environment by normalizing the taste of healthy food and breaking the pull of these addictive ingredients to allow for a healthy weight.[11–13]

Obesity in Context

The Obesity Medicine Association defines obesity as a chronic, progressive, relapsing, and treatable multi-factorial neurobehavioral disease wherein increased body fat promotes adipose tissue dysfunction and abnormal fat-mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences. Obesity and overweight are defined with cutoffs for body mass index (BMI = kg/m^2), the standard calculation to estimate adipose tissue, which is also frequently used to predict chronic disease risk.[7,14]

Obesity is often divided into subcategories:

- **Class 1:** BMI of 30 to < 35
- **Class 2:** BMI of 35 to < 40
- **Class 3:** BMI of 40 or higher

Individuals with a BMI of >25 and < 30 are categorized as having overweight, while those >30 are categorized as having obesity. Class 3 obesity is sometimes categorized as “extreme” or “severe” obesity.

Some organizations, including the Obesity Medicine Association, clarify the specific percent body mass cutoffs of >30% for men and >35% for women, which can be obtained by another measurement used for body composition, the bioelectrical impedance analysis (BIA). It measures body fat in relation to lean body mass and is said to be more accurate than BMI.[15] There are various BIA machines available that are more accessible than the Dual-Energy X-ray Absorptiometry scan (DEXA), which is considered the gold standard for clinically measuring body composition. DEXA may not be accessible to many patients due to cost and lack of insurance coverage.

While BMI is relevant for a majority of the population, several key limitations also exist. BMI cannot account for differences in body mass between adipose tissue, muscle mass, bone density, overall body composition, or racial and sex differences, particularly relating to those within the intermediate BMI ranges who hold abdominal fat (central obesity). Thus, it may be an inaccurate disease risk marker for certain groups depending on activity level and body composition.[16]

Other methods of measuring excess adiposity include measuring visceral fat by DEXA, as well as calculating the body fat percentage via body composition, which is particularly useful for those of Asian heritage and other populations with high levels of diabetes. Though we do not have disaggregated data for many subpopulations whose diet has only recently been Westernized, including Asian Americans, there are some data on waist circumference cutoffs for Asians. An important note for Asians: BMI waist circumference obesity cut points are lower (≥ 90 cm for Chinese males compared to ≥ 94 cm for Caucasian males).[17]

It is useful to consider waist circumference in addition to BMI when diagnosing overweight/obesity,[18,19] as the BMI may mislabel many in certain subpopulations, including older women, the elderly, children, or those with significant muscle mass.[13,16,20,21] These limitations notwithstanding, BMI still has substantial utility for assessing cardiometabolic health for a majority of the population.[22]

Over a billion people around the world are considered overweight or obese. According to the World Health Organization and the Centers for

Disease Control, obesity rates have nearly tripled worldwide since 1975, with more than 1.9 billion overweight adults (18 years and older). Of these, over 650 million were obese.[12] Though Americans are living longer, they are living with chronic health conditions.[23] Globally, 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. In the US, 2017–18 data shows the age-adjusted prevalence of obesity in adults was 42.4%, with no significant differences between men and women among all adults or by age group.[24]

Rates of overweight/obesity are more prevalent among some groups than the general population. Non-Hispanic Black adults had the highest age-adjusted prevalence (49.6%), followed by Hispanic adults (44.8%), non-Hispanic White adults (42.2%), and non-Hispanic Asian adults (17.4%).[25] The prevalence of obesity was 40.0% among adults aged 20 to 39 years, 44.8% among adults aged 40 to 59 years, and 42.8% among adults aged 60 and older.[26] Minority groups are especially challenged as social determinants of health, structural racism, and systemic inequities implicate their ability to engage in healthy eating patterns and physical activity.[27–31]

Access to refined and fast food as well as disparities in access to healthy foods have contributed to a dietary pattern of excess calories, high levels of animal fat and protein, and refined carbohydrates, which have contributed to the increased rates of overweight, obesity, and negative downstream health consequences.[32] Obesity is a core condition for developing metabolic syndrome, the cluster of conditions that increase heart disease risk (increased blood pressure, blood sugar, cholesterol, triglyceride levels, and excess abdominal body fat).[33]

Both obesity and diabetes have been shown to increase risk for infections and mortality by altering pulmonary mechanics, increasing aggravation of the inflammatory storm, and abnormalities in lung physiology and micrangium, all of which may increase virus infectivity and virulence.[34] Both obesity and viruses such as COVID-19 impact lower-income populations and people of color disproportionately, as access to adequate healthcare and nutrition are often lacking due to long-standing inequity embedded in our society.[28] Black, Latinx, and Native Americans die of COVID-19 at rates of more than 2.7 times white Americans. The rise in obesity rates since the year 2000[35] has made obesity an increasingly urgent problem, and sustainable and acceptable dietary solutions are a top priority for healthcare.

Obesity treatment is multi-modal and, depending on BMI cutoffs, may include medication and surgery, endoscopic procedures, and very low-calorie diets. Lifestyle medicine and behavioral therapy are the foundation of obesity treatment. The United States Preventive Services Task Force recommends intensive, multicomponent behavioral intervention for all individuals with obesity.[36] These programs include at least 12 sessions in the first year, weekly or even twice per week.[36] Many are modeled after the Diabetes Prevention Program (DPP).[37] It is important to understand all options available to treat obesity because simply telling a patient they have obesity and must lose weight has been shown to be ineffective for weight loss.[38] In fact, telling a patient they need to lose weight without providing adequate treatment can increase obesity stigma, which has been shown to worsen weight loss outcomes. Clinicians should be aware of their own obesity stigma and/or bias, and this implicit or explicit bias should not prevent them from providing all the available options for obesity treatment, including medications and surgery should they be indicated. In addition, being aware of weight bias may help prevent clinicians from exacerbating obesity stigma for patients struggling with obesity.[39–42] Obesity treatment should include a behavioral element. In addition to addressing weight bias, behavioral treatment includes a variety of components including collaborative goal setting, problem-solving, planning, stimulus control, social support, addressing emotional eating, self-monitoring, cognitive restructuring, motivational interviewing, relapse prevention, and contingency planning.[43]

Benefits of Plant-Based Diets for Obesity

Research indicates that plant-based diets are effective for (1) prevention of weight gain[1,44–46] (2) maintenance of healthy weight,1 and (3) achieving healthy weight loss.[1,44–47] Overweight/obesity risk is highest in populations consuming Western dietary patterns with their higher intake of meat, refined grains, sweets, dairy, and low levels of whole fruits and vegetables.[46,48] Key benefits of whole food, predominantly plant-based diets, center on high fiber

and water content, allowing most people to eat until satiated without overconsumption of total energy.[49,50] Further, research on overeating indicates that such behaviors may be influenced by the hyperpalatability of refined foods containing concentrated sugar, fat, and salt.[51] Overall, research indicates that the lower energy density of whole plant foods can control weight gain and maintenance for patients with overweight and obesity, as well as improve nutrient density for better health outcomes.

Prevention of Weight Gain

Large population studies consistently show that healthy plant-based diets are predictive of less weight gain, and those who transition to a more plant-based diet gain less weight over time.[46,52] Meat consumption, specifically, is associated with obesity and central obesity among adults in the U.S.[3,53] Research from the large EPIC cohort study found that high protein intake was not protective against weight gain. In contrast, protein of animal origin, especially meat and poultry, seemed to be positively associated with long-term weight gain.[54] The lowest weight gain was achieved among those consuming the diet with the least animal food.[55]

Weight Maintenance

Ongoing maintenance of lost weight can be more challenging than initial weight loss,[56] and treatment requires ongoing strategies to support healthful behaviors.[57] Whole food, plant-based (WFPB) diets are nutrient-dense and consistent with dietary guidelines and can be recommended for weight management without compromising diet quality.[58] Weight maintenance can be facilitated by a plant-based diet which reduces the need for self-monitoring and the need to restrict intake. The BROAD study offers compelling evidence for this, showing that subjects were able to sustain a plant-based diet at 12 months with very little weight regain, with education alone.[5] This is compelling given that weight regain is common in almost all diets at 12–48 months.[38]

Weight Management in Children

A 2015 study found that, though both plant-based and American Heart Association (AHA) diets demonstrated beneficial changes for cardiovascular disease in children with obesity and hypercholesterolemia (n=28), adults on the plant-based diet had seven significant beneficial changes, while adults following the AHA diet had only two.[59] Plant-based diets are considered safe and appropriate for all life stages by the Academy of Nutrition and Dietetics.[60] This study exemplifies the beneficial health and weight management effects of the diet, particularly decreased cardiovascular risk among the growing population of children with obesity and dyslipidemia.[59] Clinicians should be aware that any childhood obesity intervention should include behavioral treatment. The gold standard for childhood obesity treatment is family-based behavior therapy.[61,62]

Healthy Weight Loss

Plant-based diets, including vegan and vegetarian diets, have been shown to be effective for weight loss.[58,63] The BROAD study reported significantly greater mean BMI and weight reductions using a plant-based intervention at six months (n=33), with a mean weight loss of 10.6 kg, 2.9 kg more than the controls (n=32) ($P<0.001$, 95% CI). In addition, mean decrease in BMI was 3.9, one point more than the controls ($P<0.0001$, 95% CI).[5]

The Look AHEAD study showed that intensive lifestyle intervention, which included a calorie reduction intake of 1,200–1,800 kcal/day through reductions in total and saturated fat, along with weekly group and individual counseling, may benefit patients particularly those with early diabetes. Intensive lifestyle intervention participants (n=2,241) lost significantly more body weight than the control group which was offered 3 group sessions per year on diet, physical activity, and social support (n=2,262) at years 1 (net difference, -7.9%; 95% CI, -8.3% to -7.6%) and 4 (-3.9%; 95% CI, -4.4% to -3.5%).[64]

The NewDiets Study, a clinical trial comparing five diets from vegan to omnivorous, found that vegan diets result in significantly greater weight loss than more modest dietary recommendations. At six months, the weight loss in the vegan group was significantly different from the omnivorous, semi-vegetarian, and pesco-vegetarian groups.[65] These findings mirror several epidemiologic studies that consistently show higher dietary fiber and lower fat intakes among those following plant-based diets (vegans and vegetarians) compared to omnivores.[66–68] This trial and several epidemiologic studies show that more plant-based diets may result in greater weight loss than more

modest recommendations.[55,65,69] Another large meta-analysis of prospective cohort studies found that fruit and vegetable consumption was associated with weight loss and adiposity decrease.[70]

In control trials, vegan groups lose more weight than with more traditional therapeutic diets that reduce saturated fat and calories, indicating that the adoption of a low-fat vegan diet improves several aspects of macronutrient intake.[71,72] A two-year randomized trial found this dietary pattern to be successful in weight loss and improving health outcomes, even in specific community groups, while maintaining traditional cultural food choices.[73]

In a data analysis of weight loss at 6-months, the POUNDS LOST study showed that regardless of dietary composition, weight loss was contingent on adherence, and fiber exerted the most influence on adherence to the prescriptive diet (n=345, P < 0.0001, 99% CI).[43,74] Adherence to a weight management program was conceptualized as multi-dimensional with the two dimensions of behavioral and dietary adherence.[75] Though increasing fiber

Table 1 Relationship with amount of weight loss and various conditions[76]

Condition	Amount of weight loss needed to effect improvement
Glycemic improvement–Diabetes prevention in impaired glucose tolerance	2.5% weight loss or more; maximal impact at 10%
Glycemic improvement–Type 2 diabetes	2.5% to >15%; greater weight loss associated with greater glycemic improvement; true for all BMI classes
Triglyceride reduction	2.5% to >15%; greater weight loss associated with greater glycemic improvement; true for all BMI classes
HDL increase	5% to >15%; greater weight loss associated with greater glycemic improvement; not true for BMI >40 kg/m^2
Apnea hypopnea index improvement in obstructive sleep apnea	10%+ weight loss required for significant improvement
Knee pain and function in persons with osteoarthritis	5–10% improves knee functionality, speed, walk distance and pain; 10%+ required to improve IL-6 and CRP levels; knee MRI and X-ray findings do not change
Emergent knee pain prevalence	5–10% weight loss, with persistent maintenance required to prevent knee pain in individuals with obesity
Hepatic steatosis reduction	5–15%+; greater weight loss associated with greater improvement
Non-alcoholic steatotic hepatitis activity score	10%+ weight loss required for significant improvement
Impact of weight on quality of life score	5%–15%+; greater weight loss associated with greater improvement
Depression	5–10% may reduce risk for emergent depression; individuals with depression lose as much weight as non-depressed individuals
Mobility	5–10% loss attenuates mobility decline with aging
Urinary incontinence	5–10% improves symptoms in men and women
Sexual function	5–10% improves erectile function in men and sexual dysfunction in women
Polycystic ovarian syndrome and infertility	Improvement in ovulatory cycles and subsequent pregnancy with 2–5% weight loss, with more weight loss producing more robust effect.
Health care costs	In persons with diabetes 5–10% weight loss associated with reduction in hospitalization and medication costs, but not outpatient costs.
Mortality	16% weight loss (vertical banded gastrectomy) associated with reduction in all cause and cardiovascular mortality. 5–10% weight loss with lifestyle intervention had no effect on major cardiovascular outcomes, but in those with 10%+ weight loss, there was a reduction in those outcomes.

intake is important, it is not sufficient to induce weight loss on its own, and any dietary protocol that safely induces weight loss in patients with obesity will also lower cardiovascular, morbidity, and mortality risks. Even modest weight loss (5 to 10%) is associated with improvement in systolic and diastolic blood pressure and HDL cholesterol. For some comorbid conditions (obstructive sleep apnea and non-alcoholic steatotic hepatitis), more weight loss is needed (10% to 15%), including for sleep apnea, non-alcoholic steatotic hepatitis, and all-cause and cardiovascular mortality.[76] In choosing obesity treatment for a patient, clinicians should weigh cultural, environmental, emotional, and psychological factors, ultimately deciding on the treatment to which the patient is most likely to adhere.

Ketogenic Diets

Obesity is a chronic, relapsing, and progressive disease.[9,77] Ketogenic diets have been shown to aid in short-term weight loss.[78] Since many cultural, social, ecological, and environmental factors influence diet, it is essential to individualize a diet plan for each patient with obesity to maximize adherence,[74] and some patients may choose a ketogenic diet. However, the POUNDS LOST study showed that adherence could be more important than diet composition, and if a patient's preferences steer them towards a ketogenic diet, this may be an improvement compared to their previous diet. Like any treatment plan, ketogenic diets have risks and benefits. Some of the risks include increased mood changes and fatigue, particularly with exercise. There is ample evidence that plant-based diets can achieve equal or superior weight loss to other diets that exclude whole grains, legumes, and starchy vegetables.[58] Findings from the ARIC (Atherosclerosis Risk in Communities) study suggest that while mortality risk appears lowest at 50-55% carbohydrate intake, substituting carbohydrates with plant-based protein lowered mortality, while substituting carbohydrates with animal-based protein increased mortality.[79] Thus, patients on low carbohydrate diets should be encouraged to maximize their fruit and vegetable intake. Given concerns about cardiovascular risk, patients with coronary artery disease or history of myocardial infarction who decide on ketogenic diets should be advised of these risks, and cholesterol levels should be monitored carefully. Additionally, patients on ketogenic diets should be monitored for bowel symptoms and abdominal discomfort as they are at risk for decreased intake of soluble and insoluble fiber as well as resistant starch and fructooligosaccharides. The long-term effect of the ketogenic diet on the gut microbiota is yet unclear. Physicians supervising patients on a ketogenic diet should consider supplementation with inulin, lactulose, fructooligosaccharide, and galactooligosaccharides to increase the population of Bifidobacterium.[80]

Mechanisms

Plant-based diets have consistently been associated with reduced body weight because they directly address the primary dietary mechanisms that lead to reduced body fat.[92] The mechanisms by which WFPB diets support healthy weight maintenance and weight loss include reduced energy density, increased satiety, avoidance of addictive foods, and positive benefits for the gut microbiota. With obesity, adipose tissue and visceral fat expansion cause compression, joint stress, metabolic disorders, organ dysfunction, and increased mortality.[93] The increase in peripheral and central fat mass is a chronic and potentially reversible process. Conversely, the expansion of adipose tissues and visceral fat leads to organ dysfunction and an increased risk of mortality. Such an increased risk of mortality and morbidity can also affect metabolically healthy individuals with obesity with disease progression.[13]

Energy Density

The mechanisms by which plant-based diets cause weight loss hinge on reduced dietary energy density due to their higher fiber, higher water, low-fat content, and increased postprandial energy expenditure.[94,95] Energy density is the amount of energy in a particular weight of food, in the form of calories per gram, spanning from 0 to 9 kcal/g, along with its water content. Fat is around 9 kcal/g, carbohydrate and protein are both around 4 kcal/g, and alcohol is 7kcal/g.[90] Foods high in calorie density have a large number of calories per unit weight of food, and foods low in calorie density have far fewer calories per unit weight of food.[96]

Foods low in calorie density with higher fiber content effectively increase satiety, as volume and fiber content activate receptors in the stomach that respond to being physically full of food.[97,98] Thus, eating high-fiber foods (unrefined, plant foods) makes it possible to fill up on fewer calories without experiencing hunger.[96]

Foods lower in calorie density include whole fruits, colorful vegetables, starchy vegetables, intact whole grains, and legumes. These are also the foods highest in nutrient density. Therefore, by following a diet lower in calorie density, one also consumes a diet highest in nutrient density. In contrast, animal foods and refined foods are energy-dense, making it easier to overconsume calories without a need. Table 2 presents a sample of energy and fiber content of select plant, animal, and highly processed foods, demonstrating that, overall, unrefined plant foods maximize fiber consumption and allow one to eat food with lower energy density.

Fiber

Fiber is found only in plant foods[99] and is an essential component of a healthy eating pattern, as high fiber consumption is associated with overall lower chronic disease. Higher fiber consumption is a hallmark of plant-based diets,[100] and in observational studies, individuals consuming omnivorous diets frequently do not meet fiber recommendations while those consuming increasingly plant-based diets do.[101,102] Higher fiber intakes increase satiety, a key component of reduced energy consumption, and higher fiber consumption is implicated in weight loss.[103] Highly processed foods lacking intact fiber make up the bulk of calories consumed in America,[104] facilitating overconsumption and weight gain. These foods have become progressively cheaper and easier to access in the modern food environment.[104]

Gut Microbiota

Microbiome dysbiosis that promotes bile acid fermentation is associated with obesity.[92] Mechanisms may include impeding the abundance and variety of intestinal flora from excessive intake of unhealthy foods and lack of dietary fiber. The fermentation of fiber appears to be a factor in a

Table 2 Energy and fiber content of a selection of plant, animal, and highly processed foods (per 100 grams)[99]

Food	Kcal	Fiber (g)
Lettuce	14	1.2
Asparagus, fresh, cooked, no added fat	21	2.3
Broccoli, fresh, cooked, no added fat	35	2.7
Kale, fresh, cooked, no added fat	38	4.4
Yogurt, plain	61	0
Tofu, extra firm	83	1
Sweet potato, baked, peel not eaten, no added fat	90	3.3
Lentils, cooked from dried, no added fat	115	7.9
Brown rice, cooked, no added fat	122	1.6
Kidney beans, from canned, no added fat	135	8
Chickpeas, from canned, no added fat	146	7.3
Chicken breast, rotisserie, skin not eaten	144	0
Hard-boiled egg	155	0
Avocado	160	6.7
Tuna	200	0
Salmon, cooked	178	0
Ground turkey	201	0
Pork chop, fried, lean and fat eaten	211	0
Beef steak, lean and fat eaten	235	0
Salad dressing, Italian	240	0
White bread	270	2.3
Fast food French fries	312	3.8
Lean ground beef, 70% lean	332	0
Cream cheese	350	0
White sugar	385	0
Cheddar cheese	408	0
Croissant	406	2.6
Olive oil	884	0
Canola oil	884	0

host of mechanisms related to obesity, including intestinal barrier function, glucose function, and appetite regulation.[105] Short-chain fatty acids (SCFAs) produced by the gut microbiota through its digestion and fermentation process can modulate satiety and eating patterns, and regulate energy intake through appetite. SCFAs can also suppress intestinal mobility transit and allow for a higher uptake of nutrients.[106]

Whole Plant Foods' Effect on Satiety

Whole food, predominantly plant-based diets, have a number of characteristics that increase satiety, a key element of weight loss. Whole plant foods increase satiety more than highly processed foods lacking intact fiber to hold water and macronutrients in the stomach. Further, solid foods have a greater effect than liquid.[107] Water in food is chemically different from water taken as a beverage as it leaves the stomach more slowly and improves satiety.[108] The fiber in unrefined carbohydrates enhances satiety without adding calories. Fiber-filled foods require greater mastication, which reduces the ingestion rate, increases stomach distention, and promotes satiation. Soluble fibers delay gastric emptying and may be linked to the "second meal effect, delaying the return of hunger.[109] Though protein has demonstrated a higher satiety effect than carbohydrate, trials usually compare a ketogenic-style diet to a conventional American Heart Association diet of 30% fat (which is not very low-fat) to a diet that includes refined and processed low-fat animal foods; whole food diets are not typically included.

Food Addiction and Hyperpalatable Foods

Both food and drug dependency activate similar neural circuitry inducing biochemical change in the brain that can lead to craving beyond need.[110,111] Highly processed foods made of concentrated fat, sugar, and sodium are created to surpass the rewarding properties of whole foods such as fruits and vegetables. They cause the release of neurotransmitters dopamine and opioids expressed throughout the limbic system that can reinforce the eating behaviors driving obesity.[51] Addictive patterns of excessive eating are often attributed to the stimulating properties of these hyperpalatable foods prevalent in our modern food environment. Food addiction research indicates that it may be preferable for some people to avoid certain trigger foods altogether as opposed to eating less of them.[112] A WFPB diet may effectively overcome addiction to hyperpalatable foods in individuals with obesity through the avoidance of trigger foods containing added fat, sugar, and salt.

Significant Weight Loss Using a Plant-Based Diet

In 2021, a critical study comparing weight loss between diets demonstrated the unique benefit for overweight individuals of a minimally processed, plant-based, low-fat diet consumed in ad libitum conditions.[89] Those consuming the low-fat, plant-based diet reduced energy intake by approximately 689 kcal/day, compared to a minimally processed, animal-based, ketogenic, low-carbohydrate diet.[89] Participants on the minimally processed, animal-based diet lost weight and body fat but reported no significant differences in hunger, fullness, satisfaction, or pleasantness of meals.[89]

The 2017 BROAD study found that a WFPB diet resulted in similar weight loss at 12 months compared to other diets such as low-carbohydrate and low-fat diet, which led to significant BMI and cholesterol improvements and improvements to other risk factors.5 Similar studies have observed similar weight loss, which is: at six months 12.0 kg reduction (95% CI±1.8), and at one year 10.9 kg (95% CI±1.2) and 12.2 kg reductions (95% CI±1.3); (this last study included telemonitoring[113]).[5] Further, those on the diet had the advantage of eating to satiation without food restriction. In contrast, studies on the effects of low-carbohydrate diets have shown higher rates of all-cause mortality,[114] decreased peripheral flow-mediated dilation,[115] worsening of coronary artery disease,[116] and increased constipation rates, headache, halitosis, muscle cramps, general weakness, and rash.[117] Thus, while some evidence exists that low-carbohydrate diets may aid in weight loss, the cardiometabolic side effects are cause for concern, and dietary treatment decisions should be made on an individual basis weighing risks and benefits for the patient, as well as adherence.

Common Questions and Concerns

Don't carbs make people gain weight?

Though refined carbohydrate products like baked goods are associated with weight gain, increased carbohydrate and fiber intake as part of a plant-based, high-carbohydrate, low-fat diet are associated with beneficial effects on weight, body composition, and insulin resistance.[103] WFPB diet is primarily composed of complex and unrefined carbohydrates.[100] The healthiest cultures in the world eat a high-carbohydrate diet.[118] Carbohydrate quality is important, and complex and unrefined carbohydrates from legumes, vegetables, whole grains, and fruits differ in their health effects from refined carbohydrates found in soda, pastries, cookies, and white bread.[119]

Doesn't a low-carbohydrate diet work for weight loss?

Low-carbohydrate diets have produced weight loss in experimental and real-world settings, but the effectiveness is based on energy restriction, not the quality of the diet. Low-carbohydrate diets are typically based on high amounts of animal foods, substituting carbohydrate, the body's preferred energy source, for fat and protein. The body breaks down protein first and then fat for energy. Low-carbohydrate diets increase LDL cholesterol, which can have long-term cardiovascular effects[89,120] Substantial reduction of dietary carbohydrate can induce a state of ketosis, which may suppress appetite.

Researchers examining data from The New DIETs study found that non-compliant vegan and vegetarian participants (n=16) were still consuming a more plant-food diet at six months than other groups such as non-adherent pesco-vegetarian/semi-vegetarian (n = 15, −2.3 ± 200.3 mg; P = 0.02) and omnivorous participants (n = 7, 17.0 ± 36.0 mg; P = 0.04).[2,65] Clinicians treating patients on low-carbohydrate diets, such as ketogenic-style diets, should be vigilant in encouraging them to consume healthy whole carbohydrate foods, such as an abundance of non-starchy vegetables, berries and citrus, and those vegetables low in starch but high in resistant starch such as jicama. Some individuals on ketogenic diets have been shown to have reduced exercise tolerance due to higher levels of blood ketones.[121] Further, the long-term effects of the ketogenic diet on the gut microbiota are yet unclear. Physicians supervising patients on a ketogenic diet should consider supplementation with inulin, lactulose, fructo-oligosaccharides, and galacto-oligosaccharides, to increase the population of Bifidobacterium.[80]

Some research demonstrates greater weight loss among obese subjects on a low-carbohydrate diet compared to a low-fat, plant-based diet, though greater improvements in triglyceride levels and insulin sensitivity have been demonstrated using a low-fat diet of any kind. In a patient-centered decision-making discussion, the physician should weigh the risks and benefits of carbohydrate-restricted diets with the patient, explaining that the ketogenic mechanism ends as soon as individuals stop the diet, often resulting in regaining of weight.[122] As with any treatment to overcome disease and decrease mortality risk, including bariatric surgery with its risk of ulcers or dumping syndrome, the benefits in any particular situation may outweigh the risks. The risk of relapse with low-carbohydrate diets is the same as with any other diet.

Some people report they have tried a vegetarian diet in that past and felt hungry.

A vegan or vegetarian diet consisting of processed foods and refined grains may not supply enough nutrients, intact fiber, and water to feel satiated. Legumes and whole grains, potatoes, and soybean products like tempeh and tofu may have been lacking, and these foods allow for the feeling of fullness and satiation.[123] Potentially addictive foods with saturated fats and refined sugars may make individuals consuming a vegetarian diet that is not a WFPB diet more hungry. A well-planned, plant-based diet has all the nutrients needed for health (except for possibly vitamins B12 and D), including vitamins A, D, E, C, folate, calcium, magnesium, potassium, and fiber.[124] For most individuals, it takes time for the body to get used to the different macronutrient content (a week or two), particularly if one is used to high-density foods such as cheese and meat. Additionally, when eating a less energy-dense diet, it may be necessary to increase food volume to consume enough calories.

Isn't weight gain a normal part of aging?

Over the lifespan, metabolism naturally slows down, and body composition gradually shifts—the proportion of muscle decreases, and fat increases.

This shift makes it easier to gain weight if calorie intake and activity level stay the same. In addition, some people become less physically active as they age, increasing the risk of weight gain.[125] For those who continue eating a rich Western diet, weight gain may seem inevitable, but weight gain can be prevented using a high-fiber, plant-based diet and daily physical activity.

No diet has ever worked for me.

Generally, dieting is not associated with long-term weight loss. Individuals are challenged by interactions between biology, behavior, and the obesogenic environment.[57] A dietary plan often leads to feelings of deprivation and restriction, which is hard to maintain. Losing weight using a nutritive plant-based approach as opposed to a calorically restrictive method may allow for long-term success, healthier outcomes, and a healthier relationship with food. Further, food deprivation can lead to hormonal imbalances making us more prone to depression, a common state among dieters. Irritability, anger, anxiety, mood swings etc., are typical for dieters. A low-carbohydrate, high-protein diet; low-protein, high-carbohydrate diet; and an energy-restricted low-carbohydrate diet have all demonstrated the effect of synthesis and metabolism of tryptophan, serotonin, noradrenaline, and dopamine.[126,127] Further, when the body senses calorie restriction, metabolism will slow down to preserve energy and burn fewer calories.[81,127] A nutritious, fiber-filled dietary pattern can avoid these pitfalls, as fiber fills the stomach and offers satiety.

I just can't lose weight from diets.

Though some medical conditions can drive weight gain and prevent weight loss, including hypothyroidism, polycystic ovarian syndrome, and sleep apnea, for most individuals, weight is determined by energy intake vs. energy expenditures (calories in vs. calories out). Energy balance, the relationship between intake and expenditure, is affected by various dietary factors and physical activity behaviors. In the obesogenic modern food environment, it is extremely easy, for reasons previously discussed, to consume more energy than needed. According to a 2014 study, about 19.9% of people in North America and Europe satisfy the criteria for food addiction.[128] Further, weight loss can be a slow process, and many people have unrealistic expectations. Research indicates that any diet may work with consistent adherence,[129] but a nutritious plant-based diet may resolve many of these roadblocks related to satisfaction and enjoyment and become a life-long healthy alternative to unhealthy eating patterns.

Summary of Key Studies

We extracted data on 12 of the strongest studies in our review, all of which examine the role of vegetarian and vegan diets and plant-based food groups on weight loss and healthy weight maintenance (Appendix Table 1). Of the twelve, seven studies were randomized controlled trials or crossover trials,[5,103,130–134] three were systematic reviews (SR) and meta-analyses (MA),[70,135,136] one was an MA,[137] and one was an observational study on the EPIC cohort.[54] Of diets and components studied, six studies examined low-fat, plant-based (LFPB) diets or WFPB diets,[5,89,103,130,131,133] one examined the effect of total fruit and vegetable consumption on weight gain,[54] one examined the effect of dietary substitution of pulses on weight gain,[136] three studies examined a mix of vegan, various versions of vegetarian, and omnivorous diets on weight[132,135,137] and one examined the effect of total plant and animal protein on weight gain.[54]

Of studies examining LFPB diets, most found significant associations between LFPB diet and weight reduction. Thomson et al. found that the intervention group had significant drops in BMI, LDL-cholesterol, and HbA1c, signifying improved glycemic control.[131] A study of GEICO employees found that LFPB intervention significantly reduced weight at 22 weeks compared to the control group, with greater adherence correlating with greater weight loss. Wright et al. found significant reductions in weight, reductions in blood lipids, and increases in quality of life, in addition to improved HbA1c compared to controls at 12 months of follow-up.[5] Kahleova et al. found that LFPB diet intervention led to significant decreases in fat mass and visceral fat volume, in addition to improved glycemic control.[103] One RCT found that the LFPB diet was superior to the Mediterranean diet in eliciting weight loss, reducing homeostatic model assessment of insulin resistance (HOMA-IR), blood pressure, and lipids.[133] Another RCT found that an LFPB diet produced reduced

energy intake in an ad-libitum setting compared to a low-carbohydrate ketogenic diet. In addition, weight loss on the LFPB diet resulted in fat mass loss, while weight loss on a ketogenic diet resulted primarily in loss of fat-free mass, such as water and muscle.

One study examining food components found significant associations between animal protein and total protein consumption and weight gain but no significant association between plant-protein consumption and yearly weight gain.[54] A study examining fruit and vegetable consumption found significant associations between fruit intake and weight reduction, waist circumference, and BMI, and a reduced risk of adiposity in high quantiles of fruit and vegetable consumption compared to the lowest quantiles.[70] Another study examining pulse consumption and weight outcomes found that isocaloric substitution of pulses into the diet resulted in small but statistically significant reductions in weight.[136]

Of studies examining various diets' effects on weight loss, it was generally found that vegetarian diets resulted in weight loss to a greater extent than other diets. A meta-analysis by Barnard and colleagues found that vegetarian diets resulted in weight loss regardless of whether weight loss was the study's goal. However, studies in which weight loss was a primary goal found greater reductions in weight than other studies.[135] Finally, a random control study by Moore et al. compared weight loss outcomes between vegan, vegetarian, pesco-vegetarian, lacto-ovo-vegetarian, and omnivorous diets, finding that of non-adherent participants, those randomized to vegan and vegetarian diets experienced a greater reduction in weight than other non-adherent participants. Though, in adherent individuals, there was no mean difference in weight change at follow-up.[132]

Promising Results—Examples of Disease Reversal

Many people feel demoralized after failing to lose weight and keep it off to control chronic health conditions associated with being overweight. These case reports reflect the relief that many patients experience using a WFPB diet to effectively treat cardiometabolic risk reduction and weight loss. The prescriptive solution to rising obesity prevalence caused by increased convenience and marketing of high-fat, low nutrient food is the use of a high fiber, high carbohydrate dietary protocol, which is both therapeutic and sustainable over the long term. A low-fat, plant-based diet shows the possibility of significant weight loss both in short-term studies, as well as maintaining weight loss over the years.[81,138,139]

54-Year Old Woman Loses 50 Pounds in 6 Months

A 54-year-old female with a grade 3 obesity, BMI of 45.2 kg/m^2, and type II diabetes (hemoglobin A1c 8.1%) succeeded in losing 22.7 kg and reversed her diabetes without the use of medications using a WFPB dietary pattern. After suffering from lower extremity edema, her x-Ray revealed lower extremity atherosclerosis. She was started on a beta-blocker, an ACE inhibitor, and a statin. She underwent cardiac catheterization revealing a cardiomyopathy of a 30% proximal left anterior descending artery stenosis, a 25% proximal and a 60% distal left circumflex artery stenosis, and a 65% first obtuse marginal artery lesion.[140]

Shaken by her diagnosis, she became determined to adopt a healthy WFPB diet. She lost 22.7 kg in <6 months. Her diabetes resolved, with her hemoglobin A1c falling to 5.7% without the use of diabetes medications. Her baseline dyspnea on exertion improved considerably, and a repeat echocardiography in six months revealed a normal left ventricular ejection fraction of 55%.[140]

50-Pound Weight Loss and Reversal of Comorbidities in 9 Months

A 65-year-old male diabetic veteran lost 50 pounds after surviving two heart attacks within 62 days and triple bypass surgery. After participating in a Veteran's Hospital-sponsored Heart Disease Reversal Program, he adopted a WFPB diet under the watch of the program's doctor. He lost 9 pounds in the first month. At three months he was completely free of his angina, and at 9 months lost 50 pounds, and his diabetes medication was cut in half.[141]

Conclusion

To date, there is a wealth of data from observational and clinical studies establishing improvements in body weight using a healthy, plant-prominent diet, apparently attributable to reduced dietary

energy density and increased postprandial energy expenditure. In addition to weight loss, plant-based diets led to favorable changes in overall nutrition, plasma lipid concentrations, blood glucose, and blood pressure, which lowers risk and, in some cases, reversed chronic comorbidities.

In summary, the body of evidence presented here suggests that low-fat, plant-based diets and WFPB diets effectively reduce weight, reduce blood pressure, improve glycemic control, and reduce fat mass among individuals with obesity, as well as prevent weight gain.

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APPENDIX 1 Obesity and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Hall, 2021[89] **Randomized Crossover Trial (RCT)** n = 20 adults
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Participant data was given for the entire cohort n = 20 Age = 29.9 (1.4) years BMI = 27.8 (1.3) kg/m^2 Duration: 2 x 2-week periods, no washout
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Participants were assigned to either a (1) low-carbohydrate (LC) animal-based ketogenic diet or (2) low-fat (LF) plant-based diet for 2 weeks. They were then switched to the other diet for 2 weeks without a washout period. Diets were ad libitum in that no energy restriction was put in place. LC ketogenic diet consisted of 75% calories from fat and 10% from carbs, with a low glycemic load (6 g 1,000 kcal^{-1}). LF plant-based diet consisted of 75% calories from carbohydrates and 10% from fat, with a high glycemic load (85 g 1,000 kcal^{-1}).
Outcome(s) of interest and units	• Ad libitum energy intake • Hunger • Meal satisfaction • Fullness • Eating capacity • Energy Expenditure • Respiratory Quotient • Oral glucose Tolerance • Blood pressure • Pulse rate
Key Results (Bold qualitative assessment followed by quantitative results)	**Evidence of significantly decreased energy consumption in LF plant-based diets compared to LC ketogenic diets in ad libitum conditions.** Mean energy for subjects on the LF diet was significantly lower than energy intake on the LC diet (MD 689 +/- 73 kcal/d; p < 0.0001), with no significant effects of diet order or sex. Dietary fiber intake was significantly greater in the LF diet (60.8 +/- 2.2 g/day) compared to the LC diet (20.5 +/- 2.2 g/day). No significant differences in pleasantness or familiarity with meals were found. In addition, no significant differences in hunger, satisfaction, fullness, or eating capacity were reported between groups. LC diet resulted in significant glucose intolerance. Though both diets resulted in weight loss, the weight lost in the LC diet was primarily fat-free mass, suggesting significant water and/or muscle loss, while the LF diet resulted in loss of fat mass. In addition, LF diet resulted in lower systolic and diastolic blood pressure compared to LC diet.
Comments: Significance to clinical application	This short-term randomized crossover trial found evidence suggesting that in conditions of ad-libitum energy intake, LF plant-based diets result in much lower energy intake than high-fat, ketogenic animal-based diets. The LF diet also resulted in significant increases in fiber intake, while there were no significant differences in any measures of satiety or satisfaction with experimental diets. LF diets also resulted in better glucose tolerance than LC diets, though LF diets naturally resulted in higher postprandial insulin secretion. LF diets resulted in lower systolic and diastolic blood pressure readings, in addition to lower pulse rates. These findings suggest that LF plant-based diets may be useful in limiting energy intake in an ad libitum setting. In addition, LF plant-based diets are higher in fiber, promoting satiety, making adherence easier for individuals who eat large quantities of food. Plant-based diets should be considered as a primary tool in weight loss and maintenance and improving chronic disease risk profiles.

First author, year, study design (bold), name of study (if applicable), sample population	Barnard, 2021[133] **Randomized Crossover Trial (RCT)** n = 62 overweight and obese adults (BMI between 28 and 40 kg/m^2)		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Group 1 (Mediterranean first) n = 32 Age = 56.6 (10.9) years BMI = 34.3 (2.7) kg/m^2 81.3% female	Group 2 (low-fat vegan first) n = 30 Age = 58.3 (8.4) years BMI = 33.7 (3.4) kg/m^2 73.3% female	Duration 2 x 16-week crossover periods, with 4 weeks of washout in between
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Mediterranean (Med) diet = PREDIMED protocol Participants were asked to consume >2 daily servings of vegetables, >2-3 daily servings of fresh fruits, >3 weekly servings of legumes, >3 weekly servings of fish or shellfish, and >3 weekly servings of nuts or seeds, and to select white meats (with visible fat removed) instead of red meats. Subjects were asked to limit high-fat dairy, processed meat, sweets, and added salt. High-fat plant foods could be consumed ad libitum. Participants were asked to use extra virgin olive oil instead of other fats or oils in food preparation, using 50 g per day as part of (not in addition to) their regular food intake. Low-Fat Vegan Diet (LFVD) Diet consisted of fruits, vegetables, whole grains, and legumes, with limited nuts, seeds, and avocados, and an aimed daily calories from fat of 10%. All animal products, added sugars, oil, and salt were to be avoided. Supplemented with Vitamin B12.		
Outcome(s) of interest and units	• Bodyweight • Blood pressure • Body composition • Plasma lipids • HOMA-IR (a measure of insulin resistance) • Oral glucose insulin sensitivity (OGIS) • Predicted insulin sensitivity		
Key Results (Bold qualitative assessment followed by quantitative results)	**This randomized crossover trial provides evidence that ad libitum LFVD may be superior to the Med diet in reducing weight, fat mass, visceral fat mass, increasing insulin sensitivity, reducing LDL-cholesterol, and reducing blood pressure.** During the first 16-week phase of the study period, the Med group lost, on average, -1.5 kg (95% CI -2.9 to 0.02 kg), and those on the LFVD lost -7.9 kg (95% CI -9.3 to -6.5). During the second study period, weight change was 1.4 kg (95% CI 0.4 to 2.4 kg) on the Med diet and -4.0 kg (95% CI -5.6 to -2.4 kg) on the LFVD. The overall treatment effect of LFVD compared to Med diet was -6.0 kg (95% CI -7.5 to -4.5 kg), with most reduction in weight on the vegan diet attributable to fat mass and volume (treatment effect -3.4 kg; 95% CI -4.7 to -2.2 and treatment effect -314.5 cm3; 95% CI -446.7 to -182.4).		
Comments: Significance to clinical application	This randomized crossover trial provides convincing evidence of a superior effect of LFVD compared to the Med diet in weight loss, improving insulin sensitivity, reducing blood lipids, and improving blood pressure. More research is needed, but this study shows strong evidence that LFVD is superior to attenuating multiple chronic disease risk factors and reducing weight in overweight individuals. This may be because LFVD is more "extreme" in its restrictions, and, therefore, even if participants don't fully adhere, they still likely end up with a significantly healthier diet than their baseline.		
First author, year, study design (bold), name of study (if applicable), sample population	Kahleova, 2018[103] **Randomized Crossover Trial (RCT)** n = 75 overweight/obese adults		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Study characteristics were reported as overall statistics: n = 75 Age = 53.2 (12.6) years BMI = between 28 and 40 kg/m^2 89% female Duration: 16 weeks		

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention (n=38): plant-based, high-carbohydrate, low-fat (vegan) diet consisting of fruits, vegetables, whole grains, and legumes. Participants were instructed to avoid added fats, sugars, salt, and all animal products. High-fat plant-based foods were also limited. Controls (n=37): habitual diet Covariates: total energy intake
Outcome(s) of interest and units	• Change in body composition • Change in insulin resistance (measured via HOMA-IR) • Change in BMI/bodyweight • Changes in dietary intake
Key Results (Bold qualitative assessment followed by quantitative results)	**This RCT found that a vegan dietary intervention with increased carbohydrate intake, fiber, and decreased fat intake resulted in significant decreases in weight, BMI, fat mass, visceral fat volume, and HOMA-IR compared to the control group after adjusting for total energy intake.** BMI and body weight decreased significantly in the vegan group (treatment effect -2.0; 95% CI -2.6 to -1.5 kg/m^2 for BMI, and treatment effect -6.5; 95% CI -8.9 to -4.1 kg for body weight). Fat mass and visceral fat volume were reduced only in the intervention group (treatment effect -4.3; 95% CI -5.4 to -3.2 kg for fat mass and treatment effect -223; 95% CI -328 to -120 cm3 for fat volume).
Comments: Significance to clinical application	This RCT found evidence that vegan diet intervention was superior to control diet in reducing body weight, BMI, body fat, visceral fat, and improving HOMA-IR, a measure of insulin resistance. These findings suggest that a WFPB diet may be a beneficial tool in weight management, especially in individuals with high BMI and poor dietary habits to begin with.

First author, year, study design (bold), name of study (if applicable), sample population	Wright, 2017[5] **Randomized Crossover Trial (RCT)** n = 65 subjects ages 35-70 from general practice in Gisborne, New Zealand, diagnosed with obesity or overweight and at least one of type 2 diabetes, ischemic heart disease, hypertension, or hypercholesterolaemia.		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Whole food, plant-based (WFPB) diet n = 33 Age = 56 (9.9) years BMI = 34.5 (1.6) kg/m^2	Standard Care n = 32 Age =56 (9.6) years BMI = 34.2 (2.3) kg/m^2	Duration 12 months, with measures at 6 and 12
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention: Ad libitum WFPB diet containing whole grains, legumes, fruit, and vegetables. High-fat plant foods like nuts and avocado were limited, refined oils, added salt, and added sugar were minimized. Vitamin B-12 supplements were supplied. The intervention group received 12 weeks of support groups.		
Outcome(s) of interest and units	• Change in BMI • Change in cholesterol • Change in medication usage • Quality of life (QOL)	• CVD risk factors • CVD events • Progression to surgery • Transfer to a higher level of care	
Key Results (Bold qualitative assessment followed by quantitative results)	**This RCT examined the difference between a WFPB diet intervention and the standard of care for individuals at high risk of CVD. This study found highly significant decreases in BMI and weight at 6 and 12 months.** At 6 months, mean BMI intervention reduction was 4.4 kg/m^2 (95% CI 3.7-5.1), and at 12 months was 4.2 kg/m^2 (95% CI 3.4-5). For BMI and weight, "at 6 months the between-group analyses showed differences of 3.9 (95% CI 2.9-4.9) kg/m^2, and 10.6 (95% CI 7.7-13.5) kg, which favoured the intervention."		
Comments: Significance to clinical application	This RCT provided evidence that a low-fat, WFPB dietary intervention produced superior weight-loss and glycemic control results compared to standard of care. This evidence suggests that in addition to decreasing waist circumference, weight, and HbA1c to a greater extent than the control group, the WFPB diet group also had statistically significant improvements in various QOL measurements. Therefore, WFPB diets should be suggested as methods of reducing weight and CVD risk factors in obese subjects. In addition, WFPB diets may have some beneficial effects on glycemic control for diabetics.		

First author, year, study design (bold), name of study (if applicable), sample population	Huang, 2016[137] **Meta-Analysis (MA)** n = 12 randomized controlled trials
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 1151 total participants Study characteristics presented as ranges: Age = 18-82 years BMI = 25-53 kg/m^2 Duration: between 9 and 72 weeks (median duration = 18 weeks)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	8 studies examined vegan diets and 4 studied lacto-ovo-vegetarian (LOV) diets and their effect on weight-loss
Outcome(s) of interest and units	• Overall weight reduction between vegetarian and non-vegetarian diets • Secondary analysis examining differences between vegan and LOV diets, general weight vs. obese populations, energy restriction vs. no energy restriction, follow-up greater than vs. less than 1 year; all comparisons are of weight change
Key Results (Bold qualitative assessment followed by quantitative results)	**This MA found that vegetarian diet groups saw statistically significant weight loss in RCTS with follow-up of 9 weeks or more.** In a sensitivity analysis, those randomized to vegan diets lost more weight, on average, compared to those randomized toLOV diets. In addition, energy restriction led to greater weight loss than non-energy restricted studies, while studies with greater follow-up found greater mean weight loss. Surprisingly, less weight loss was observed in studies examining overweight or obese participants, compared to studies sampling from the general population. Studies that implemented energy restriction had greater weight loss (MD -2.21 kg; 95% CI -3.31, -1.12) compared to those without energy restriction (MD -1.66; 95% CI -2.85, -0.48), when examining vegetarian diets.
Comments: Significance to clinical application	This MA provides evidence that in short to medium term RCTs, vegetarian diet intervention, including vegan and LOV diets, leads to significant weight loss. It is surprising that weight loss was found to be lower in overweight populations, though studies with longer follow-up and more extreme plant-based diets showed increased weight loss compared to LOV and short-term dietary interventions. This MA, therefore, adds to the body of evidence that more "extreme" plant-based dietary recommendations may be successful in inciting weight loss by setting the bar for adherence higher, as failure to fully adhere still results in significant and beneficial dietary changes.

First author, year, study design (bold), name of study (if applicable), sample population	Kim, 2016[136] **Systematic Review (SR) and Meta-Analysis (MA)** n = 21 RCTs comparing the effects of diets with whole dietary pulses compared to diets without pulses on weight loss outcomes
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 940 Age = 51.3 (IQR 46.6-56.6) years BMI = 30.2 (IQR 27.6-31.4) kg/m^2 Duration: greater than 3 weeks, with a median follow-up of 6 weeks (IQR 4-12 weeks)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention was assigned the control diet with supplemental dietary pulses. Intervention diet and control diet were matched isocalorically.
Outcome(s) of interest and units	• Weight change • Change in waist circumference • Change in body fat %
Key Results (Bold qualitative assessment followed by quantitative results)	**This MA found suggestive evidence that dietary pulse consumption was associated with reductions in weight in RCTs.** Dietary pulse supplementation reduced weight in both "neutral–energy-balance and negative–energy balance diets [-0.29 kg (95% CI: -0.56, -0.03 kg; P =0.03) and -1.74 kg (95% CI: -3.19, -0.30 kg; P = 0.02), respectively]" Significant weight reduction was found in overall analysis of dietary pulse arms compared to control arms (MD -0.34 kg; 95% CI -0.63, -0.04) with no evidence of heterogeneity.
Comments: Significance to clinical application	This MA provides suggestive evidence that dietary pulse consumption may lead to small degrees of weight loss in short-term RCTs for middle-aged, overweight/obese populations. Given that pulses are excellent sources of fiber, protein, and micronutrients, this publication's findings suggest that an increase in dietary pulse consumption may be another tool in lifestyle interventions that could lead to significant weight loss.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Moore, 2015[142] **Randomized Crossover Trial (RCT)** n = 63 overweight and obese adults		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Vegan n = 12 Age = 48.2 (2.0) years BMI = 32.5 (1.8) kg/m^2	Pesco-Vegetarian n = 13 Age = 48.8 (2.2) years BMI = 35.8 (1.4) kg/m^2	Omnivorous n = 12 Age = 51.0 (2.5) BMI = 36.3 (1.6) kg/m^2
	Vegetarian n = 13 Age = 53.0 (1.1) years BMI = 35.1 (1.4) kg/m^2	Semi-Vegetarian n = 13 Age = 42.7 (2.7) BMI = 35.1 (1.5) kg/m^2	Duration 6 months, with measures at 2 and 6 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan, Vegetarian, Pesco-Vegetarian, Semi-Vegetarian, and Omnivorous diets		
Outcome(s) of interest and units	• Dietary adherence • Weight loss • Change in animal product intake (in mg of cholesterol)		
Key Results (Bold qualitative assessment followed by quantitative results)	**Significant differences in decreases in weight among non-adherent participants of vegan and vegetarian diets compared to omnivorous diets at 6 months were observed. However, there was no significant difference in weight loss when comparing only adherent participants. Given the small sample size of the study, this could be due to the limited power of the trial to detect differences between groups.** Weight loss was significantly greater in vegan/vegetarian diet groups (-6.0 +/- 6.7%) compared to omnivorous diet groups (-0.4 +/-0.6%, p = 0.04) at 6 months. In adherent participants, there was no difference in weight loss (F = 2.78, P = 0.08) among vegan and vegetarian participants (n = 9, −8.3 ± 3.1%), pesco-veg/semi-veg (n = 11, −5.0 ± 3.5%), or omnivorous participants (n = 5, −6.9 ± 1.7%).		
Comments: Significance to clinical application	This study identified no significant difference in weight loss among four versions of plant-based diets and an omnivorous diet. However, due to limited statistical power, these findings should be interpreted with caution. In addition, this study found that non-adherent participants had differences in weight loss, with non-adherent vegans and vegetarians having the largest degree of weight loss among any group. This suggests that though these groups were non-adherent, those randomized to vegan and vegetarian diets still ended up with diets that supported weight loss, suggesting that more extreme diets can help individuals improve dietary intake even when adherence is not perfect.		

First author, year, study design (bold), name of study (if applicable), sample population	Schwingshackl, 2015[70] **Systematic Review (SR) and Meta-Analysis (MA)** n = 17 prospective cohort studies (North America and Europe) examining the relationship between fruit and vegetable consumption and changes in anthropometric measures in adults.
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 563,277 participants (range per individual study: 206 to 233,755 participants) Overall age and weight not reported. Duration: ranged from 9 months to 24 years
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Fruit and vegetable consumption in g/year Covariates Each study examined adjusted for various anthropometric and lifestyle factors.
Outcome(s) of interest and units	• Change in bodyweight • Change in obesity status • Change in waist circumference • Change in BMI

Key Results (Bold qualitative assessment followed by quantitative results)	**This MA of cohort studies found that higher fruit intake was inversely associated with weight change, though the same association was not found for vegetables. In addition, fruit consumption was associated with decreases in weight circumference and reduced gains in BMI. Finally, the highest quantiles of fruit and vegetable, fruit, and vegetable intake were all associated with reduced risk of adiposity compared to the lowest quantiles.** "100-g higher fruit intake was inversely associated with a weight change (decrease), with the combined regression coefficient of -13.68 g/year (95% CI, -22.97 to -4.40)." "Every 100-g increase in vegetables was associated with a non-significant 1.69 g/year (95% CI, -10.37 to 13.74; I2 = 97.2%) change (increase) in body weight." In addition, there was a "significant association between 100 kcal increase in fruit intake and changes (decrease) in waist circumference (beta: -0.04 cm/year, 95% CI, -0.05 to -0.03; I2 = 60.6%)."
Comments: Significance to clinical application	This SR and MA found evidence that fruit and vegetable consumption were associated with reduced risks of various measures of adiposity, maintenance of BMI, and reduced waist circumference. These findings suggest that increased consumption of fruits and vegetables may be an important tool to reduce obesity in various populations.

First author, year, study design (bold), name of study (if applicable), sample population	Barnard, 2015[135] **Systematic Review (SR) and Meta-Analysis (MA)** n = 15 RCTs examining weight change with vegetarian diet intervention
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Total n = 755 participants Age and BMI not aggregated Duration: included trials were greater than or equal to 4 weeks duration
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian (excluding meat, poultry, and fish), or vegan (excluding all animal products) diets; no energy restrictions
Outcome(s) of interest and units	• Change in body weight compared to baseline or control group
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian and vegan diet interventions with no energy restriction resulted in significant decreases in body weight, regardless of whether or not the study's goal was to reduce body weight.** In studies with higher baseline weights, smaller proportions of female participants, older participants, or longer study durations, greater weight loss was reported. Vegetarian diets were associated with a change in body weight of -3.4 kg (95% CI -4.4 to -2.4). In completer analysis (analysis of all individuals who completed the intervention), vegan intervention was associated with a weight change of -4.6 kg (95% CI -5.4 to -3.8). Overall results were robust to sensitivity analysis. In studies where weight loss was the study's goal, the effect of vegetarian intervention on weight change was -3.4 kg (95% CI -4.0 to -2.7).
Comments: Significance to clinical application	This MA suggests that vegetarian and vegan dietary interventions resulted in significant weight loss from the study baseline regardless of whether this was the study's goal. This weight loss was also achieved without implementing energy restriction, suggesting that vegetarian and vegan diets naturally reduce caloric intake, resulting in weight loss. Dietary counseling towards plant-based diets may be a successful lifestyle-based method to reduce weight and improve health outcomes, especially with high adherence to diet plans.

First author, year, study design (bold), name of study (if applicable), sample population	Halkjaer, 2011[54] **Observational Cohort Study** European Prospective Investigation into Cancer and Nutrition (EPIC) n = 89,432		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Women n = 52,307 Age = 54.0 (5th–95th percentile: 36.0-64.0) BMI = 24.6 (22.0-36.0)	Men n = 37,125 Age = 54.0 (39.7-65.0) BMI = 26.0 (21.4-32.1) kg/m^2	Mean follow-up = 6,5 years

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intake of total protein, animal protein, and plant-based protein Covariates Stratified by gender and 6 study centers, then adjusted for baseline intake of fat, carbohydrates, alcohol, baseline age, weight, height, physical activity, education level, follow-up time, changes in smoking status from baseline, and for women, baseline menopausal status and use of hormone replacement therapy
Outcome(s) of interest and units	• Change in weight • Change in waist circumference
Key Results (Bold qualitative assessment followed by quantitative results)	**This study found a significant positive association between 150 kcal increases in total and animal protein consumption and yearly weight gain, while there was no association between plant protein and weight gain.** Sensitivity analysis revealed that much of the association between animal protein and weight gain could be attributed to chicken and red and processed meats, as opposed to dairy and fish. 150 kcal increase in total protein and animal protein was associated with yearly increases in weight of 78g (95% CI 35 to 120) and 82g (95% CI 41 to 124). No significant association was found between plant-protein consumption and weight change.
Comments: Significance to clinical application	This observational study suggests a significant association between increased total and animal protein consumption and yearly weight gain. These findings should be considered when examining lifestyle changes for individuals who may be overweight or obese, as weight maintenance can help reduce the risk of CVD or T2D later in life.

First author, year, study design (bold), name of study (if applicable), sample population	Ferdowsian, 2010[130] **Randomized Crossover Trial (RCT)** n = 113 employees of Government Employees Insurance Company (GEICO) between ages 21-65 years with a BMI > 25 kg/m^2 and/or previous diagnosis with T2D		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Intervention n = 68 Weight = 98.7 (2.8) kg	Control n = 45 Weight = 100.1 (3.5) kg	Average age and BMI were not reported for either group, except that age at baseline was significantly different between the groups (p = 0.05) Duration: 22 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-fat vegan diet with B12 supplementation, plus group meetings and education sessions		
Outcome(s) of interest and units	• Change in body weight • Anthropometric measures • Blood pressure • Lipid profile • Dietary intake		
Key Results (Bold qualitative assessment followed by quantitative results)	**Low-fat vegan dietary intervention significantly reduced weight at 22 weeks of follow-up in the intervention group compared to the control group. Predictors of weight loss included dietary adherence, attendance at focus group meetings, baseline weight, and several weigh-ins.** Bodyweight decreased by an average of 5.1 (0.6) kg from baseline to 22 weeks in the intervention group and increased by 0.1 (0.6) kg in the control group (p for between-group effects < 0.001). This corresponded to a BMI decrease of 2.0 kg/m^2 in the intervention group compared to the control group. Baseline weight, dietary adherence, and the number of weigh-ins were significant predictors of weight loss, while age, gender, meeting attendance, and change in fat and fiber consumption were not significant predictors.		
Comments: Significance to clinical application	This article showed that a low-fat, plant-based dietary intervention in overweight and/or diabetic insurance workers successfully reduced weight and blood triglycerides in 22 weeks. Adherence to diet and group activities was a significant predictor for weight loss, suggesting that developing a community around plant-based dietary interventions may improve adherence and lead to greater weight loss.		

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TYPE 2 DIABETES

Key Points for Practitioners

- WFPB diets can be used not only for prevention but also for the treatment of T2D.
- The attributes of WFPB diets that are particularly helpful for diabetes treatment include the lower fat content, high fiber content, and high water content,[19] leading to overall lower energy density.
- Appropriate dosing[19] of intensive, therapeutic lifestyle change is essential in using diet for diabetes treatment. Transitioning to a low-protein, low-fat, plant-based diet has delivered better results than simply reducing meat and adding more vegetables.[19]
- Due to the potentially rapid effects of plant-based dietary treatment for T2D, caution and close glucose monitoring with patients on medications are advisable, as there is the potential for sudden drops in blood glucose and blood pressure levels.[19]
- Heme iron is absorbed at a higher rate from animal foods, and its pro-oxidative effect can promote insulin resistance.[20,21]
- Using a plant-based diet to restore insulin sensitivity and treat T2D has the potential to improve other chronic conditions as it reduces inflammation, the unifying mechanism in metabolic, obesity, and cardiovascular disorders.[7,10,12,14,15,19,22]
- If patients express interest in trying a WFPB diet of some kind, it is helpful to share ACLM patient-facing resources and tools for practical guidance on plant-based eating.

ABSTRACT | The prevalence of diabetes is rising in the United States and worldwide, posing a major public health concern. There is an urgent need to curb this rapidly rising incidence. Epidemiological studies have found a lower prevalence of type 2 diabetes (T2D) among plant-based (vegetarian/vegan) populations as compared to nonvegetarians. Nonvegetarian diets are rich in calorie-dense foods, such as processed foods, refined grains, and animal-derived products, which influence metabolic abnormalities leading to insulin resistance, obesity, and diabetes. Dietary interventions using whole food, plant-based (WFPB) diets have been highly effective in the prevention and treatment of diabetes, offering a safe and effective way to achieve serum glycemic control and insulin homeostasis. In addition, WFPB diets promote weight loss, which is a primary surrogate of insulin resistance (IR) in most individuals. Healthy plant-based diets not only improve IR but also improve the common modifiable cardiovascular risk factors, including serum lipids, serum glucose concentration, and systolic and diastolic blood pressure. The current treatment for T2D centers around medications which slow the progression of the disease without achieving remission or cure, whereas dietary lifestyle changes of adopting a WFPB diet can not only prevent progression of diabetes but also achieve remission. Healthy plant foods—whole grains, vegetables, legumes, fruits, nuts, and seeds—are within reach of many individuals living with T2D. Diabetes remission should be the primary goal in the management of T2D. The emerging outcome data in many studies suggest that plant-based diets may be a practical solution to prevent and treat chronic diseases, including diabetes.

Diabetes in Context

Diabetes mellitus is a group of metabolic disorders in which either the pancreas does not produce enough insulin to regulate blood glucose, or the body cannot use insulin effectively.[1] This results in hyperglycemia. Chronic hyperglycemia leads to damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[2,3] Clinically, diabetes is diagnosed when hemoglobin A1c (HbA1c) is 6.5% (48 mmol/mol) or higher,[1] and HbA1c 5.7–6.4% (39–46 mmol/mol) is considered prediabetes.[4]

Diabetes mellitus is a global health problem with a worldwide prevalence of 8.8% and is associated with multiple comorbidities and high health care costs.[5] The Centers for Disease Control report that 10.5% of the US population have diabetes and 34.5% have prediabetes.[6] Many of those with diabetes are undiagnosed, with estimates indicating that 26.9 million people are diagnosed and 7.3 million are un- or underdiagnosed.[6]

Of the diagnosed diabetes reported in the US, 90% are type 2 diabetes (T2D).[7] Patients with T2D typically show abnormalities in their lipid metabolism, such as higher levels of fasting and postprandial triglycerides, higher levels of small, dense low-density lipoprotein (LDL) particles, and lower levels of high-density lipoprotein (HDL) cholesterol.[5] This state can further worsen beta-cell dysfunction and IR, increasing the incidence for unfavorable macrovascular endpoints (e.g., cardiovascular disease (CVD), myocardial infarction, and CVD mortality) and microvascular complications.[5] It is important to improve the management of T2D in order to achieve both glycemic and lipid goals.[5] T2D is now the leading cause of blindness in developed countries as well as the leading cause of kidney disease through its microvascular complications.[8] Blood pressure (BP) levels in T2D patients are, on average, higher which is the primary cause of cardiovascular diseases in these patients.[8]

Of the different types of diabetes categorized, the most common is type 2, in which the body produces insufficient insulin or cannot use insulin effectively. The focus of this report is T2D, as this condition is lifestyle-driven, and its causes are largely modifiable, particularly with diet.[7]

Benefits of Plant-Based Diets for Type 2 Diabetes

Plant-predominant diets are associated with decreased risk of developing T2D across all age and sex categories.[9] Even small amounts of meat consumption have been shown to increase the risk of developing diabetes.[10–13] One longitudinal study examining adult Seventh-Day Adventists without diabetes at baseline (N=8,401) found that after 17 years of follow-up, those who consumed meat just once per week had a 29% higher risk of developing diabetes than those who refrained, and this risk increased to 38% if the meat was processed. Lifelong adherence to a vegetarian diet in this population was associated with a 74% reduced risk of developing diabetes compared to a diet that included weekly meat consumption.[13–15] As shown in Figure 1, T2D prevalence in this population among meat-eaters remained approximately twice that of individuals avoiding meat.[13,15]

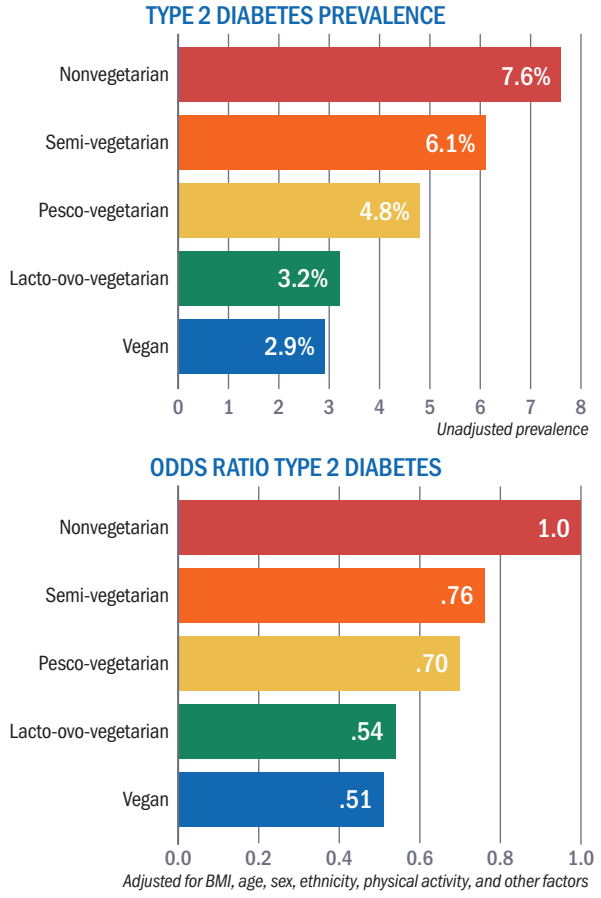

Figure 1 Type 2 diabetes (a) prevalence and (b) adjusted odds ratio of developing type 2 diabetes among individuals with varying dietary patterns[13]

Consumption of processed meat five or more times per week is associated with increased risk of T2D. In the Nurses' Health Study II, there was a 91% increased risk of diabetes among participants who reported eating meat (n=91,246).[16] Consuming red meat 5 or more times per week compared to <1 time per week, increased risk of T2D by 59%. These studies suggest that while a Western dietary pattern is associated with overall diabetes risk, meat consumption is independently associated with increased risk for diabetes.[13]

Diet as a modifiable lifestyle factor plays an important role in treating diabetes.[17] The American Diabetes Association (ADA) recommends an individualized medical nutrition therapy for glycemic and lipid management, and no single dietary approach for patients with T2D has been recommended, though a common theme emerges for successful dietary intervention that includes a high fiber, plant-based diet.8 Research consistently shows that meat consumption is associated with increased diabetes risk,[13] while vegetarian diets rich in fiber and low in saturated fat are the most beneficial for the prevention and treatment of diabetes. Plant-based diets are inversely associated with risk of developing diabetes, independent of the positive association of meat consumption with diabetes development.[13,17] Although more long-term intervention trials are required, mounting evidence supports the view that vegan, vegetarian, and plant-based dietary patterns should be clinically used in both medical and public health contexts to achieve better glycemic control in individuals with T2D,[18] as well as treatment for patients with a goal of remission.[19]

Mechanisms

Excess weight and IR have long been identified as the underlying causes of T2D.[23] Mechanisms by which plant-based diets act to address these causes to reduce diabetes risk include maintaining healthy weight and lipid mass, both overall and within pancreatic and hepatic cells. These benefits lead to protection of beta-cell function, a decrease in inflammation, improved insulin sensitivity, and avoidance of IR.[9,19]

Beta-Cell Function (and Mass)

Caloric intake exceeding energy needs causes glucotoxicity (hyperglycemia) and lipotoxicity (elevated free fatty acid levels), which disrupt glucose and insulin metabolic relationships. Pancreatic lipotoxicity inhibits beta-cell insulin production, reducing available insulin to maintain glucose homeostasis. Impairment of insulin secretion worsens over time, paralleled by progressive decline in both pancreatic B-cell function and mass, ultimately leading to persistent hyperglycemia.[24] Caloric restriction has demonstrated the rapid correction of glucotoxicity and lipotoxicity, leading to the removal of intracellularly accumulated triglycerides (and their precursors) and restoration of beta-cell insulin production.[19,25]

Heme Iron

The highly absorbable heme iron in meat acts as a prooxidant that leads to the production of reactive oxygen species (ROS), known to damage the insulin-producing pancreatic cells.[26] Even moderately elevated iron stores are associated with increased risk for T2D.[21,26,27] Iron overload increases risk for IR, T2D, and cardiovascular disease due to increased fatty acid oxidation.[27,28] Increased oxidative stress in the pancreatic islet cells has been observed in mouse models.[28] Conversely, reductions in stored iron, through either dietary changes or phlebotomy, have been found to increase insulin sensitivity by 40%.[21,26,29] The lower iron stores in vegetarians compared to meat-eaters appear to improve insulin sensitivity and enhance glucose disposal.[21]

Inflammation

Inflammation is suggested to be the unifying pathogenic mediator for IR, excess weight, T2D, and cardiovascular diseases.[30] In the human diet, saturated fatty acids (SFA) are derived from animal sources,[31] while trans-fatty acids (TFAs) originate in the meat and milk of ruminant animals[31] resulting from bacterial biohydrogenation of unsaturated fatty acids in the rumen. Partial hydrogenation of unsaturated fatty acids in vegetable oils during the industrial production of certain foods produces TFAs, as well.[32] Most TFA has similar physical properties

to SFA. Excess intake of SFA or TFA can promote lipotoxicity in several target organs by direct effects represented by inflammatory pathways by complex activation of toll-like receptor pathways (TLR-4 and TLR-2) releasing inflammatory cytokines, responsible for chronic systemic inflammation.[32]

The high-fat, low-fiber Western diet promotes the overgrowth of gram-negative pathogens, with consequent increased intestinal translocation of bacterial lipopolysaccharides resulting in endotoxemia from the toxic byproducts.[33] This interacts with specific cellular receptors of the host's immune system (TLR-4/CD-14), culminating in an inflammatory cascade that precedes the development of insulin resistance, obesity, diabetes, and cardiovascular disease.[33] At the cellular level, the adaptive inflammatory response is exerted through TLRs signaling the lipopolysaccharides from gram-negative bacteria, CpG DNA, and flagellin.[34] A 2014 Harvard study reported that as total red meat consumption increased among women from the Nurses' Health Study, so did biomarkers of inflammation.[35]

Branched-Chain Amino Acids

Animal-derived protein is rich in branched-chain amino acids (BCAAs).[36,37] Meat and dairy (whey protein and casein) are rich sources of leucine.[31] Leucine, isoleucine, and valine are essential BCAAs important for regulation of growth, protein biosynthesis, and metabolism, but also appear to contribute to obesity-related IR.[38] Elevation of BCAAs in human obesity was first reported in 1969.38 Recent advances in the metabolic role of BCAA have been recognized as a "metabolic signature" predicting insulin resistance in human subjects.[38,39] The Western-style diet provides conditions for excessive stimulation of mammalian target of rapamycin complex 1 (mTORC 1), a critical nutrient-sensitive enzyme that promotes growth and cell proliferation in response to glucose, energy, growth factors, and amino acids. This can lead to insulin resistance, diabetes, and obesity.[38] In contrast, plant-derived polyphenols and flavonoids are identified as natural inhibitors of mTORC1 and exert anti-diabetic and anti-obesity effects.[40]

Energy Density

Plant-based diets are rich in fiber with significant water content from vegetables and fruits and low in fat. As a result, they have low energy density. In many individuals, this allows for ad libitum eating resulting in satiety with less total energy consumption.[41,42] Conversely, animal-derived products high in fat and without fiber make them high in energy density leading to excess consumption of total energy.[43] Dietary interventions with plant-based foods, void of meat and other animal-derived products, usually result in low total energy consumption conferring beneficial effects in weight loss and glycemic control.[13,44]

Insulin Resistance and Intracellular Lipids

Insulin resistance and excess weight appear to have a bi-directional relationship,[45] usually resulting from excess caloric intake. Excess calories lead to the deposition of ectopic fat in the liver, pancreas, and muscle. In the pancreas, lipotoxicity inhibits beta-cell function by reducing insulin production. In most organs, intracellular fat interferes with glucose uptake by affecting the glut-4 transporter, even before weight gain.[46] This suggests that excess energy can rapidly promote insulin resistance due to increased oxidative stress in a matter of days, even before excess energy is stored to cause weight gain.[47]

Studies using magnetic resonance imaging have demonstrated lipid deposition in muscle and liver cells which leads to insulin resistance.[48] Intervention trials have shown plant-based diets can improve insulin resistance and reverse diabetes.[19]

Besides general adiposity, visceral fat contributes to insulin resistance, possibly from increased proinflammatory cytokines originating in visceral fat cells and adipose tissue-resident macrophages.[49] Intracellular fat accumulation within muscle and liver cells appears to aggravate insulin resistance which, in turn, contributes to type 2 diabetes.[50–52] Possible mechanisms suggest insulin resistance is aggravated by the specific amino acids and fat that are particularly abundant in meats and that saturated fatty acids in meat products may increase the insulin response which, in turn, increases the respiratory quotient and reduces fat oxidation.[53]

Whole Food, Plant-Based Diets

Glycemic control can be achieved (in many cases without medications) by avoiding excess calorie consumption, either by reducing the volume of food or by choosing low energy-density foods. WFPB diets, naturally low in fat and high in fiber, satisfy these measures, having the key attributes that improve glycemic control, insulin resistance, and beta-cell function.[19]

Meat products are generally higher in fat content than grains, legumes, vegetables, and fruits.[54] Not only can higher dietary fat increase excess energy content and contribute to the accumulation of intracellular lipids, but high-fat foods also appear to downregulate the genes responsible for mitochondrial oxidative phosphorylation in muscle tissue.[55] Among those who avoid animal products, intramyocellular lipid concentrations are significantly lower, compared with age- and weight-matched omnivores (−9.7, 95% CI −16.2 to −3.3, P = 0.01).[56] T2D remission has only been demonstrated with consumption of a very low-energy diet,[57] and the diet that offers the greatest reduction in fat content is a WFPB diet.[58]

Therapeutic Dosing

As with pharmaceutical therapeutics, appropriate dosing[19] is imperative to achieve an intended outcome. Similarly, achieving remission in T2D requires a decrease in basal insulin secretion in patients and increased glucose sensitivity, just as aspirin for pain relief requires 325-650 mg once or twice a day.[10,19,25,41,59,60] Practitioners have found the greatest success in achieving diabetes remission using an *intensive* dose of a WFPB dietary treatment.[19] However, caution must be exercised regarding the potential of sudden drops in blood glucose and blood pressure, especially if the patient is on medications for these conditions, which may require urgent adjustment.[9]

Common Questions and Concerns

But I thought you had to avoid carbs to control blood sugar?

Refined carbohydrates such as white flour and sugar are fast absorbed from the gastrointestinal tract, entering the circulation quickly, and this burdens the pancreas to produce insulin in excess amounts. On the other hand, unrefined carbohydrates in whole foods with their high fiber content slow the absorption rate of glucose with an attended slow rise in blood glucose level, thereby decreasing the demand on the pancreas for insulin release. This, in turn, improves insulin sensitivity. High complex carbohydrate-based diets have been shown to decrease blood glucose levels and HbA1c.[9,61]

Isn't a Keto diet good for diabetes?

A ketogenic diet may help maintain a low level of blood sugar and help with weight loss in the short term, but it does not address IR.[19] The excess fat intake leads to the deposition of triacylglycerol, the storage form of fat, in the liver and pancreas, causing lipotoxicity, the root cause of diabetes.[62] As a result, meat consumption over time is highly predictive of weight gain, ultimately leading to insulin resistance.[9,14] In addition, toxic compounds from the breakdown of meat by the gut microbiome, namely trimethylamine and its conversion to trimethylamine N-oxide (TMAO) and advanced glycation end products (AGE) have been implicated in the pathogenesis of T2D,[63] as have nitrosamines in processed meat and the heme iron in meat.[64]

What about low-carbohydrate diets in general for remission?

Overall safety concerns exist regarding the cardiometabolic effects of low-carbohydrate diets,[65] and long-term observational studies in humans have not been conducted. Higher red and processed meat intake have been consistently associated with increased risk of T2D as well as other chronic diseases, including cardiovascular disease, which should arouse concern.[66]

Summary of Key Studies

Plant-based diets offer encouraging results in improving T2D risk profiles, glycemic control, weight loss, and blood lipids. We extracted 12 of the highest-quality studies from our review to analyze the effect of plant-based diets on markers of T2D risk, symptom management, and glycemic control (see Appendix Table 1). Of the data extracted, three studies were randomized controlled trials (RCTs),[25,67,68] one was an observational cohort study,11 five were meta-analyses,[69–73] and three were systematic reviews.[18,74,75] All studies examined one form of low-fat, plant-based diet, vegan diet, or vegetarian diet, compared to a control or comparison diet. Outcomes of interest were changes in weight, waist circumference (WC), body composition, HbA1c, glucose sensitivity, insulin resistance, and changes in blood lipids.

Of the randomized controlled trials, one study found that a long-term, low-fat vegan diet intervention was as effective in reducing weight and HbA1c as the ADA guidelines. The vegan diet had greater decreases in both HbA1c and weight compared to the ADA diet, though these group-by-time interactions were not significant.[67] Another study examining a brown-rice-based vegan diet intervention found that the intervention group had greater decreases in HbA1c and waist circumference than the control.[68] Another RCT found that plant-based dietary intervention was associated with decreases in BMI, visceral fat volume, fat mass, insulin resistance, glucose sensitivity, basal insulin secretion, C-reactive protein, and improved homeostatic model assessment for insulin resistance (HOMA-IR) scores.[25] An observational cohort study within the Adventist Health Study (AHS) cohort found that vegan and lacto-ovo-vegetarian diets were associated with decreased incidence of T2D.[11]

Overall conclusions in systematic reviews were that plant-based dietary patterns improved markers of glycemic control, such as reductions in HbA1c. In addition, a plant-based dietary intervention resulted in weight loss and reduction in the need for T2D medications. Successful diets in the management of T2D all centered on plant foods: Mediterranean, vegan, vegetarian, DASH diet, and Ma-Pi 4 (macrobiotic) diets.[18,74,75] One meta-analysis found that a vegetarian diet was associated with lower odds of T2D compared to control diets. Subgroup analysis found that men on vegetarian diets had greater reductions in odds of T2D compared to men in control groups, whereas there was no effect of vegetarian diets for women and Southeast Asian populations, suggesting heterogeneity among populations.[70] This discrepancy may be explained by the regional difference in understanding and practice of a vegetarian diet. For example, Indian vegans may eat greater amounts of butter or ghee (clarified butter), which differs from the vegan dietary practice of Western countries.[76,77]

Another meta-analysis examining observational cohort studies found a significant reduction in risk of T2D with vegan and vegetarian dietary patterns. This study also found a dose-response relationship between adherence to a plant-based dietary pattern and T2D.[72] Another meta-analysis of RCTs found that a vegetarian diet was associated with decreased HbA1c, fasting glucose levels, LDL-C, weight, and BMI.[73] Though there was some heterogeneity across systematic review and meta-analysis outcomes, the majority of studies examining plant-based dietary effects on T2D show reductions in HbA1c, weight, blood lipids and cholesterol, and improvements in glycemic control and insulin sensitivity. Plant-based dietary interventions should be considered as a low-cost treatment for risk reduction and symptoms of T2D.

Promising Results—Examples of Disease Reversal

Appropriate dosing and high patient adherence in the context of lifestyle modification are essential to achieving T2D remission. Researchers clarify that "remission has not been reported with inadequately dosed lifestyle changes, such as eating more salad, or simply reducing meat consumption." However, "remission is achievable for a majority of short duration (<8 years) T2D patients, and many with longer duration, with sufficiently intense LM interventions."[19,62,78]

Rapid Remissions

Lim et al's 2011 case-control study (n=11) exemplifies appropriate therapeutic dosing of diet and

lifestyle intervention showing immediate remission of T2D in 1-4 weeks. (49.5 ± 2.5 years, BMI 33.6 ± 1.2 kg/m^2, nine male and two female) were studied before and after 1, 4, and 8 weeks of a 2.5 MJ (600 kcal)/day diet. Basal hepatic glucose output, hepatic and peripheral insulin sensitivity and beta cell function were measured. After one week of restricted energy intake, fasting plasma glucose normalized in the diabetic group (from 9.2 ± 0.4 to 5.9 ± 0.4 mmol/l; p = 0.003). Insulin suppression of hepatic glucose output improved from 43 ± 4% to 74 ± 5% (p = 0.003 vs. baseline: controls 68 ± 5%). Hepatic triacylglycerol content fell from 12.8 ± 2.4% in the diabetic group to 2.9 ± 0.2% by week 8 (p = 0.003). The first-phase insulin response increased during the study period (0.19 ± 0.02 to 0.46 ± 0.07 nmol min−1 m−2; p < 0.001) and approached control values (0.62 ± 0.15 nmol min−1 m−2; p = 0.42). Maximal insulin response became supranormal at 8 weeks (1.37 ± 0.27 vs. controls 1.15 ± 0.18 nmol min−1 m−2). Pancreatic triacylglycerol decreased from 8.0 ± 1.6% to 6.2 ± 1.1% (p = 0.03).[62]

Case Study: Reversal from "Healthy" to Plant-based Diet

A 44-year-old woman with grade 3 obesity, T2D, and depressed left ventricular heart function (heart failure), eliminated her diabetes by adopting a healthy plant-based diet and improved her cardiovascular health. She lost 22.7kg in 5 1/2 months, and her ventricular systolic function normalized. At the same time, she was able to discontinue all glucose-lowering medications. This case demonstrates the feasibility of dietary interventions for individuals in reversing metabolic comorbidities.

Conclusion

Cumulative evidence demonstrates that T2D can be prevented and treated without pharmacological interventions or surgery, using a WFPB dietary regimen. Remission of T2D should be the primary clinical goal, and this is feasible for many individuals using a low-fat, WFPB diet. This treatment is shown to be well-tolerated and facilitates weight loss without feelings of hunger or deprivation.[80]

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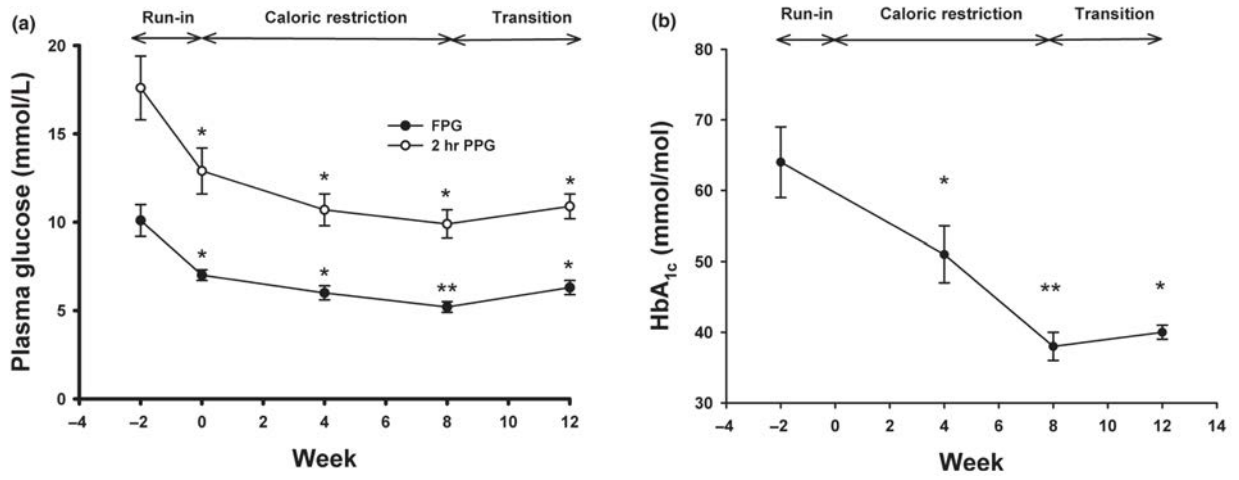

*(a) Fasting plasma glucose (closed circles) and 2-hr plasma glucose after an OGTT (open circles) were measured at weeks −2, 0, 4, 8, and 12. (b) HbA1c was determined at weeks −2, 0, 4, 8, and 12. *: p < 0.01, **: p < 0.001 compared to values at week −2*[79]

Figure 2 (a) Changes in fasting plasma glucose (FPG), 2-hr plasma glucose after an OGTT (PPG), and (b) HbA1c during the study periods.

APPENDIX 1 Type 2 Diabetes and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	de Carvalho, 2020[74] **Systematic Review** RCTs and cohort studies examining relationship between diet and glycemic control in individuals with T2D
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Total sample size not reported, 7 total studies. Mean age of study populations ranged from 51.90-59.20 years Mean BMI of study populations ranged from 23.10-35.10 Duration: 8wk to 4 yr (RCTs); 6 months (cohort)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan, Vegetarian, DASH, Mediterranean, and conventional diabetic diet n=3 RCTs for vegetarian and vegan diets; n=1 RCT and n=1 cohort study for DASH and Mediterranean diets
Outcome(s) of interest and units	• Change in HbA1c
Key Results (Bold qualitative assessment followed by quantitative results)	**This systematic review has gathered evidence showing that a variety of plant-based dietary patterns are effective in improving glycemic control, including vegan, vegetarian, DASH, and Mediterranean diets.** This systematic review found an average decrease in HbA1c of 0.80%. In vegan or vegetarian studies, the mean decrease was 0.68%, and studies examining DASH and Mediterranean dietary patterns showed an average 1.7% decrease in HbA1c.
Comments: Significance to clinical application	This systematic review presents evidence that various plant-based diets may help improve glycemic control, via reduction in consumption of saturated fat, increased consumption of low-glycemic index foods, increases in fiber consumption, and increases in plant-food consumption overall. For those faced with poor glycemic control, plant-based diets may provide a low-cost, non-medicinal means of improving control of glycemic risk factors.

First author, year, study design (bold), name of study (if applicable), sample population	Johannesen, 2020[75] **Systematic Review** RCTs with greater than 4 weeks of duration on plant-based diet and glucose metabolism in subjects with T2D, overweight/obesity, or CVD, published after 2010
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 946 total participants, 9 studies Overall age and BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan, Vegetarian, and Lacto-Ovo-Vegetarian diet
Outcome(s) of interest and units	• Fasting plasma-glucose and insulin concentrations • HbA1c levels • C-peptide concentrations • Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index values
Key Results (Bold qualitative assessment followed by quantitative results)	**5 studies observed a significant improvement in glycemic control in the plant-based diet intervention group, with 4 reporting a significant difference compared to control group; 4 studies did not observe any significant benefit of plant-based diet interventions.**
Comments: Significance to clinical application	This systematic review shows that low-fat, plant-based diets are associated with improvement in markers of glycemic control and weight loss in some, but not all, studies. Authors state no clear conclusions can be drawn based on these findings.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Papamichou, 2019[18] **Systematic Review** RCTs in people with T2D with duration greater than 6 months evaluating different diets on diabetes control/ management
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 15 RCTs Mean overall age and BMI not reported Duration: >= 6 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-carbohydrate diet, Low-fat diet, High-Protein diet, Ketogenic diet, Mediterranean diet, Atkins diet, Vegan diet, Vegetarian diet, Ma-Pi 4 diet
Outcome(s) of interest and units	• Change in weight • Blood pressure • Change in lipids • Change in HbA1c • Change in body composition • Fasting plasma glucose
Key Results (Bold qualitative assessment followed by quantitative results)	**This systematic review found three randomized controlled trials examining plant-based diets, all of which showed significant benefit for various risk factors for T2D. Mediterranean diet resulted in greater reduction in weight and HbA1c and delayed need for diabetes medication; vegetarian diet led to greater weight loss and insulin sensitivity, while vegan diet improved glycemia measures and HbA1c, as did Ma-Pi 4 diet.**
Comments: Significance to clinical application	This systematic review found three relevant articles examining the effects of plant-based diets on risk factors of T2D. Articles suggested that plant-based diets may reduce LDL cholesterol, lead to greater weight loss, and may reduce HbA1c, a marker of insulin resistance. A larger body of research is needed, but this systematic review provides some evidence that plant-based diets may help to improve risk factors of T2D, obesity, and glycemia.

First author, year, study design (bold), name of study (if applicable), sample population	Picasso, 2019[71] **Systematic Review and Meta-Analysis** RCTs, cohort, or cross-sectional studies examining the effects of vegetarian diet on metabolic syndrome (MetS)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N=103,008 across 6 RCTs, 2 cohort studies, 63 cross-sectional studies Overall age and BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet
Outcome(s) of interest and units	• Systolic blood pressure (SBP) • Diastolic blood pressure (DBP) • Fasting glucose, triglycerides • Waist circumference (WC) • HDL cholesterol (HDL-C)
Key Results (Bold qualitative assessment followed by quantitative results)	**Meta analyses showed no significant association between vegetarian diet and metabolic syndrome (Mets) (5 cross-sectional studies) or with components of MetS in cohort and RCT studies. Meta-analysis of cross-sectional studies demonstrated significant associations between vegetarian diet and decreases in SBP, DBP, fasting glucose, WC, and HDL-C, but heterogeneity of effects was high.** Meta-analysis of cross-sectional studies showed that vegetarian diet was not associated with MetS (OR 0.96, 95% CI 0.50, -1.85, p= 0.9) but was associated with decreased SBP (MD -4.18 mmHg, 95%CI -5.57 to -2.80), DBP (MD -3.03 mmHg, 95% CI -4.93 to -1.13), fasting glucose (MD -0.26 mmol/L, 95% CI -0.35to -0.17), WC (MD -1.63 cm, 95% CI -3.13 to -0.13), and HDL-C (MD -0.05 mmol/L, 95% CI -0.07 to -0.03).
Comments: Significance to clinical application	This systematic review found no effect of vegetarian diet on metabolic syndrome in randomized controlled trials or cohort studies. However, in cross-sectional studies there were significant associations between vegetarian diets and improved markers of metabolic syndrome progression, though these studies had a high risk of bias, and cannot determine causality.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Qian, 2019[72] **Systematic Review and Meta-Analysis** Observational studies on plant-based dietary patterns and incidence of T2D in individuals older than 18 years
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 307,099 individuals, 9 studies Overall mean age and BMI were not reported (mean age ranged from 36-64 yr and BMI 23.0 to 26.7kg/m^2)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Plant-based diet, defined as diets with a high consumption of plant foods and a low consumption of animal foods
Outcome(s) of interest and units	• T2D incidence • Plant-based diet adherence
Key Results (Bold qualitative assessment followed by quantitative results)	**This meta-analysis of observational studies shows a strong inverse association between plant-based dietary patterns and risk of T2D and a significant dose-response relationship between increasing plant-based diet adherence score and decreased risk of T2D.** Meta-analysis found an inverse association between plant-based diet patterns and T2D risk (pooled RR of 0.77; 95% CI 0.71, 0.84), with modest heterogeneity across studies. Dose-response analysis suggested a highly significant ($p < 0.001$) and inverse association between increasing plant-based diet adherence score and risk of T2D.
Comments: Significance to clinical application	This meta-analysis provides strong evidence of an inverse relationship between plant-based dietary patterns and the development of T2D. Therefore, recommendation of increased consumption of plant foods and decreased consumption of animal foods may be prudent for reducing T2D risk.

First author, year, study design (bold), name of study (if applicable), sample population	Viguiliouk, 2019[73] **Systematic Review and Meta-Analysis** RCTs >=3 weeks evaluating effects of vegetarian diet in people with diabetes
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 664 total participants, 9 studies Age = 56 years (range 32-61 years) BMI = 34.4 kg/m^2 (range 23.5-35.1 kg/m^2) Duration: Median follow-up of 12 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan, vegetarian, and lacto-ovo-vegetarian diets
Outcome(s) of interest and units	• HbA1c • Fasting glucose • Fasting insulin • LDL-C • Non-HDL-C • HDL-C • Triglycerides • Bodyweight • BMI • Waist circumference • SBP • DBP
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diets were associated with decreased HbA1c fasting glucose levels, LDL-C, non-HDL-C, weight, waist circumference, and BMI.** Compared to control diets, vegetarian diets were associated with a decrease in HbA1c (MD = -0.29%; 95% CI -0.45, -0.12%); fasting glucose levels (MD =-0.56 mmol/L; 95% CI -0.99, -0.13 mmol/L) ; LDL-C (MD = -0.12 mmol/L; 95% CI -0.20, -0.04); non-HDL-C (MD=-0.13 mmol/L; 95%CI -0.26, -0.01);body weight (MD = -2.15 kg; -2.94, -1.34 kg); BMI (MD = -0.74 kg/m^2; 95% CI -1.09, -0.39 kg/m^2); waist circumference (MD= -2.86cm; 95%CI -3.76, -1.96). There were no significant associations between vegetarian diet and fasting insulin, HDL-C, triglycerides, SBP, or DBP.
Comments: Significance to clinical application	This meta-analysis shows significant evidence of improved glycemic control and reductions in risk factors common to T2D and cardiovascular disease (CVD). Vegetarian dietary intervention, focusing on whole foods, should be considered as a lifestyle modification for management of glycemic control and T2D risk factors.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Kahleova, 2018[81] **Randomized Controlled Trial** Overweight adults with no history of diabetes
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 75 Intervention n = 38 Age = 52.6 (14.7) years BMI = 33.1 (1.3) kg/m^2 Control n = 37 Age = 54.3 (9.9) years BMI = 33.6 (1.15) kg/m^2 Duration: 16 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-fat, plant-based diet (75% calories from carbohydrate, 15% from protein, and 10% from fat) though no meals were provided
Outcome(s) of interest and units	• BMI • Lean mass • Fat mass • Visceral fat volume • Basal insulin secretion • Beta-cell glucose sensitivity • Homeostasis Model Assessment (HOMA-IR) for fasting insulin resistance • HbA1c and C-peptide concentrations • Postprandial insulin, glucose, and C-peptide
Key Results (Bold qualitative assessment followed by quantitative results)	**This study shows that after a 16-week plant-based diet intervention, there were significant time and intervention-dependent effects on decreased BMI, visceral fat volume, fat mass, insulin resistance, fasting plasma glucose and c-peptide, and basal insulin secretion.** Intervention group experienced significant time-intervention interaction effects: BMI (-2.0 kg/m^2; 95% CI -2.6, -1.5), visceral fat volume (-224 cm2; 95% CI -328, -120), fat mass (-4.3 kg; 95% CI -5.4, -3.2), lean mass (-1.2 kg; 95%CI -2.0, -0.5). Compared to controls, intervention group experienced significant decreases in basal insulin secretion (-54.2 pmol/min/m2; 95% CI -86.5, -21.9), HOMA-IR (-1.0; 95% CI -1.2, -0.8),fasting plasma glucose (-0.4 mmol/L; 95%CI -0.6, -0.2) and fasting plasma C-peptide (-1.0 ng/mL; 95% CI -1.6, -0.4). No significant treatment effect on fasting insulin glucose sensitivity, but significant beneficial changes from baseline in intervention group. No significant changes in HbA1c in either group.
Comments: Significance to clinical application	This study shows that a plant-based dietary intervention may improve risk profiles for the development of T2D in overweight individuals. In this study, plant-based diet reduced visceral and total fat mass, both of which act as independent risk factors for diabetes. Plant-based diet also improved insulin and glucose sensitivity markers, though these effects were not differentiated between benefits from weight reduction vs. plant-based diets independent of weight loss. However, both arms of the study reduced caloric intake by approximately 500 calories, though there were more beneficial effects found in the plant-based intervention compared to the control group.

First author, year, study design (bold), name of study (if applicable), sample population	Lee, 2017[70] **Systematic Review and Meta-Analysis** Cohort and cross-sectional examining the association between vegetarian diet and the incidence or prevalence of T2D
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N=478,613 across 14 studies; 2 cohort and 12 cross-sectional Age range: 20-88 yrs BMI of included study subjects was not reported. Included studies covered many regions, including India, the United States, Barbados, Taiwan, Italy, Canada, Pakistan, and China
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet
Outcome(s) of interest and units	• Prevalence or incidence of T2D

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diet was associated with lower odds of T2D compared to control diets. In subgroup analysis, vegetarian men but not women had lower odds of T2D. No significant effect was identified in studies with Southeast Asian populations. In addition, vegans and lacto-ovo-vegetarian (LOV) diet adherents had the lowest odds of T2D for any vegetarian subgroup.** In overall meta-analysis, vegetarian diet was associated with decreased odds of T2D (OR: 0.73; 95% CI: 0.61, 0.87). Men (OR: 0.614; 95% CI: 0.527, 0.716), but not women (OR: 0.569; 95% CI 0.298, 1.086) had lower odds of T2D compared to non-vegetarians. Association was stronger for the studies conducted in the Western Pacific region (OR 0.514, 95% CI: 0.304, 0.871) and Europe/North America (OR 0.756, 95% CI: 0.589, 0.971). Southeast Asia region showed no significant association between vegetarian diet and T2D risk. Finally, vegans (OR: 0.593; 95% CI: 0.386, 0.911) and LOV (OR: 0.564; 95% CI: 0.517, 0.616) individuals had the lowest odds of diabetes of any subgroup.
Comments: Significance to clinical application	This study suggests that vegetarian diet was associated with a lower odds of diabetes, with two caveats: no significant effect was found in vegetarian women and Southeast Asian subcategories, suggesting perhaps that vegetarian diet had minimal effect on these subcategories, potentially because their diets are more closely aligned to vegetarian, even if subjects do not identify as vegetarian.

First author, year, study design (bold), name of study (if applicable), sample population	Lee, 2016[68] **RCT** Korean individuals diagnosed with Type 2 Diabetes (T2D)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 93 <u>Brown-Rice vegan diet</u> n = 46 Age = 57.5 (7.7) BMI = 23.9 (3.4) kg/m^2 <u>Korean Diabetes Association Diet</u> n = 47 Age = 58.3 (7.0) BMI = 23.1 (2.4) kg/m^2 <u>Duration:</u> 12 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan diet consisting of whole grains, fruit, vegetables, and legumes, with instructions to eat brown rice, avoid white rice, avoid processed foods made with of rice or wheat flour, avoid all animal products including fish, and favor low-glycemic foods Control was conventional diet recommended by Korean Diabetes Association 2011 Covariates: total energy intake and waist circumference
Outcome(s) of interest and units	• Change in HbA1c level • Secondary endpoints: BMI, waist circumference, systolic/diastolic blood pressure, fasting blood glucose, LDL-cholesterol, HDL-cholesterol, and triglycerides
Key Results (Bold qualitative assessment followed by quantitative results)	**Significant reductions in HbA1c were observed in both groups, but vegan diet group exhibited greater decreases in HbA1c compared to control. In addition, vegans experienced significant decreases in BMI and waist circumference after 12-week dietary intervention.** <u>Glycemic control</u> HbA1c levels decreased in both the vegan group (-0.05%, $p < 0.01$) and the conventional diet group (-0.02%, $p < 0.05$), with a significant time x group interaction effect ($p = 0.017$). BMI (-0.5 kg/m^2; $p < 0.01$) and waist circumference (-3.1 cm; $p < 0.01$) decreased significantly in the vegan diet group but not the conventional diet group. Blood pressure, cholesterol, and triglyceride levels did not significantly change in either group.
Comments: Significance to clinical application	This study suggests that a brown rice based vegan diet approach was successful in producing statistically significant decreases in HbA1c, BMI, and waist circumference among Koreans with T2D. This suggests that high adherence to a whole food, plant-based vegan diet may be beneficial in the management of T2D.

First author, year, study design (bold), name of study (if applicable), sample population	Tonstad, 2013[11] **Observational Cohort Study** Adventist Health Study (AHS) Cohort Adventist men and women across the U.S. and Canada who were free from diabetes at enrollment Adventist Health Study-2

Appendix continued

Study/analysis groups, mean age, mean BMI (SD), total N, duration	N= 41,387 Vegans n = 3545 Age = 59.6 (13.5) years BMI = 23.8 (4.4) kg/m^2	Lacto-ovo Vegetarians n = 14,099 Age = 59.5 (13.9) years BMI = 25.6 (4.8) kg/m^2	Non-Vegetarians n = 17,695 Age = 56.1 (13.0) years BMI = 28.2 (5.9) kg/m^2
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan, Lacto-Ovo-Vegetarian (LOV), Pesco-Vegetarian, Semi-Vegetarian, and Non-Vegetarian diets. Covariates For models of diabetes incidence, variables adjusted for include "age, BMI, ethnicity, gender, educational level, income, TV watching, sleep, alcohol, physical activity and cigarette smoking."		
Outcome(s) of interest and units	• Incident diabetes		
Key Results (Bold qualitative assessment followed by quantitative results)	**In the AHS cohort, vegan, LOV, and semi-vegetarian diets were associated with lower incidence of T2D after adjusting for ethnic, anthropometric, lifestyle, and socioeconomic status variables compared to non-vegetarian diets.** In the fully adjusted model, vegan (OR: 0.381; 95% CI: 0.236, 0.617), LOV (OR: 0.618; 95% CI: 0.503-0.760), and semi-vegetarian (OR: 0.486; 95% CI 0.312-0.755) diets were associated with reduced risk of developing type II diabetes, though Pesco-vegetarian diets were not associated with lower incidence of diabetes.		
Comments: Significance to clinical application	This study suggests that plant-based diets were associated with reduced incidence of diabetes in the Adventist population, even after accounting for socioeconomic status, race, age, gender, anthropometric and lifestyle factors. These findings suggest a benefit of plant-based diets on reducing the risk of Diabetes, though research on Adventist populations are not readily generalizable because of their unique community and lifestyle practices.		
First author, year, study design (bold), name of study (if applicable), sample population	Barnard, 2009[10] **Randomized Controlled Trial (RCT)** Individuals with T2D		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 99 Low-fat vegan diet n = 49 Age = 56.7 (9.8) years BMI = 33.9 (7.8) kg/m^2	American Diabetes Association guidelines diet n = 50 Age = 54.6 (10.2) years) BMI = 35.9 (7.0) kg/m^2 Duration: 74 weeks	
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-fat vegan diet consisting of vegetables, fruit, grains and legumes, and avoiding animal products and any fatty foods, both plant and animal-based and favoring low-GI foods		
Outcome(s) of interest and units	• HbA1c • Plasma glucose • Plasma triglycerides	• Cholesterol (total, LDL, HDL, non-HDL) • Urinary albumin • Weight	
Key Results (Bold qualitative assessment followed by quantitative results)	**Both diets were associated with significant weight loss and reductions in blood lipids, but there was no significant difference between diets. After controlling for changes in medications, the low-fat vegan diet was significantly associated with greater reductions in HbA1c, total, LDL, and non-HDL cholesterol compared to ADA diet.** Body weight: vegan group= -4.4 kg, control group= -3.0 kg; p = 0.25 (between group t-test) Controlling for the effects of changes in medication, the mean difference from baseline in vegan vs ADA group for HbA1c was -0.40% vs 0.01% change (p = 0.03); total cholesterol was -20.5 vs -6.8 (p=0.01); non-HDL cholesterol was -19.5 vs -6.1 (p=0.02); LDL cholesterol was -13.5 vs -3.4 (p=0.03). No significant differences in VLDL or triglyceride were observed.		
Comments: Significance to clinical application	This RCT provides evidence that a low-fat vegan diet is equally as effective in reducing risk metrics of T2D in a diabetic population as American Diabetes Association guidelines. This study is interesting in that it studies a free-living population, simulating what a vegan diet intervention would look like in an outpatient setting, likely making the results more generalizable to free-living populations. Both ADA guidelines and low-fat vegan diets can be recommended to lower the risk of T2D and manage symptoms in those who already have T2D, though there may be a greater effect size with vegan diets that was not revealed in this study due to sample size limitations.		

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CARDIOVASCULAR DISEASE

Key Points for Practitioners

- Key benefits of plant-based dietary treatment for CVD include the control of hypertension, insulin, inflammation, and oxidative stress[45,67,68,71–74,85,158]
- Plant-based diets lower risk factors of triglycerides, overweight, and other biomarkers of CVD[116,161]
- Intervention studies in both children[162] and adults[127,163] demonstrate the safety and effectiveness of plant-based interventions for a variety of populations
- A strict low-fat (~10%) whole food, plant-based diet has been shown to achieve a serum cholesterol level of ≤150 mg/dL or less, which would avoid cardiovascular events[90,135]
- Both refined and animal foods harm the fragile endothelial cells that line all arteries, and plant foods filled with antioxidants prevent damage[45,66,67,69,70]
- Populations eating largely plant-based diets have lowest rates of CVD4
- If patients express interest in trying a whole food, plant-based diet, it is helpful to share ACLM patient-facing resources and tools for practical guidance on plant-based eating

ABSTRACT | The burden of cardiovascular disease (CVD) is increasing globally and continues to be the leading cause of death worldwide,[1] responsible for roughly one in four deaths in the U.S. alone.[2] Modifiable lifestyle risk factors are associated with most acute myocardial infarctions,[3] including many dietary risk factors including red and processed meat, saturated fat, refined carbohydrates, excess sodium, and inadequate fiber. Populations consuming diets centered on whole plant foods have better cardiovascular risk profiles and lower rates of cardiac events and mortality.[4] Lifestyle medicine practitioners can best support cardiac health in patients by encouraging adoption and maintenance of a whole food, predominantly plant-based diet.

Cardiovascular Disease in Context

Cardiovascular disease (CVD) is a group of heart and blood vessel disorders that include coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other circulatory conditions, including heart failure, arrhythmias, and stroke.[5,6] The most common cause of CVD is Ischemic Heart Disease (IHD), often developed by atherosclerotic narrowing of the coronary arteries. Over the past fifty years, there has been a significant drop in CVD-related mortality.[7] However, despite substantial advances over the past decade in all areas of cardiovascular medicine, CVD remains the leading cause of death across the world.[2–6]

As outlined in the most recent Global Burden of Cardiovascular Disease data, the risk factors for CVD and the associated burden of heart disease continue to rise in low- to middle-income nations.[6] In addition to conventional risk factors (hypertension, smoking, diabetes, obesity, hyperlipidemia, chronic kidney disease), psychological factors[8] and social determinants of health[6,9] play a significant role.

Food insecurity as a social determinant of health is an important factor contributing to CVD burden.[10] At a population level, 90% of the attributable cardiovascular risk is modifiable through lifestyle changes.[8] Diet-induced risk is an important contributor to CVD risk.[11,12] Atherosclerosis has been shown to be associated with dietary intake of red and processed meat,[13] saturated fat,[14,15] and refined carbohydrates.[16,17] Globally, the diet-induced risk is primarily due to increased consumption of sodium and low intake of whole grains and fruits,[18] as well as overconsumption of ultrapocessed foods.[19–21] The cost of healthcare and lost productivity due to CVD in the U.S. is in excess of $300 billion per year,[22,23] and suboptimal diet has been shown to be contributing to over 18% of this spending.[24]

Pathophysiology of CVD

CVD begins with progressive endothelial injury,[25] inflammatory oxidative stress, diminution of nitric oxide production, foam cell formation, and development of plaques that may rupture to cause a myocardial infarction (MI) or stroke.[26] Heart attacks and strokes are usually acute events caused by blockages that prevent blood from flowing to the heart or brain. The most common reason for this is a buildup of deposits made of fat, cholesterol, calcium, and other substances on the inner wall of the blood vessels that supply the heart or brain.[1] Diet has long been implicated in the pathophysiology of CVD with excess amounts of added oils, dairy, meat, fowl, fish, and sugary foods. Insufficient micronutrient density and disproportioned macronutrients are also studied variables.[18,27] These foods can injure or impair endothelial function after each ingestion, making food choices a major, if not the major, cause of coronary artery disease.[25,28–31] Most CVD can be prevented by addressing behavioral risk factors such as unhealthy diet and obesity, physical inactivity, tobacco use, and harmful alcohol use.[32]

Inflammation

Inflammation, as it relates to atherosclerosis and CVD, is a complex and highly regulated interaction between many cellular and molecular mechanisms.[33] There are multiple sources of inflammation, some modifiable and others non-modifiable. Smoking, dyslipidemia, diabetes, obesity, perivascular fat deposition, reactive oxygen species, diet, and gut microbiome have been shown to contribute to arterial inflammation, and increased risk of CVD.[34] Diet plays a significant role in inflammation and cardiovascular risk.

In a recent analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, it was shown that diets with high inflammatory potential (red meat, processed meat, organ meat, refined carbohydrates, sugar-sweetened beverages) are associated with increased risk of CVD.[35,36] Diets high in saturated fat have been shown to increase levels of C-Reactive Protein (CRP), Tumor Necrosis Factor Alpha (TNF alpha), Interleukin 6 (IL-6), Vascular Cell Adhesion Protein 1(VCAM-1) and Intercellular Adhesion Molecule 1 (ICAM-1).[37,38] The consumption of hydrogenated trans fats has been shown to increase the levels of multiple markers of inflammation and the overall risk of CVD,[39,40] as have diets high in refined carbohydrates[41] and sugars.[42] Diets rich in polyunsaturated fats and fiber have been shown to lower inflammatory markers.[43]

Inflammation and hypertension interact as CVD begins to make structural changes in the arteries. Inflammation is marked by circulating inflammatory molecules, including CRP and IL-6,[44] which are predictors of future CVD.[45] One study of men and women in their 40's with high BMIs (n=29) showed a significant and drastic reduction in systemic inflammation, as indicated by decreased CRP. Reducing systemic inflammation appears essential, considering that increased inflammation and oxidative stress emerge as underlying pathophysiologic mechanisms of aging and age-related diseases.[46–48] An inability to scavenge and quench reactive oxygen and nitrogen species that can harm endothelial cells is linked to oxidative stress and CVD.[49]

According to some research, added oils are not causally implicated in CVD, though it does appear that the type of fat is more important to oxidative stress and inflammation, notably saturated fatty acids, which come from animal foods. On the other hand, vegetable oil used in place of animal fat has consistently shown to lower CVD.[50,51]

Trimethylamine N-oxide (TMAO)

Dietary nutrient intake and its metabolism by the gut microbiome have recently been associated with CVD risk. In particular, TMAO, a metabolite of the gut microbiota, is a predictor of incident CVD events.[52] L-carnitine, an abundant nutrient in red meat, accelerates atherosclerosis in mice via gut microbiota-dependent formation of trimethylamine (TMA) and TMAO. This production happens via a multistep pathway involving an atherogenic intermediate, γ-butyrobetaine (γBB). The contribution of γBB in gut microbiota-dependent L-carnitine metabolism in humans is still unknown. However, studies with oral d3-L-carnitine or d9-γBB before versus after antibiotic exposure reveal that gut microbiota contributes to the initial two steps in a metaorganismal L-carnitine→γBB→TMA→TMAO pathway in subjects.[52,53] Observational research, including Mendelian randomization studies, find reverse causation between TMAO levels and chronic disease like CVD, in that the disease is causally associated with TMAO levels.[38]

The gut flora processes dietary carnitine into TMA, which the liver converts into TMAO.[54] Elevated levels of TMAO have been shown to be associated with increased risk of coronary artery disease, myocardial infarction, and peripheral arterial disease, independent of conventional risk factors.[55] Elevated levels of TMAO have also been shown to predict risk of major adverse cardiac events such as myocardial infarction, stroke, and death.[54,56] Fasting levels of TMAO have been shown to predict atherosclerotic burden and extent of coronary artery disease.[57] Similar prognostic utility of TMAO has been demonstrated in individuals with diabetes,[58] peripheral arterial disease,[59] and congestive heart failure.[60] These findings are independent of traditional cardiovascular risk factors and have been validated in two systematic reviews and meta-analyses.[61–63] Based on these observations, TMAO levels of greater than 6 μM are predictive of high risk and adverse cardiovascular events.[64] While TMAO levels predict risk, the mechanisms and causal link are now well established. It appears that elevated TMAO levels could be markers of reverse causation.[65]

Effects of Plant-Based Diets on CVD and CVD Risk Factors

There are a variety of mechanisms by which plant-based nutrition can lead to decreased blood pressure, including improved vasodilation,[45] anti-inflammatory effects,[45,66,67] greater antioxidant content,[68–70] improved insulin sensitivity,[68,71–74] decreased blood viscosity,[75,76] altered baroreceptors,[68] modifications in both the renin-angiotensin (cardiac blood outcome),[71,77,78] and sympathetic nervous systems,[78–80] as well as modification of the gut microbiota.[78]

A whole food, plant-based (WFPB) diet can restore the ability of endothelial cells to produce nitric oxide (NO).[81] NO maintains vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in the blood, playing a crucial role in normal endothelial function.[81]

Protective benefits of the plant-based dietary pattern on cardiovascular function include lower risk of hypertension, obesity, inflammation, and insulin resistance.[18,82–84] Studies demonstrate that dietary cholesterol, saturated fat, and animal foods increase risk for CVD, while WFPB diets are associated with a more favorable cardiovascular disease biomarker profile and better vascular structural and functional parameters.[18,82–84] Dietary patterns that minimize or avoid dairy, meat, other animal products, and oils reduce modifiable risk factors of CVD.[27,82,85–109] WFPB diets not only contain protective components that decrease risk, such as high fiber and antioxidants, but are also low or devoid of food components that increase risk, including saturated fat and added sugar, both associated with risk of CVD.[110]

Plant-Based Benefits for Cardiovascular Risk and Risk Factors

Accumulating evidence indicates the merits of plant-based diets to control and manage CVD due to the beneficial changes in cardiometabolic risk factors such as lower total serum cholesterol and glucose, BMI, inflammation, and blood pressure.[110] Vegetarians have been found to have lower blood pressure and lower cardiovascular mortality.[111]

These positive effects may be due to lower intakes of dietary cholesterol and saturated fat from red and processed meat, and conversely higher intakes of fiber, plant protein, and phytonutrients from whole grains, fruits, nuts, and vegetables,[110] which can protect against risk factors including type 2 diabetes, as well as high sensitivity to CRP and the inflammatory IL-6 molecule.[112] It appears that a WFPB diet reduces inflammation, possibly due to eliminating these risk factors.[66,67,113]

Population studies show that increased intake of plant foods reduces risk for CVD, including the Adventist Health Study-2, which found that 'meat' proteins are associated with increased risk, whereas nut and seed proteins are associated with lower risk.[114] A systematic review and meta-analysis found that vegetarian-based dietary patterns have been associated with favorable biomarkers of low-grade inflammation as indicated by immune biomarkers (CRP, TNF alpha, fibrinogen, natural killer cells, leukocytes, lymphocytes, thrombocytes, interleukins, and immunoglobulins).[115] These markers work synergistically as a protective response to environmental, mechanical, or pathological challenges and are predictors of CVD risk, all-cause mortality, diabetes, and some cancers. Evidence suggests that plant-based diets may attenuate markers or chronic inflammation.[115]

The Nurses' Health Study data provided compelling evidence that diet and lifestyle strongly influence CVD incidence and point to high levels of heme iron and saturated fatty acids in red meats. A significant inverse association was observed in this study between those adhering to a plant-predominant Mediterranean dietary pattern and CVD risk.32 In the MESA study (Multi-Ethnic Study of Atherosclerosis), apolipoprotein C-III found on 6%-7% of HDL particles are adversely associated with CVD. Apolipoprotein C-III is a proinflammatory atherogenic lipoprotein that appears to impair the removal of triglycerides from the blood.[116]

Long-term practices associated with the pillars of lifestyle medicine, particularly the consumption of a whole food, plant-predominant diet, and/or regular endurance exercise, are associated with lower cardiometabolic risk.[117] Additionally, plant-based diets provide beneficial effects on blood pressure and are inversely associated with sodium intake, as demonstrated in the Dietary Approaches to Stop Hypertension (DASH) study, the Coronary Artery Risk Development in Young Adults (CARDIA) study, and three prospective cohorts of the Nurses' Health Study I and II.[118] A 2021 meta-analysis of 13 studies (N= 1,427,989) found that unprocessed meat consumption was associated with a 9% higher incidence (95% CI 1.06, 1.12; n=12 studies) of IHD, and processed meat was associated with an 18% higher risk (95% CI, 1.12 to 1.25; n=10 studies).[119] In this same analysis, poultry consumption was unrelated to IHD risk.[119] This underscores the benefit of plant-based diets that avoid both red and processed meat.

Those with obesity are more likely to develop CVD.[120–122] For those at higher genetic risk for obesity, a plant-based dietary pattern has been shown to significantly attenuate the risks of CVD. A large prospective study (N= 121,799) published in 2021[123] found that those with this genetic predisposition may be more responsive to the benefits of a healthy plant-based eating pattern and that healthy plant-based dietary patterns can attenuate their genetic risk for obesity and CVD comorbidities.[123] Researchers saw a 26% decreased risk for myocardial infarction (HR 0.74 [0.60, 0.91]).123 This confirms an earlier study showing a 25% reduced risk of ischemic heart disease among participants using a vegetarian diet (RR 0.75, 95% CI 0.68 to 0.82).[124] The modified risk factors included controlling blood pressure and HDL cholesterol levels.[123]

Plant-Based Interventions

Intervention studies find that plant-based diets are effective in improving all cardiometabolic markers, such as in an intensive, 10-day health promotion program (n=16) that significantly reduced body weight, body mass index, triglyceride, total cholesterol, low-density lipoprotein cholesterol, blood glucose, and the homeostasis model assessment of insulin resistance.[125] The Lyon Diet Heart Study, a randomized, single-blind trial, demonstrated that a Mediterranean-type diet rich in omega-three fats, fruits, and vegetables may reduce the rate of recurrence after an initial myocardial infarction and that the protective effects of the diet are maintained up to four years after the first infarction.[126] A multicenter randomized controlled GEICO study

corroborates these results, demonstrating that a low-fat, plant-based diet yielded significant improvements in health metrics, including plasma lipids and weight.[127] These simple nutrition interventions in widely divergent regions demonstrate that dietary changes towards a plant-predominant pattern yield cardio-protective results.[126,127]

Dietary intakes can also modify TMAO. An increase in d3-TMAO generation was observed in omnivores over vegans/vegetarians (>20-fold; P = 0.001) following oral d3-L-carnitine ingestion, whereas fasting endogenous plasma L-carnitine and γBB levels were similar in the vegans/vegetarians (n = 32) versus omnivores (n = 40).[53] In humans, dietary L-carnitine is converted into the atherosclerosis- and thrombosis-promoting metabolite TMAO via two sequential gut microbiota-dependent transformations: (a) initial rapid generation of the atherogenic intermediate γBB, followed by (b) transformation into TMA via low-abundance microbiota in omnivores and, to a markedly lower extent, in vegans/vegetarians. Gut microbiota γBB→TMA/TMAO transformation is induced by omnivorous dietary patterns and chronic L-carnitine exposure.[53]

Plant-Based Benefits for Comorbidities with CVD

Hypertension

Hypertension is a leading risk factor for heart failure and stroke. Though first-line therapies for all stages of hypertension include weight loss and exercise, studies show that a plant-based diet is the more effective intervention. This has been demonstrated since the late 1930s with Dr. Walter Kempner's rice diet, which demonstrated normalization of blood pressure with a high complex carbohydrate diet,[128] and the Dietary Approaches to Stop Hypertension (DASH) controlled feeding study, which reduced both systolic and diastolic blood pressure by 5.5 mmHg and 3.0 mmHg, respectively, in their intervention group.[129] The diet high in fruits and vegetables but otherwise similar to the control diet also lowered blood pressure but not to the same extent as the DASH diet. However, other studies have shown that the specific components of the DASH diet, fruits, vegetables, whole grains, and nuts, were each associated with decreased blood pressure.[11,27,82,83,85,130] A prospective cohort study of N=4,109 nonsmokers (n=3423 non-vegetarians and n=686 vegetarians) demonstrated that vegetarian diets may protect against hypertension beyond lower abdominal obesity, inflammation, and insulin resistance.[131]

Studies show that the nutritional and lifestyle factors that determine the lipid profile in populations suggest that the known age-dependent rise of atherogenic plasma lipoproteins is partly preventable.[132] Individuals diagnosed with congestive heart failure (CHF) have a 50% five-year mortality rate,[133] and approximately 650,000 new cases of CHF are diagnosed annually. Low-fat, plant-based diets have been shown to improve plasma lipid concentrations, reduce blood pressure, and lead to the regression of atherosclerotic lesions compared to progression of lesions on a usual care control group diet.[107] However, a scarcity of data exists with regard to plant-based diets in the treatment of CHF.[134] In one study where three patients consumed a plant-based diet for an average of ~79 days, follow-up cardiac magnetic resonance images revealed significant improvements in angina, shortness of breath and fatigue: 92% increase in ejection fraction [mean ± standard deviation for all data] (22.0 ± 6.9% vs 42.2 ± 18.4%), 21% reduction in left ventricular mass (214 ± 90 g vs 170 ± 102 g), 62% increase in stroke volume (55.8 ± 24.3 cc vs 90.3 ± 30.6 cc) and 17% increase in cardiac output (3.6 ± 1.2 L/min vs 4.2 ± 1.6 L/min).[134]

Diabetes

Although the Framingham cohort study first established diabetes as a major risk factor for CVD,[135] the American Heart Association now considers this risk factor to be controllable. Adults with diabetes are more likely to die from heart disease than from diabetes itself.[136] Cardiologists should be prepared for this common comorbidity and be involved in the diabetes care of their patients. Though diabetes care was traditionally in the purview of primary care physicians and/or endocrinologists, the two diseases mandate a multidisciplinary approach[137] that lifestyle medicine is well-positioned to address.[138] Expertise in type 2 diabetes (T2D) care may fall under a cardiovascular specialist with or without endocrinology specialist care.

Plant-based diets have demonstrated effectiveness in controlling blood sugar and insulin sensitivity, thus ameliorating T2D, as they help control excess body weight through dietary fiber intake and decreased saturated fat. Dietary fiber regulates and controls macronutrients, particularly glucose,and supports a healthy gut lining to avoid inflammation and toxins leaking into the blood. Further, animal protein and fat have been linked to insulin resistance and higher incidence of T2D.[139–141] More information on the benefits of plant-based diets for T2D can be found in the paper on T2D in this series.

Hyperlipidemia

Diets high in saturated fat have been shown to increase LDL-C,[142] a known causal factor in atherosclerosis development, and CVD.[143] Apolipoprotein B, the main structural protein of LDL, is directly associated with CVD. Both apolipoprotein C-III and apolipoprotein B are lipoproteins that promote macrophage foam cell formation, which is the hallmark of the fatty streak phase of atherosclerosis. These deposits in the arterial wall initiate an inflammatory response.[144]

Mechanisms include a decrease in fat intake, particularly LDL particles, to lessen oxidation, which controls nitric oxide damage to fragile endothelial cells.[145–148] Inversely, plant-based diets may reduce reactive oxygen species (ROS), which induces aortic stiffness potentially progressing to heart failure.[149–151]

Obesity

Overweight and obesity is a leading risk factor and comorbidity of CVD.[152] Though mortality from heart disease substantially declined in the first decade of the 21st century due to medical therapies, obesity may be responsible for the tremendous rise in chronic disease rates, including cancer and diabetes, and a deceleration of CVD mortality since 2011.[153] Weight loss, even a modest amount (5% of body weight), has demonstrated risk reduction of CVD and comorbidities.[154,155] The paradox is that though weight loss decreases risk factors for CVD, there may be a protective effect of obesity resulting in an inverse correlation between body mass index (BMI) and mortality in certain groups of people, including those mildly overweight (class I), those with kidney disease, and the elderly.[156,157] Though cardiorespiratory fitness may be a better gauge of CVD risk than BMI, weight loss among overweight individuals can reduce physiologic and hemodynamic risk factors for CVD.[157]

Though traditional weight loss has relied on calorie restriction or surgical intervention, plant-based diets have the advantage of higher diet quality to improve overall health.[158] In control trials, vegan groups lose more weight than with more traditional therapeutic diets that reduce saturated fat and calories, indicating that the adoption of a low-fat vegan diet improves several aspects of macronutrient intake, provided that adequate attention is paid to micronutrient-rich foods shown to decrease the risk of heart disease.[159,160] More information on the benefits of plant-based diets for obesity can be found in the paper on obesity in this series.

Common Questions and Concerns

Will patients get enough protein, fat, and vitamin B12 to support cardiometabolic health?

A well-planned whole food, plant-based diet provides all nutrients needed for optimal health and healing for the general public and those with CVD,[164,165] with the potential exception of vitamins B12 and D.[165] For treatment of chronic disease, beneficial effects are dose-dependent, where patients experience benefits dependent on sufficiently dosed lifestyle changes.[164,166]

Is there a risk to the consumption of all meat, or just red and processed meat?

Red and processed meat have been linked to cardiovascular disease in multiple studies.[167,168] Some studies show a dose-dependent relationship between animal food consumption and cardiovascular disease and mortality.[169] Yet others show no associations between unprocessed meat and poultry intake and CVD or mortality.[167] A 2020 prospective cohort study found that processed meat, unprocessed red meat, or poultry were significantly associated with incident cardiovascular disease, though fish intake was not.[170] Many studies have suggested that CVD can be effectively treated and,

in some cases, the progression halted by lowering saturated fat, cholesterol, and animal protein, and incorporating nutrients from a plant-based diet.[117,124,125,171–174] Plant-based diets are associated with lower risk and incidence of CVD, [117,145,164,174] for instance, in the European Prospective Investigation into Cancer and Nutrition-Oxford study, vegans had the lowest prevalence of hypertension.[175]

Will patients be willing to make this significant change to their diet?

Research indicates that better adherence to a plant-based diet is associated with lower risk for CVD and better treatment results.[117,164] As their most trusted authority, healthcare practitioners can successfully guide their patients to implement this behavior change. It may need to be a collaborative effort;[176] it can take a village. For instance, a group may consist of a team made up of the primary care physician, nutritionist, nurse/nurse practitioner, and wellness coach, along with support group meetings or group sessions.[177] Behavior change techniques have been shown to aid in compliance, such as discovering the behavior change determinants of the patient to access at what stage of change the patient is presently at to ensure their ability to make goals for themselves. Using motivational interviewing can be a useful tool for the practitioner to convey empathy through reflective listening and to recognize resistance.[176,178,179] Inclusion of the patient's family, support group, or confidant is helpful.[180,181]

Will patients adhere to a plant-based diet?

Caring, empathetic practitioners increase the likelihood of patient adherence to their recommendations.[176,179] Knowing the patient's concerns, beliefs, cultural context, and attitudes are important to their adherence.[176] Research shows that adherence to any diet depends on the same measures, including the patient's motivation.[132] Further, practitioners who demonstrate healthy lifestyle habits themselves have the most success in helping their patients to adopt healthier habits.[182] Incorporating counseling, motivational interviewing and collaboration can inspire behavior change.[176,183] The POUNDS LOST study demonstrated that weight loss was contingent on adherence and that fiber exerted the most considerable influence on adherence.[184,185] A safe and healthy plant-based dietary treatment that induces weight loss will lower CVD risk.[186] In a randomized crossover trial of adults (N=62) with high BMI (30 kg/m^2 to 37 kg/m^2), adherence was high to both diets.[163]

Early Studies and Case Studies Highlighting a Path Toward Halting CVD Disease Progression

Esselstyn Patient Cohort

Dr. Caldwell Esselstyn, physician at the Cleveland Clinic, had demonstrated the arrest of coronary artery disease (CAD) in both a small study (N=19),[89] as well as a more recent case series following N=198 consecutive patients.[93] All participants were intensively counseled in plant-based nutrition and instructed to consume minimal to no amounts of nuts and seeds, avocado, and nut butters, and avoid all refined foods, added sugars, and animal foods. The results demonstrated that a strict low-fat (<10%) plant-based diet can lower serum cholesterol to <150 mg/dl to stabilize severe CVD.[88] Most of the volunteer patients with CVD responded to intensive counseling, and those who sustained plant-based nutrition for a mean of 3.7 years experienced a much lower rate of subsequent cardiac events than the nonadherent patients. This dietary approach to treatment provides proof of concept that a low-fat, plant-based diet can, on its own, produce meaningful symptom improvement in patients and deserves a wider test to see if adherence can be sustained in broader populations.[92]

Lifestyle Heart Trial

In the Lifestyle Heart Trial, a prospective, randomized, controlled trial to determine whether comprehensive lifestyle changes affect coronary atherosclerosis after one year, n=28 patients were assigned to an experimental group (low-fat vegetarian diet, smoking cessation, stress management training, and moderate exercise), and n=20 to a usual-care control group.[173] A total of 195 coronary artery lesions were analyzed by quantitative coronary angiography. The average

percentage diameter of stenosis regression was from 40.0 (SD 16.9)% to 37.8 (16.5)% in the experimental group yet progressed from 42.7 (15.5)% to 46.1 (18.5)% in the control group.[173] When only lesions greater than 50% stenosed were analyzed, the average percentage diameter stenosis regressed from 61.1 (8.8)% to 55.8 (11.0)% in the experimental group and progressed from 61.7 (9.5)% to 64.4 (16.3)% in the control group.[173] Overall, angiographic findings in the experimental group following a comprehensive lifestyle program found regression in 82% and less progression of angiographic stenosis compared to a control group following usual care after only one year,without the use of lipid-lowering drugs.[173]

Patients in the experimental group sustained a weight loss of 5.8 kg (12.8 lbs) at 5 years; weight in the control group did not change significantly from baseline.[173] LDL levels were decreased at 5 years by 20% below baseline in the experimental group and 19.3% in the control group. HDL levels and blood pressure did not differ between the 2 groups.[173] Reported frequency of angina at 5 years decreased 72% in the experimental group and 36% in the control group perhaps by changing platelet endothelial interactions, vasomotor tone, or other dynamic characteristics of stenoses.[173] Cardiac events occurred significantly more frequently in the control group compared with the experimental group during the 5-year follow-up (risk ratio for any event for the control group=2.47, 95% CI 1.48-4.20).[173]

The LDL reductions seen at 5 years are comparable to those achieved with lipid-lowering drugs in an ambulatory population. The study was relatively small, though provided a promising proof-of-concept path forward to halting the natural progression of coronary atherosclerosis and reducing cardiac symptoms and events.[173]

CVD and Plant-Based Diets: A Summary of Key Randomized Trials, Systematic Reviews, and Meta-Analyses Studies

Beyond the work on diet and disease treatment, we explored the growing body of research examining the role of plant-based diets on the prevention of various forms of cardiovascular disease and extracted data from our strongest studies, the details of which are in Appendix Table 1 below. Of the 13 studies reviewed, four were randomized controlled trials,[127,162,187,188] and nine were a mix of systematic reviews and/or meta-analyses.[124,174,189–195] Multiple studies examined the effect of plant-based diets on risk factors like anthropometric measurements and blood lipids,[127,162,187,188,190–192,194] while other studies examined the effects of plant-based diets on cardio- and cerebrovascular disease incidence and mortality.[124,174,189,193,195]

Many studies examining plant-based diets and anthropometric and blood measurements showed a beneficial effect of plant-based diets. Mishra et al. found that an 18-week low-fat vegan diet intervention significantly improved BMI and cholesterol markers compared to the control group.[127] Macknin et al. found that both children and their parents had reductions in weight and blood risk markers for cardiovascular disease after four weeks on a low-fat, plant-based (PB) diet.[162] The plant-based diet also outperformed the American Heart Association's dietary recommendations in terms of blood markers and weight loss. Shah et al. confirmed these findings, showing superior improvements to CVD risk profiles in those assigned a PB dietary intervention.[188] The CARDIVEG study showed similar weight and blood lipids reductions between Mediterranean and vegetarian diets, though vegetarian diets showed a more drastic drop in LDL-cholesterol.[187] In meta-analyses, findings of reduced weight and blood lipids were mostly confirmed, except for in Lopez et al., where beneficial effects of PB diets were only found in blood pressure reduction in individuals with >130 mmHg systolic blood pressure at baseline.[194]

As Aggarwal et al. found in their 2018 systematic review, weight management is pivotal among lifestyle modifications in managing heart failure.[196] A cross-sectional study corroborates this and suggests that a plant-based diet is a more important intervention.[118] Several studies show that those on plant-based diets significantly lower systolic and diastolic blood pressure and significantly lower odds of hypertension (0.37 and 0.57, respectively) compared to non-vegetarians, which was achieved with the use of fewer antihypertensive medications and with a lower blood pressure reading.[131,197–202]

For studies examining incidence and mortality from various forms of CVD, there seems to be consistency in risk reduction for IHD but conflict in results involving other forms of CVD. Kwok et al. found significant reduction in risk for IHD in vegetarians, but this was primarily observed in Adventist Health Cohorts.[189] Dinu et al. confirmed these results, finding a significant risk reduction of IHD and a non-significant risk reduction for cerebrovascular disease in vegetarians.[124] A systematic review on heart failure presented suggestive evidence that risk of heart failure was decreased in vegetarian populations in multiple cohort studies.[174] Another study by Glenn et al. found no reduction in risk with vegetarian diets and stroke but a significant risk reduction in coronary heart disease incidence and mortality.

The Complete Health Improvement Program (CHIP), which centers on a whole food, plant-based eating pattern, has demonstrated rapid and meaningful reductions in chronic disease risk factors using lifestyle intervention centering on a plant-based diet. A total of 1003 people (aged 56.3 ± 12.1 years, 68% female) participated in one of 27 CHIP interventions throughout Canada between 2005 and 2011. Significant overall reductions (P<0.001) were recorded in the participants' BMI (-3.1%), systolic blood pressure (-7.3%), diastolic blood pressure (-4.3%), total cholesterol (-11.3%), low-density lipoprotein cholesterol ([LDL-C] -12.9%), triglycerides (-8.2%), and fasting blood sugar (-7.0%). Participants with the highest classifications of these markers at program entry experienced approximately 20% reductions in these measures in 30 days.203 Encouragingly, protective effects from plant-based diets may mitigate genetic susceptibility to CVD from obesity.

Conclusion

Modern cardiology has had significant success in managing the acute and potentially fatal presentations of CVD, but efforts have been unsuccessful in halting the disease, addressing potential methods to halt CVD progression, and managing a worldwide epidemic.[88] Nutritional and other lifestyle medicine methods applied in an intensive or interventional manner similar to other CVD treatments with a focus on prescription of a plant-predominant diet would benefit patients as part of a comprehensive treatment plan for individual and population health.[203]

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APPENDIX 1 Cardiovascular Disease and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Heianza, 2021[123] **Prospective Cohort Study** UK Biobank study Study population: White, British participants in the UK Biobank Study complete and plausible dietary data (at least one web-based 24-h dietary assessment) and outcome information based on the hospital records and the death registry Exclusions: • History of CVD (myocardial infarction, or stroke), cancer, diabetes, doctor-diagnosed high BP • Antihypertensive medication use • British, not of white ethnicity
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N= 121,799 By quartiles of healthy plant-based diet index: Age (mean, SD) / BMI (mean, SD) 53.8 (8.1) / 26.9 (4.3) 55.1 (8.0) / 26.3 (4.1) 55.6 (7.8) / 26.0 (4.1) 56.0 (7.6) / 25.5 (3.9)

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposure of interest: Interactions between genetic predisposition to obesity and CVD events and quartiles of a healthful plant-based diet index (Previous dietary exposure groups) 1. Healthful plant-based diet 2. Overall plant-based diet 3. Unhealthy plant-based diet Genetic Risk Score (GRS) for obesity—genetic predisposition to obesity previously calculated in the primary analysis of European-descent individuals Covariates: age, sex, and the top five principal components of ancestry, college, education history, the Townsend Deprivation Index, smoking habit, total energy intake, multivitamin supplement use, alcohol intake, physical activity, sleep duration, and TV watching hours
Outcome(s) of interest and units	Hypertension and subsequent CVD events Incidence of CVD was indicated as a composite endpoint of MI or stroke "Incidence of MI and stroke were based on UK Biobank's algorithms that used inpatient hospital and death registry data linked to the study."
Key Results (Bold qualitative assessment followed by quantitative results)	There were significant interactions between GRS and healthful plant-based diets. Among individuals with a higher GRS, higher adherence to a healthful plant-based diet was associated with: • Lower levels of BMI (P-interaction <0.0001) • Lower mean arterial blood pressure (P-interaction = 0.02) • Lower probability for untreated high blood pressure (P-interaction = 0.0036) • Lower risk of developing CVD or MI **(i.e., those in tertile 3 vs. tertile 1 of healthful plant-based diet index) (HR 0.66 [95% CI: 0.52, 0.83] for CVD; HR 0.54 [0.39, 0.74] for MI)**
Comments: Significance to clinical application	For those with genetic susceptibility towards obesity, adherence to healthy plant-based dietary patterns may significantly attenuate risks of CVD.

First author, year, study design (bold), name of study (if applicable), sample population	Glenn, 2019[193] **Systematic Review and Meta-Analysis** n = 7 prospective cohort studies of 1 or more years follow-up Adventist Mortality Study, the Heidelberg Study, the Adventist Health Study-2 (men), the Adventist Health Study-2 (women), and EPIC-Oxford, Oxford Vegetarian Study, Health Food Shoppers
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 197,737 participants across 7 studies Age and BMI not reported (age ranged from 10-89) Duration: Studies were included with follow-up > 1 year
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian dietary pattern compared to researcher- included non-vegetarian dietary patterns
Outcome(s) of interest and units	• Cardiovascular disease (CVD) mortality • Coronary Heart Disease (CHD) mortality • Stroke mortality • CVD incidence • CHD incidence and stroke incidence

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Comparison of vegetarian diet groups to non-vegetarian diet groups yielded mixed results. There was no significant reduction in risk of CVD or stroke mortality associated with vegetarian diet, though vegetarian diet was significantly associated with a reduced risk of CHD mortality and incidence.** When compared with non-vegetarian dietary patterns, no significant association was found between vegetarian diet and CVD (RR 0.92; 95% CI 0.84, 1.02) with no evidence of heterogeneity. There was a significant protective effect of vegetarian dietary pattern with CHD mortality (RR 0.78; 95% CI 0.69, 0.88) with no suggestive evidence of heterogeneity (p = 0.07). There was no evidence of a significant protective effect of vegetarian diet on stroke mortality (RR 0.92; 95% CI 0.77, 1.10) with no evidence of heterogeneity. There was a significant protective effect of vegetarian diet on CHD incidence (RR 0.72; 95% CI 0.61, 0.85). For CHD mortality, removing results from the Adventist Mortality Study, the Heidelberg Study, the Adventist Health Study-2 (men), the Adventist Health Study-2 (women), and EPIC-Oxford introduced significant heterogeneity.
Comments: Significance to clinical application	This meta-analysis found reduced risk of CHD incidence and mortality in vegetarian diet groups, but not in CVD or stroke incidence and mortality. These findings suggest that vegetarian diets or increases in plant consumption should be recommended for reducing incidence and mortality from CHD. "The overall certainty of the evidence was graded as 'very low' for all outcomes, owing to downgrades for indirectness and imprecision."

First author, year, study design (bold), name of study (if applicable), sample population	Lopez, 2019[194] **Meta-Analysis** n = 11 RCTS
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 983 participants Age = 44.2 (22.8) years Overall BMI not reported Duration: 3–28 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan diet compared with any less restrictive diet, including: Lacto-Ovo-Vegetarian, American Heart Association, American Diabetes Association Guidelines, 3 types of omnivorous diet, DASH-typ, weight-adjusted, portion-controlled, and unsupervised diet
Outcome(s) of interest and units	• Pre- and post-intervention systolic and diastolic blood pressure
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegan diets were not significantly associated with systolic or diastolic blood pressure reduction in the overall analysis. However, in individuals with high blood pressure at baseline, statistically significant reductions in systolic and diastolic blood pressure were observed with vegan diet compared to control.** Compared with less-restrictive diets, vegan diets did not significantly reduce systolic or diastolic blood pressure (systolic: -1.33 mmHG; 95% CI -3.50-0.84; diastolic: -1.21 mmHG; 95% CI -3.06-0.65), with no evidence of heterogeneity in systolic blood pressure findings, but significant evidence of heterogeneity with diastolic blood pressure findings. In a priori specified sensitivity analysis of participants with starting systolic blood pressure >= 130 mmHG, vegan diet reduced systolic (-4.10 mmHG; 95% CI -8.14, -0.06) and diastolic (-4.01 mmHg; 95% CI -5.97, -2.05 mmHg).
Comments: Significance to clinical application	In a meta-analysis of randomized controlled trials examining the effects of vegan diet on blood pressure, significant reductions in blood pressure were only observed in a subgroup analysis of individuals with high blood pressure at baseline. This could be due to the fact that these individuals could have unhealthy lifestyle, and changing their dietary habits would likely yield larger effects on blood pressure reduction than in a healthy population. Therefore, this study suggests that a vegan diet intervention could be useful in managing blood pressure in individuals with high blood pressure.

First author, year, study design (bold), name of study (if applicable), sample population	Benatar, 2018[192] **Meta-Analysis** n = 40 publicly-funded cross-sectional studies on individuals who were vegan for >1 year, and did not have any comorbidities included: Adventist Health Study 2 EPIC-Oxford studies MJ Health database study

Appendix continued

Study/analysis groups, mean age, mean BMI (SD), total N, duration	Vegans n = 12,619 Non-vegans n = 179,630 Overall BMI and Age not reported (>18 years)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan Diet (followed for at least 6 months) vs omnivorous diet
Outcome(s) of interest and units	• BMI • Waist circumference (WC) • Blood pressure • Triglycerides • LDL cholesterol • Fasting glucose • Insulin resistance • Place of study: Asian studies had differential effects compared to non-Asian studies
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegan diet was associated with a more favorable cardio- metabolic profile compared to an omnivorous diet;** **Vegans had lower BMI, waist circumference, LDL, triglyceride, fasting glucose, SBP, and DBP compared to controls.** In Asian study populations, there was no difference between vegans and controls in BMI or WC. In non-Asian study populations, vegans had a lower BMI (1.92 kg/m^2; 95% CI -2.52 to -1.32) and waist circumference (-4.93 cm; 95% CI -7.70 to -2.16). Blood glucose MD= -0.23 mmol/L (95% CI -0.35 to -0.10), LDL-cholesterol MD= -0.49 mmol/L (95% CI -0.62 to -0.36) for vegans compared to controls. No statistically significant difference in Asian studies; in non-Asians, LDL was 0.60 mmol/L (95% CI -0.74 to -0.47) Triglycerides MD=-0.14 mmol/L (95% CI -0.24, -0.05), though in studies from Asia, vegans had higher triglycerides than the control group (+0.15 mmol/L; 95% CI 0.02, 0.28) Blood Pressure No difference in blood pressure between vegans and controls in Asian populations. In non-Asian populations, MD in SBP= -5.87mmHg (95% CI -9.19 to -2.56) and DBP= -3.19mmHg (95% CI -5.90 to -0.48)
Comments: Significance to clinical application	This meta-analysis shows that those following a vegan diet in non-Asian study populations tend to have improved CVD risk profiles compared to those following non-vegan diets. However, there is heterogeneity of effect of vegan vs non-vegan diet on CVD risk factors. This may be because various dietary patterns followed in Asia may be much closer to vegan or vegetarian compared to western patterns.
First author, year, study design (bold), name of study (if applicable), sample population	Sanches Machado d'Almeida, 2018[174] **Systematic Review** n = 14 studies on dietary patterns and prevention of heart failure
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 188470 across 14 studies; n=5 RCTs, n=7 cohort, and n=2 cross-sectional Age and BMI not reported (age range 57–83 yrs) Duration of RCTs and cohorts ranged from 1–21 yrs
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Mediterranean, DASH, Paleolithic, and vegetarian diets
Outcome(s) of interest and units	• Heart failure (HF) development and mortality • Outcome-free survival
Key Results (Bold qualitative assessment followed by quantitative results)	**"The Mediterranean and DASH diets showed a protective effect on the incidence of HF and/or worsening of cardiac function parameters."**
Comments: Significance to clinical application	This systematic review suggests moderately conflicting evidence as to the effects of various plant-based diets and heart disease. However, it also shows that multiple high-quality studies have found associations between increased Mediterranean and DASH diet adherence and reduced incidence of HF and mortality. These plant-based diets should be considered as potential lifestyle measures for the prevention of heart failure in at-risk populations.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Shah, 2018[188] **Randomized Controlled Trial** n = 100 participants with coronary artery disease			
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Vegan Diet n = 50 Age = 63.0 (57.0-68.0)	American Heart Association (AHA) Diet n = 50 Age = 59.5 (53.0-67.0)	Baseline BMI not reported for any groups Duration: 8 weeks	
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	AHA diet vs vegan diet, along with nutritional counseling, recipe books, and grocery deliveries that adhered to dietary interventions were delivered on a weekly basis. Covariates: age, race, baseline waist circumference, diabetes, and prior myocardial infarction (MI)			
Outcome(s) of interest and units	• Primary endpoints: high sensitivity C-reactive protein (hsCRP) concentration • Secondary endpoints: white blood cell count and cell types, white blood cell cellular adhesion molecules, other markers of neutrophil activity, and urine F2-isoprostane/creatinine ratio, anthropometric data (body mass index, waist circumference), glycemic markers, lipid profiles, and quality of life as measured by the EuroQol 5 Dimensions Questionnaire			
Key Results (Bold qualitative assessment followed by quantitative results)	**8-week vegan diet intervention was more successful than AHA recommendations in reducing hsCRP concentration. In addition, both diets produced significant weight loss, with no significant differences in lipid profiles, blood cell counts, and quality of life.** Vegan diet resulted in a significant 33% lower hsCRP concentration after adjustment for age, race, baseline waist circumference, presence of diabetes mellitus, and prior MI (beta estimate = 0.67; 95% CI 0.47, 0.94). Degree of weight loss was not statistically different between the two groups. Both groups resulted in significant weight loss within their intervention group (measured as BMI and WC). There were no significant differences in fasting glucose, HbA1c, or insulin concentrations between groups. Vegan diet resulted in a nonsignificant 12% reduction in LDL cholesterol compared to AHA diet after adjustment for baseline LDL. Blood cell markers showed no statistically significant difference between the two groups.			
Comments: Significance to clinical application	Vegan diet was successful in reducing concentrations of hsCRP in a short-term randomized controlled trial. HsCRP is closely associated with cardiovascular disease, with previous research showing that reductions in hsCRP can lead to reductions in cardiovascular events. Prudent vegan diets, therefore, could be used as a lifestyle tool to manage risk profiles of cardiovascular disease among CAD patients. Vegan diet or AHA diet may be beneficial for weight loss, glycemic control, and improvement in blood lipids.			

First author, year, study design (bold), name of study (if applicable), sample population	Sofi, 2018[187] **Randomized Controlled Trial** CARDIVEG study Overweight omnivores with low-to-moderate cardiovascular risk recruited in Florence, Italy			
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Overall n = 118 Age = 50 (21-75) BMI = 30.6 (4.9)	Vegetarian diet n = 60 Age = 49.5 (24-70) BMI = 30.1 (4.7)	Mediterranean diet n = 58 Age = 52 (21-75) BMI = 31.1 (5.1)	Duration 3 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet vs Mediterranean diet			
Outcome(s) of interest and units	• Primary outcomes were differences in changes in body weight, BMI, fat mass from baseline • Secondary outcomes were differences in changes in all of the circulating cardiovascular risk parameters from baseline, including lipid profile, glycemic profile, oxidative stress profile, and inflammatory profile			

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian and Mediterranean diets (MD) were equally effective in weight reduction at 3 months, showing no significant difference in treatment effect between groups. In addition, reductions in oxidative stress were observed in both groups equally, reducing cardiovascular risk profile. In contrast, vegetarian diet significantly reduced LDL cholesterol compared to MD, and MD significantly reduced triglyceride compared to vegetarian.** Primary outcomes Both dietary interventions resulted in significant body weight reductions (vegetarian: -1.88 kg; 95% CI -2.42, -1.35; Mediterranean: -1.77kg; 95% CI -2.29, -1.25), naturally resulting in BMI reductions, as well (vegetarian: –0.64 kg/m^2; 95% CI, –0.84 to –0.43 and Mediterranean: 0.67 kg/m^2; 95% CI, –0.86 to –0.47). Both diets produced significant fat mass reductions (vegetarian: -1.23 kg; 95% CI -1.67, -0.80; Mediterranean: -1.46 kg; 95% CI -1.93, -1.01). Secondary outcomes Those in the vegetarian diet arm experienced decreases in LDL cholesterol, no changes in triglycerides, decreases in uric acid, and vitamin B12, while the Mediterranean diet group saw no changes in LDL, but decreases in triglycerides (LDL cholesterol: 9.10 mg/dL; P=0.01; triglycerides: 12.70 mg/dL; P<0.01; vitamin B12: 32.32 pg/mL; P<0.01; and uric acid levels: 0.22 mg/dL; P<0.01). No differences in oxidative stress were observed between the two groups. Vegetarian diet resulted in a reduced level of leukocyte-derived reactive oxygen species level (-8.42%).
Comments: Significance to clinical application	This 3 month dietary intervention showed that vegetarian and Mediterranean dietary interventions were equally effective in reducing weight, BMI, and fat mass. In addition, each diet differentially effected inflammatory profile but had similar effects on oxidative stress. These findings suggest that the adoption of a plant-based diet can improve the risk profiles of those at high risk of cardiovascular events. Vegetarian and Mediterranean diets are useful lifestyle tools that should be used for the improvement of cardiovascular risk profiles.

First author, year, study design (bold), name of study (if applicable), sample population	Dinu, 2017[124] **Systematic Review and Meta-Analysis** n = 86 cross-sectional and 10 prospective cohort studies examining the association between plant-based diets (vegetarian, vegan), all-cause mortality, heart disease incidence and mortality, and cancer incidence and mortality (total, colorectal, breast, prostate, and lung)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Cross-Sectional Studies n = 249,049 Prospective Cohort Studies n = 72,298 vegetarians >=18 yrs
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures Vegan or vegetarian diet compared to reference omnivore diet
Outcome(s) of interest and units	Vegetarians • "Incidence and mortality from cardio- and cerebrovascular diseases" • "Risk factors for chronic degenerative diseases (body mass index, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood glucose)"
Key Results (Bold qualitative assessment followed by quantitative results)	Vegetarians had significantly lower risk of combined incidence or mortality of ischemic heart disease (IHD) (RR = 0.75; 95% CI 0.68, 0.82). Vegetarian diet was not significantly associated with reduced risks of cerebrovascular disease incidence or mortality (RR = 0.93; 95% CI 0.78, 1.10) and cardiovascular disease incidence or mortality (RR = 0.93; 95% CI 0.86-1.00). Cross-sectional studies: Vegetarian diet was significantly associated with lower BMI (-1.49), serum total cholesterol (-28.16 mg/dL), LDL-cholesterol (-21.27 mg/dL), HDL-cholesterol (-2.72 mg/dL), serum triglycerides (-11.39 mg/dL), and blood glucose levels (-5.08 mg/dL) compared to omnivores. Vegan diet had significantly lower BMI (-1.72), serum total cholesterol (-31.02 mg/dL), LDL-cholesterol (-22.87 mg/dL), and blood glucose levels (-6.38 mg/dL), but nonsignificant lower HDL-cholesterol and triglycerides compared to omnivores.
Comments: Significance to clinical application	This study shows that vegetarian diet is associated with significantly reduced risk of IHD incidence or mortality but not significantly associated with cerebrovascular disease or CVD disease risk compared to omnivorous diet. These findings suggest that the effects of vegetarian diet may be specific to IHD, though it would be interesting to see the differentiated effects of vegetarian diet on risk of incidence and mortality.

First author, year, study design (bold), name of study (if applicable), sample population	Li, 2017[190] **Systematic Review and Meta-Analysis** n = 112 randomized controlled trials 3 or more weeks in duration comparing the effects of replacing animal protein with plant protein.
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 5774 across 112 trials Age = 54 Overall BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Plant protein vs. animal protein consumption "Of 112 trials, 94 used soy as the sole plant protein intervention, and 74 used dairy as the sole animal protein intervention. Other plant protein sources included various pulses, nuts, barley, and seeds; other animal protein sources included meat, fatty fish, and eggs."
Outcome(s) of interest and units	• LDL-Cholesterol (LDL-C) • Non-HDL-Cholesterol (Non-HDL-C) • Apo-B
Key Results (Bold qualitative assessment followed by quantitative results)	Substitution of plant-based protein for animal-based protein resulted in reductions in LDL-C, non-HDL-C, and Apo-B. Mean difference (MD); 95%CI LDL-C= -0.16 mmol/L; 95% CI -0.20, -0.12 with evidence of substantial heterogeneity Non-HDL-C= -0.18 mmol/L; 95% CI -0.22, -0.01 Apo-B= -0.05 g/L; 95% CI -0.06, -0.03
Comments: Significance to clinical application	This study shows that short-term substitution of animal protein with plant protein has resulted in reductions in markers of cardiovascular disease risk, specifically with blood lipids and Apo-B. Though there was significant heterogeneity in studies examined, there appears to be an overall trend of improving CVD risk profiles with plant food consumption.

First author, year, study design (bold), name of study (if applicable), sample population	Yokoyama, 2017[191] **Systematic Review and Meta-Analysis** n = 30 observational studies and 19 clinical trials on plant-based diets (of 4 or more weeks) and plasma lipids
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 1484 Age = 48.6 years Overall BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet (meat less than once per month), semivegetarian diet (meat more than once per month but less than once per week), vegan diet (no animal products), and lacto-ovo/pescatarian diets
Outcome(s) of interest and units	• LDL-C • HDL-C • Total cholesterol (TC) • Triglycerides
Key Results (Bold qualitative assessment followed by quantitative results)	**Plant-based diets are associated with lower total LDL and HDL cholesterol but not with triglyceride concentrations.** Vegetarian diets on plasma lipids Vegan diet was associated with lower mean concentrations of TC (-29.2 mg/dL; 95%CI, -34.6, -23.8) LDL-C (-22.9 mg/dL; 95%CI, -27.9, -17.9); HDL-C (-3.6 mg/dL; 95%CI, -4.7, -2.5); and nonsignificant decrease in triglycerides (-6.5 mg/dL; 95%CI, -14.0, 1.1) compared with individuals following omnivorous diets. In clinical trials, consumption of vegetarian diets was associated with a mean reduction in TC (-12.5 mg/dL; 95%CI, -17.8, -7.2); LDL-C (-12.2 mg/dL; 95%CI, -17.7, -6.7); and HDL-C (-3.4 mg/dL; 95%CI, -4.3, -2.5) and a nonsignificant increase in triglyceride concentration (5.8 mg/dL; 95%CI, -0.9, 12.6).
Comments: Significance to clinical application	Overall, this study found that vegetarian and vegan diets were primarily associated with lower mean concentrations of TC, LDL-C, and HDL-C in observational studies and experimental studies; this association was not observed for triglycerides. These findings suggest that vegans and vegetarians may have better cardiovascular risk profiles compared to omnivorous individuals, though causation can only be inferred from the clinical trials, as many of the observational studies in this meta-analysis were cross-sectional.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Macknin, 2015[162] **Randomized Controlled Trial** n = 30 children-parent pairs with a last recorded BMI > 95th percentile and child cholesterol > 169 mg/dL			
Study/analysis groups, mean age, mean BMI (SD), total N, duration	<u>Children + Plant-Based (PB)</u> n = 14 Age = 15.0 (9-18) BMI percentile = 96.36 (2.63)	<u>Children + American Heart Association Diet (AHA)</u> n = 14 Age = 15.0 (9-18) BMI = 98.01 (1.81)	<u>Parents + PB</u> n = 14 Age = 46.5 (37.0, 61.0) BMI = 33.26 (7.69)	<u>Parents + AHA</u> n = 14 Age = 46.0 (36.0, 51.0) BMI = 37.08 (12.66) <u>Duration:</u> 4 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	PB diet: complete avoidance of all animal products, no added fat from oils or margarine, and limited intake of nuts, seeds, and avocado AHA dietary recommendations: allowed 30% calories from fat, < 7% of calories from saturated fat, < 300 mg of cholesterol daily, and < 1500 mg of sodium daily <u>Covariates:</u> age, sex, baseline values			
Outcome(s) of interest and units	• "The biomarkers of inflammation were myeloperoxidase [MPO] and high sensitivity C-reactive protein (hsCRP), IL-6, ALT, and AST." • "CVD risk biomarkers were total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), HgbA1c, fasting glucose and insulin." • Additional measures included height, weight, mid-arm circumference, waist circumference, and blood pressure			
Key Results (Bold qualitative assessment followed by quantitative results)	**Both PB and AHA children's groups saw significant decreases in multiple CVD risk measures, suggesting both diets were effective. Children in the PB group saw greater decreases in weight, cholesterol, LDL, and BMI-z score, while in the adult arm of the study, the PB group saw greater decreases in BMI, weight, and LDL-C.** <u>PB children group</u> BMI Z-score (−0.14), systolic blood pressure (−6.43 mm Hg), weight (−3.05 kg), mid-arm circumference (−2.02 cm), total cholesterol (−22.5 mg/dL), LDL (−13.14 mg/dL), hsCRP (−2.09 mg/L), MPO (−75.34 pmol/L), and insulin (−5.42 uU/ml); all p<0.05 <u>AHA children group</u> Weight (−1.55 kg), waist circumference (−2.96 cm), mid-arm circumference (−1.14 cm), high density lipoprotein (−2.93 mg/dL), and MPO (−69.23 pmol/L); all p<0.05 Both groups had statistically significant increases in HbA1c (PB +0.17%, AHA +0.21%). <u>PB adult group</u> BMI (−1.29kg/m^2), systolic blood pressure (−7.96mm Hg), weight (−3.64kg), mid-arm circumference (−1.32cm), total cholesterol (−33.79mg/dL), HDL (−8.14mg/dL), LDL (−27.0mg/dL), and Hgb A1C (−0.16%); all p<0.05 <u>AHA adult group</u> BMI (−0.73kg/m^2), weight (−2.01kg), and HDL (−4.93mg/dL), AST (+4.43 U/L); all p<0.05 Significant between group differences: PB group had significantly lower BMI Z-scores and hsCRP levels. Parents in the PB group had significantly lower total cholesterol, LDL, and HbA1C than parents in the AHA group.			
Comments: Significance to clinical application	This study suggests that PB diet and AHA diet are useful tools for reductions in CVD risk profiles, at least in the short term. PB diet may have been more successful because of the reduction of percent of calories from fat, thereby reducing the amount of calorie-dense food being consumed, thereby reducing calories consumed.			

First author, year, study design (bold), name of study (if applicable), sample population	Kwok, 2014[127,189] **Systematic Review and Meta-Analysis** Adventist Health Study, Adventist Health Study II, Adventist Netherlands, EPIC-Oxford Study, German Vegetarian Study, Health Food Shoppers Study, Japanese Zen Priest Study, Oxford Vegetarian Study n = 8 prospective cohort studies of vegetarian diet vs non-vegetarian controls or general population
Study/analysis groups, mean age, mean BMI (SD), total N, duration	<u>Study and participant characteristics:</u> n = 183,321 participants across 8 studies; 6 prospective and 2 unclear on whether prospective or retrospective 1 study left out of analyses because of high risk of bias Age ranged from 25 to 100; BMI not reported

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian, non-meat eaters or other groups (priests, monks, Seventh Day Adventist, etc.) which are non-meat eaters vs. non-vegetarians of the same community or general population Covariates: all adjusted for age and sex, but other important cofounders varied
Outcome(s) of interest and units	• Mortality (7 studies) • Ischemic Heart Disease (IHD) or cardiac event (7 studies) • Cerebrovascular disease (6 studies)
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diet was associated with decreased risk of IHD in both Seventh Day Adventist (SDA) and non-SDA populations. SDA studies showed a greater degree of heterogeneity than non-SDA studies. In gender-specific analysis, vegetarian diet was associated with reduced risk of mortality and IHD in men but not women.** Relative risks (95% CI) are comparing vegetarians to non-vegetarians <u>SDA Studies</u> • Death: RR 0.68 (0.45-1.02) • IHD: RR 0.60 (0.43-0.83) • Cerebrovascular disease: RR 0.71 (0.41-1.20) <u>Non-SDA Studies</u> • Death: RR 1.04 (0.98-1.10) • IHD: RR 0.84 (0.74-0.96) • Cerebrovascular disease: RR 1.05 (0.89-1.24) <u>Pooled Relative Risks for all studies</u> • Death: RR 0.87 (0.68-1.11) • IHD: RR 0.71 (0.57-0.87) • Cerebrovascular disease: RR 0.93 (0.70-1.23)
Comments: Significance to clinical application	This meta-analysis shows that a vegetarian diet may lead to a significant reduction in risk of ischemic heart disease. However, non- SDA populations showed a much more modest effect of vegetarian diet than SDA populations. There was a high degree of heterogeneity, especially in SDA studies.

First author, year, study design (bold), name of study (if applicable), sample population	Mishra, 2013[127] **Cluster Randomized Controlled Trial** n = 291 participants > 18 years and with BMI >= 25 kg/m^2 and/or previous diagnosis of T2D; employees of GEICO from 10 different work sites across the US		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	<u>Intervention</u> n = 142 Age = 44.3 (15.3) BMI = 34.7	<u>Control</u> n = 149 Age = 46.1 (13.6) BMI = 35.3	<u>Duration</u> 18 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Intervention group was asked to follow a low-fat vegan diet consisting of whole grains, legumes, fruits, and vegetables with no restriction on energy intake. Animal products were to be avoided, minimize oils for a target of <3g fat per serving, and favor low GI foods. They also received weekly nutrition education and cooking demonstrations. The control group underwent no dietary changes or education. <u>Covariates:</u> gender, cluster, medication changes, and baseline values		
Outcome(s) of interest and units	• Change in weight, BMI, total cholesterol, LDL and HDL cholesterol, total:HDL cholesterol ratio, triglycerides, systolic blood pressure, diastolic blood pressure, HbA1c		
Key Results (Bold qualitative assessment followed by quantitative results)	**The low-fat vegan intervention group saw significant improvements in risk factors for cardiovascular disease (CVD) after 18 weeks of intervention compared to the control group (no diet changes). Significant improvements remained after adjustment for gender, cluster, medication change, and baseline value.** Compared to the control group, the low-fat vegan intervention group experienced statistically significant improvements in weight (-4.3 kg; 95% CI -5.5 to -3.1), BMI (-1.6 kg; 95% CI -2.0 to -1.1), total cholesterol (-12.6 mg/dL; 95% CI -20.9 to -4.9), LDL cholesterol (-11.1 mg/dL; 95% CI -17.2 to -5.1), HDL cholesterol (-4.1 mg/dL; -6.1 to -1.6), HbA1c (-0.7%; 95% CI -1.2 to -0.3), and an increase in triglycerides (14.1 mg/dL; 95% CI 1.3 to 27).		
Comments: Significance to clinical application	A low fat vegan diet was effective in reducing measures of CVD risk in a short-term intervention among corporate employees. Even those who did not complete the study in the intervention group showed some benefit from temporarily following the intervention. These findings suggest that low-fat, whole food, plant-based dietary interventions may be successful in managing risk factors for CVD.		

MD=mean difference

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CHRONIC KIDNEY DISEASE

Key Points for Practitioners

- Whole food, plant-based diets offer two advantages for prevention and treatment of CKD. First, higher consumption of plant foods are protective against the disease; second, lower consumption of animal and higher protein foods reduce renal burden.[25]
- Animal foods do not contain fiber. Fiber aids in creating and maintaining a healthy microbiome to address toxins, as well as producing anti-inflammatory compounds and reducing the production of uremic toxins. Fiber also controls potassium absorption to avoid hyperkalemia, and those who need to restrict potassium content can focus on low-potassium plant foods, such as such as apples, berries, cabbage cauliflower, eggplant, and yellow squash.[2,26–28]
- Plant-based diets are the key to controlling acid load to keep metabolic acidosis in check and thus slow progression of kidney disease.[25,26]
- Plant-based diets, rich in fruits, vegetables, dietary fiber, and potassium, are associated with lower risk of kidney stone formation versus animal-based diets.[27]
- Unrefined plant food intake lowers risk of hyperphosphatemia, as phosphorous is bound to plant phytates.[20]
- Marked improvements in all markers of CKD (albuminuria, metabolic acidosis, hyperphosphatemia, hypertension, glycemic control) have been documented in patients following a whole food, plant-based diet.[28]
- Specific dietary components are associated with specific benefits for CKD (see Table 1).
- Adherence and satisfaction with plant-based diets among elderly patients appear to be equivalent to more conventional lower-protein diets.[29]
- Whole food, plant-based diets are associated with other health benefits such as cardiometabolic health, healthy weight, and longevity.[1]
- Existing evidence on plant-based diets and CKD can be communicated to patients to support their ability to make informed decisions about their diet and course of treatment.[1]
- If patients express interest in trying a whole food, plant-based diet of some kind, it is helpful to share ACLM patient-facing resources and tools for practical guidance on plant-based eating.

ABSTRACT | Dietary patterns focusing on whole plant-based foods may be pivotal in managing chronic kidney disease (CKD). Predominantly plant-based diets may delay progression and help to control common chronic conditions that are often associated with CKD, including type 2 diabetes, cardiovascular disease, hypertension, obesity, and kidney stones, improving multiple comorbidities simultaneously.[1] Provided that potassium levels are monitored, plant-based diets pose minimal to no risk for CKD patients and may delay or avoid the need for dialysis.[2–4]

Consuming plant protein over animal protein treats and prevents CKD,[5] and the fiber in plant foods allows for a shift away from the production of uremic toxins and other nitrogenous wastes. The lower protein level of a plant-based diet has favorable effects on secondary hyperparathyroidism,[6] peripheral insulin resistance,[7] hyperlipidemia,[8] hypertension, and acid-base disorders.[9] Plant anions may mitigate

metabolic acidosis to slow CKD progression. Plant phosphorus has a bioavailability of less than 50% as compared to animal phosphorus, and phosphorous is identified as a burden on the kidneys and may worsen renal osteodystrophy and hyperparathyroidism.[10] Both the reduction of phosphate in the diet, as well as its source (animal- versus plant-derived) appear to be important.[5]

For those with CKD, goals can center on slowing the progression of kidney failure, minimizing uremic toxicity, diminishing proteinuria, and lowering the risk of complications, including cardiovascular disease, bone disease, and blood pressure control.[11] A plant-based diet naturally lower in protein has been shown to help accomplish all of these treatment goals.[5]

Chronic Kidney Disease in Context

Chronic Kidney Disease (CKD) describes the gradual loss of renal function: filtering wastes, toxins, and excess fluids from blood to be excreted in the urine. Electrolytes and wastes accumulate until kidney function is significantly impaired, often with few symptoms in the early stages of the disease.[12,13]

As one of the top ten leading causes of premature death,[14] CKD affects more than one in seven American adults (15%) or 37 million people. Most (90%) individuals with CKD do not know that they have it.[15] Diabetes and high blood pressure are common comorbidities and the leading causes of end-stage renal disease (ESRD), which is also associated with increased all-cause mortality.[16] Other risk factors include obesity, older age, glomerulonephritis (a disease that damages the kidney's filtering units), inherited diseases such as polycystic kidney disease, malformations at birth, lupus or other immune diseases, and obstructions such as kidney stones or an enlarged prostate, as well as repeated urinary tract infections.[17]

Treatment of chronic renal failure can be challenging since individuals may not feel ill or present symptoms until advanced stages.[18] Comorbidities may be recognized and treated first without consideration of renal risk, and though recommendations to follow a healthy diet may be offered to keep CKD from worsening, there is much confusion over what constitutes a healthy diet, even among practitioners. Low protein diets are recognized as beneficial, but adherence to conventional low protein dietary substitutes can be low due to palatability and cost. The Kidney Disease Outcomes Quality Initiative (KDOQI) nutrition guidelines were recently updated to "suggest that increased fruit and vegetable intake may decrease body weight, blood pressure, and net acid production" based on a grade 2C recommendation,[19] which aligns with the tenets of lifestyle medicine.

Benefits of Plant-Based Diets for Chronic Kidney Disease

Focusing on plant-based foods to improve diet quality for CKD patients while reducing total animal-based foods has been shown to improve kidney function.[2–4] These dietary improvements reduce the need for medications, reduce disease complications, decrease progression, and, thus, increase patient survival.[2,20] Observational data demonstrate an association between red and processed meat and an increased risk for CKD. One cross-sectional study (N=5,316) found that those with the highest plant protein intake demonstrated a 30% lower risk for CKD compared to those with the lowest. Conversely, the highest quartile of animal protein intake had a 37% higher risk for CKD.[21] In another study, a pattern of high intakes of whole grains, vegetables, fruits, and low-fat dairy foods was associated with a 20% lower urinary albumin-creatine ratio (the measure for protein loss in the urine indicating kidney malfunction).[22]

Whole food, plant-based diets have the dual advantages of supplying nutrients and antioxidants that support and potentially heal damaged kidneys and eliminate the processed and animal foods associated with greater risk for CKD.[23,24] For patients with CKD, focusing on dietary quality instead of traditional recommendations that focus on the quantity of nutrients consumed could revolutionize treatment from simply lessening the damage to healing, with few risks.[20]

Table 1 Potential beneficial effects of plant nutrients in patients with CKD[2]

Plant nutrients	Characteristics	Potential benefits
Proteins[35–38]	• Plant proteins have lower bioavailability than animal proteins • Plant-based diets can be low in protein • Plant proteins are rich in glycine and alanine	Favourable effects on glomerular haemodynamics and proteinuria
Carbohydrates[2,26,58–64]	• Plant-based diets are rich in fibre (non-absorbable carbohydrate polymers) and can be low in refined carbohydrates • Plant-based diets supply absorbable complex carbohydrates, such as starch, that are an important energy source	Increased stool viscosity, which promotes stoll motility and delays the absorption of potassium, glucose and free-fatty acids and so results in lower insulin release and higher fat oxidation, improving blood lipid levels and potentially enabling long-term weight loss
		Increased faecal bacterial mass and nitrogen excretion
		Favourable shift in gut bacteria from a proteolytic profile to a saccharolytic profile resulting in increased production of short-chain fatty acids and reduced production of uraemic toxins, bacterial translocation and inflammation
Fats[70,86,100]	• Plant-based diets are rich in essential monounsaturated and polyunsaturated fatty acids and low in saturated fatty acids	Improved blood lipid profile
		Reduction in body weight mainly due to reduced intake of saturated fat
		Anti-inflammatory, antioxidant and vasculoprotective properties
Anions and cations[107–109]	• Plant-based diets have a lower non-volatile acid load than animal-based diets	Improved control of metabolic acidosis
Phosphorus[29,54,115]	• Absorption of phosphate from plant sources is less efficient than from animal sources	Improved control of CKD-mineral bone disorders
Potassium[71,76,77]	• Potassium intake from plants contributes to promotion of alkalinity through the exchange of hydrogen ions in the distal part of the nephron	Improved control of metabolic acidosis
Sodium[46,80–82,105,106]	• Plant-based diets are generally low in sodium	Improved blood pressure control

Chronic Kidney Disease and Dietary Mechanisms

Several underlying mechanisms play a role in kidney dysfunction and CKD progression. This includes a decreased glomerular filtration rate (GFR), used to measure kidney function, which may be due to elevated dietary acid load, as the retention of acid is associated with downstream effects of kidney function.[30,31] Metabolic acidosis is a common complication of CKD resulting from the inability of the kidneys to excrete the daily dietary acid load. Metabolic acidosis increases the risks of hypertension,[32] heart failure,[33] muscle wasting,[34] bone loss, chronic inflammation, progression of renal failure, and death.[35]

High-protein diets may worsen kidney function in individuals with kidney disease from the body's demand to eliminate the excess waste products of protein metabolism. High-protein diets are also associated with higher urinary calcium excretion, increasing risk for kidney stone formation.[36] High-protein diets are associated with increased metabolic acidosis and oxidative stress, contributing to kidney damage.[37] Further, these diets will likely limit the bioactive compounds, including isoflavones and fiber, that control glycemic load and protect the kidneys.[38]

With respect to mortality, one study found a decreased risk of all-cause mortality in end-stage renal disease patients with higher plant-based diet pattern scores.[39] Two studies found benefits from low-protein, plant-based diets supplemented with ketoanalogues.[6,40] Improvements in serum phosphate and calcium levels were also noted, along with a reduction in parathyroid hormone levels.[40] Another study found a very low protein, vegan diet to be safe and effective in elderly patients with Stage 5 CKD in delaying the onset of dialysis.[41]

Protein Quality? Plant-Based vs. Animal Proteins

Some CKD patient guidelines emphasize protein from animal sources due to their "high value" to assure that essential amino acids are not limited, but this measurement is based on animal studies and considered outdated.[42] Plant-based proteins contain all essential amino acids and offer the benefits of the fiber and isoflavones present.[43] Dietary interventions can be particularly effective in controlling protein intake. For example, varying oral protein intake levels affect GFRs in subjects with healthy kidneys, and chronic excess protein consumption can inhibit function.[44–46] This was demonstrated decades ago in a study that administered a vegetarian soy-based diet, low in both fat and protein for two months resulting in highly significant decreases in total serum cholesterol (28%). The soy diet had other benefits, such as lowering LDL-cholesterol, apolipoprotein B, and urinary protein excretion, all reversed upon discontinuation of the diet.[47] No other treatment for kidney disease has been shown to lead to disease reversal by addressing the underlying development of disease.

Higher risk from animal proteins is likely due to the acidic quality of meat, and the creation of more metabolites in the gut and their effective excretion, particularly trimethylamine N-oxide (TMAO). TMAO is the byproduct of the breakdown of the amino acid carnitine in meat associated with an increased risk of heart disease.[48] High circulating levels of TMAO are linked with increased risk for chronic kidney disease and kidney fibrosis development. In addition, animal studies show that reducing TMAO results in improved CKD and cardiac hypertrophy.[49] Research suggests that the kidney becomes less efficient at eliminating TMAO with increased red meat intake, and, quite

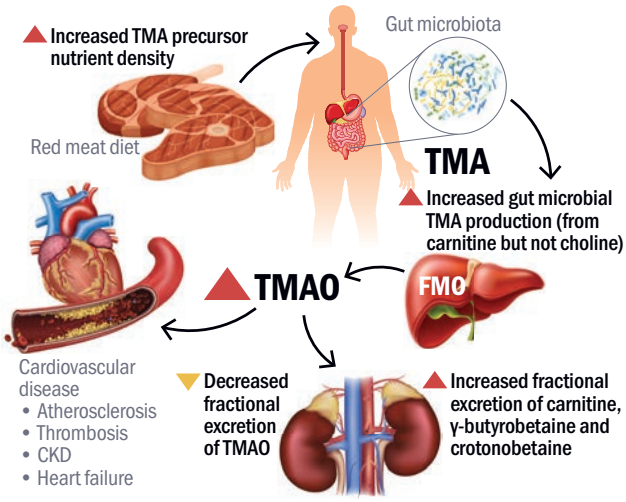

Figure 1 Effect of a red meat containing diet on the metaorganismal trimethylamine N-oxide pathway[48]

remarkably, discontinuation of red meat reduces plasma TMAO within 4 weeks.[48]

The primary source of acid production in the body can be traced to diet. Acid in the diet comes primarily from protein which releases sulfuric acid when metabolized. The Western diet favoring animal protein made of sulfur-based amino acids promotes an acidic environment in the body.[26,50] In contrast, plant foods are alkaline, which protects against dietary acid load. Plant-based proteins satisfy requirements for those with CKD and offer other inherent health benefits compared with animal-based proteins.[16,31,36,47,51,52] Research suggests that in people with decreased kidney function, substituting animal foods from the diet with plant protein sources is associated with a lower CKD risk.[24,53]

Hyperphosphataemia

Hyperphosphataemia is a condition of excess phosphorus levels in the blood, commonly caused by kidney failure. As increasing amounts of phosphorus are absorbed from red meat, dairy, chicken, and fish, phosphorus is filtered through the kidney, and levels in the blood rise.[54] Plant foods offer an advantage here because phosphorus is not as efficiently absorbed from plant sources compared to animal sources, thus decreasing the burden on the kidneys.[29]

Whole plant foods provide higher amounts of magnesium, an effective inhibitor of calcium oxalate growth (kidney stones),[55] whereas a high calcium

diet emphasizing dairy may inhibit magnesium absorption.[56,57] Plant foods also provide antioxidants to combat free radical damage, as well as the optimal ratios of essential fatty acids,[23,58] indicating that a diet full of whole plant foods offers protection against hyperphosphatemia, a concern for CKD patients.[20]

Toxins, the Microbiome, and Fiber, the Hidden Hero

Polysaccharides found in plant foods contain dietary fiber to decrease toxins and facilitate the excretion of nitrogen. Fiber increases fecal bacterial mass, as shown in a meta-analysis of 14 controlled trials.[59] This non-digestible polymer is consistently associated with lower blood lipid levels, total cholesterol, and body weight, all of which lower stress on the kidneys.[60,61] In observational studies, fiber was associated with a higher estimated glomerular filtration rate (eGFR), lower inflammation, and a lower CVD risk,[62–64] though similar outcomes are not necessarily observed for isolated fiber supplements.[65] Fiber intake increases intestinal motility as well as fecal excretion. It allows the gut microbiota to build numerous beneficial colonies of bacteria and reduce uremic toxin production. Despite evidence demonstrating the benefits of plant-based diets containing fiber, most CKD patients consume well below recommendations (25 g/day for women and 38 g/day for men[66]). Nutritional guidelines do not highlight the benefits of consuming foods with fiber, which include protecting the kidneys against dialysis.[67–70] In addition, whole plant-food treatment can lower production of uremic toxins.[25]

Gut microbiota breaks down and ferments animal protein, which produces toxins normally cleared by the kidneys. Excessive animal food in the diet of CKD patients leads to alteration of the colonic environment in microbial dysbiosis and disturbances in the intestinal mucosa barrier. This state enables bacteria and endotoxins to slip through the intestinal barrier, which in turn stimulates monocytes and leads to increased synthesis of inflammatory cytokines.[2]

Hyperkalemia

Although there is a concern about hyperkalemia in CKD patients, recent case studies indicate that lack of fiber from whole foods may be the ameliorating factor. Because fiber promotes stool quantity and frequency, it facilitates the excretion of potassium.[60,71,72] Restricting plant foods for these patients deprives them of their benefits.[73] Fruits and vegetables are naturally rich in potassium and readily absorbed by the proximal intestine, but absorption may be influenced by alkaline load and the fiber available to facilitate deposition and decrease transit time.[74] Feeding trials in healthy people suggest that potassium recovery from animal-based diets is about 80% and 50–60% from plant-based diets.[75,76] Hyperkalaemia is a concern because high potassium can rapidly cause arrhythmias without symptoms. Caution around potassium intake and monitoring is advisable. The lower availability of plant potassium may be advantageous to CKD patients without precipitating hyperkalemia;[77] however, close monitoring of all patients' potassium levels as they transition to a whole food, plant-based diet is essential to facilitate any medication adjustments that may be needed by the practitioner.

Kidney Stones

Though the oxalate content of plant foods has been a concern, observational studies indicate that vegetarians have a lower risk for kidney stones,[78,79] likely due to higher alkali and water levels and the reduced sodium within plant foods.[80–82] The inconsistency could also relate to the microbiome and the recently discovered role of *Oxalobacter formigenes* and other bacteria that require oxalate for survival which may reduce the amount of oxalate available for absorption and, ultimately, excretion in urine,[51,83] though more research in this area is needed.

Filtration

Animal-based protein induces hyperfiltration,[26,84–86] which temporarily overworks the kidneys, while an equivalent amount of plant protein does not induce the same stress. One study found that an animal protein-based diet led to hyperfiltration with increased GFR versus a plant-based protein diet in nonproteinuric patients with type I diabetes.[86,87] Conversely, one study found an increased risk of albuminuria with Western dietary patterns derived *a posteriori*. In the same analysis, the authors found a decreased risk of microalbuminuria in DASH-designated dietary patterns.[72] Hyperfiltration over the long-term is linked with irreversible damage of nephrons and development of progressive kidney disease as seen in diseases such as diabetes.[88]

Common Questions and Concerns

The need for low-protein, low potassium diets may indicate that plant-based diets are not ideal for patients with compromised kidney function.

Though plant foods generally contain more potassium than animal foods, the accompanying fiber decreases potassium absorption and helps to avoid hyperkalemia by facilitating the excretion of potassium.[60,71,72] Fruits and vegetables are naturally rich in potassium which is readily absorbable by the proximal intestine. However, absorption may be influenced by alkaline load. Since the metabolic breakdown of proteins increases acidity, meat and cheese have the highest potential for renal acid load, whereas fruits and vegetables have the lowest. Also, dietary recall may underestimate potassium consumption by failing to account for the cooking loss. Soaking, freezing, or boiling leads to a 60–90% potassium loss of several raw foods and introduces inaccuracy by not accounting for this differential bioavailability.[89,90] Sauces and juices lack fiber, which uniquely increases potassium consumption compared to whole food form. Plant foods with low potassium content, such as apples, berries, cabbage cauliflower, eggplant, and squash, are a good choice for those who need to restrict potassium. Other low-potassium plant foods include bread, noodles, and rice.[91,92]

What is the proper diet for those on dialysis?

There is a paucity of evidence evaluating the potential benefits of plant-based diets in patients undergoing dialysis. However, one recent study revealed that function of daily activities in hemodialysis patients on vegetarian diets was similar to that of non-vegetarians.[93] Two studies showed that soy consumption reduced inflammatory markers and lipoprotein (a) levels.[94,95] Though nutritional indicators such as BMI or muscle mass might be lower among dialysis patients, dialysis adequacy can be maintained with a plant-based diet, which has the advantage of higher nutritional value than traditional dietary recommendations.[93]

Traditionally, patients on dialysis are discouraged from adopting plant-based diets mainly due to two perceived risks: inadequate protein intake and hyperkalemia, yet general population studies show that the risk of nutritional deficiencies from plant-based diets is low. Even strict vegans meet the minimum requirements for protein.[96,98] Further, patients on dialysis on plant-based diets have also been reported to attain adequate protein intake (1.1–1.25 g/kg/day) without signs of undernutrition.[93,99] Though research of patients on dialysis adhering to plant-based diets is limited, the linoleic acid (omega-6 polyunsaturated fatty acid) level as a proportion of total plasma fatty acids was demonstrated to be inversely associated with markers of inflammation and risk of death.[100] Oils, meats, and eggs are rich sources of linoleic acid.[101] Low-fiber intake has also been associated with higher concentrations of inflammatory biomarkers.[102–104] All dialysis patients should supplement with B vitamins as these are water-soluble and readily lost with dialysis.

How concerning is the high phosphorous level in plant foods for those with compromised kidney function, and why?

Though phosphorous is in plant foods, it is not absorbed efficiently. Animal protein is the primary source of bioavailable phosphorus.[26] Phosphorous in plant foods is primarily bound to phytate, which is poorly absorbed since humans lack the enzyme phytase to break it down. Thus, a plant-based diet may be beneficial in reducing the phosphorus load on the body and improving vascularization.[26]

The benefit and workload comparison of the standard low-protein diet (such as the National Kidney Foundation's diet) is often recommended. Is it a plant-based diet?

The National Kidney Foundation states: "Eating more plant-based foods such as vegetables and grains in place of animal-based foods such as red meat may help prevent and slow the progression of chronic kidney disease, type 2 diabetes, high blood pressure, and heart disease."[105] On their website they recommend the DASH Diet (Dietary Approaches to Stop hypertension) or a Plant-Based Diet.[106]

Plant-based diets reduce the renal load on the kidneys, from the accompanying fiber, from avoidance of excess protein, and a reduced acid load. The kidneys regulate acid-base homeostasis, and acid-load is primarily modulated by diet.[2] A higher acid load accelerates kidney damage and eGFR

decline, whereas an alkaline diet reverses these processes.[107–109] Compared with animal-based diets, plant-based diets have a lower non-volatile acid load, as they are richer in organic anions than cations.

Additionally, the increased fiber intake found in plant foods allows the gut microbiota to generate more short-chain fatty acids, which are alkali. The alkali state reduces the generation of uremic toxins, which also contributes to the alkaline state.[110–114]

Summary of Key Studies

A selection of more high-quality studies relevant to plant-based diets and CKD outcomes is displayed in Appendix Table 1. Multiple studies demonstrate favorable associations and clinical markers for CKD between plant-based diets, naturally low in protein. The risk of kidney stones from uric acid crystallization decreases with vegetarian diets,[52] as does fibroblast growth factor-23 (FGF23). Both phosphorous excretion and accumulation show improvement,[115] as do glomerular filtration rate (eGFR), renal plasma flow (RPF),86 and albuminuria; thus, mortality rates are better as well, as summarized in Table 1, below.[39,41,65,72,116]

In the one study examining uric acid crystallization, the authors found that the risk of crystallization was reduced in those randomized to a vegetable protein diet (VPD).[52] Another study that examined fibro-blast growth factor-23 (FGF23) plasma levels demonstrated that a vegetarian dietary intervention decreased FGF23 levels. FGF23 is responsible for maintaining phosphorous homeostasis. A decrease in FGF23 indicated a decreased phosphorous load due to reduced absorption in vegetarian diets.[115]

Such findings are not new to the literature. A 1995 study on eGFR found that a vegetable protein dietary intervention in nonproteinuric type I diabetes patients led to decreased eGFR and renal blood flow, suggesting decreased renal load is associated with plant protein.[86] Considering that diabetic kidney disease is the most prevalent form of CKD and the leading cause of end-stage kidney disease, plant-based dietary interventions may be capable of largely reducing mortality rates.[14] In fact, a 2011 prospective cohort analysis of the Nurses' Health Study data found an increased risk of albuminuria from Western dietary patterns along with the decreased risk of microalbuminuria using the plant-predominant DASH dietary patterns.[72]

Though fiber has been demonstrated to be a critical factor in renal outcome by controlling waste products left to the kidneys to filter,[117] one study found no difference in the eGFR and albuminuria between randomized groups taking a soluble fiber supplement and those without supplementation.[65] This may indicate that many of the benefits of fiber intake likely come from intact fiber found in whole plant food itself and not from isolated fiber in supplemental form.[65]

With respect to mortality, more than one study found a decreased risk of all-cause mortality in end-stage renal disease patients with higher plant-based diet pattern scores, as well as a significant association between plant-based diets and slower renal function decline.[39,116] Another study saw improvements in serum phosphate and calcium levels while reducing parathyroid hormone levels on a plant-based diet supplemented with ketoanalogues.[40] Finally, another found equivalent survival with a low-protein, plant-based diet intervention compared to dialysis treatment in senior CKD patients.[41] As Table 1 describes, the literature indicates that plant foods with intact fiber have an irreplaceable role in overcoming CKD, its comorbidities, and the risk for mortality.

Promising Results—Examples of Disease Reversal

Though research on interventions that produce remission is still emerging, the following examples are promising and support the value of incorporating a dietary intervention even when other treatments are also used.

Reversal of CKD in an Elderly Man with Multiple Comorbidities

A recent case study demonstrates the ability of a strict whole food, plant-based diet to restore health for a 69-year-old male with type 2 diabetes, hypertension, and stage 3 CKD.[29] His history included class 2 obesity, hypertension, hyperlipidemia, and type 2 diabetes, requiring approximately 210 total insulin units daily (140 units insulin glargine and ~20–25 units insulin lispro) and three meals daily. After comprehensive counseling, being provided a food guide, and switching to a whole food, plant-based diet

without calorie or portion restriction or mandated exercise, the patient rapidly reduced his insulin requirements by >50% and subsequently experienced improvements in weight. He was taken off carvedilol, hydrochlorothiazide, amlodipine, and sitagliptin within the first two months due to blood pressure, blood glucose, and cholesterol improvements. His estimated eGFR increased from 45 to 74 mL/min after 4.5 months post-dietary transition. His pravastatin dose was cut in half, and microalbumin/creatinine ratio decreased from 414.3 to 26.8 mg/g. Phosphorus level returned to the normal range. See Table 2 for the food guide provided by his physician.[29]

Table 2 Food guide provided to treat 69-year-old male with type 2 diabetes, hypertension, hyperphosphataemia, and stage 3 CKD[29]

'Allowed' foods	• Non- starchy vegetables • Starchy vegetables (potatoes and beans) • Whole grains, including whole grain flours • Fresh fruit (not dried, no juices or smoothies) • All spices • Ground flaxseed and chia seed • Water, non-dairy plant-'milks', tea
Foods to avoid	• Meat (including fish and poultry) • Dairy foods • Added pure fats (all oils, butter, margarine) • Eggs • Vegan 'replacement' foods—fake meats, fake cheeses • Refined flours • Predominantly 'added sugar' foods (candy, snack/energy bars, cookies, cakes, pastries) • Soda, fruit juice, sports drinks, energy drinks, blended coffee and tea drinks
Foods to enjoy sparingly	• Unsalted, raw or dry roasted nuts, natural nut butters • Avocadoes • Coconut • Seeds • Dried fruit • Added sweeteners (maple syrup, fruit juice concentrate, added sugars) • Coffee, alcohol • Refined soy protein and wheat protein (tofu, seitan)

Multiple Conditions Controlled by the Creeping Polypharmacy

This case details a 57-year-old woman with essential hypertension, obesity, type 2 diabetes, hyperlipidemia, and CKD, a set of comorbidities that is not uncommon in the US. She presented with a GFR between 31 and 35 mL/min conferring a kidney disease classification of G3bA3 (moderately to severely decreased renal function with severely increased albuminuria). Her conditions required multiple medications to control, and the need for polypharmacy continued to increase. This patient was motivated to include more whole grains, fruits, vegetables, and legumes into her diet and reduce her consumption of processed foods, refined grains, added sugars and salts, and animal products. After three months, her blood work showed improvement in metabolic acidosis, proteinuria, and hyperphosphatemia without an increase in serum potassium levels. She was not only able to avoid additional medications but reduced her existing medication burden, including calcium acetate (phosphorous binder), amlodipine (antihypertensive), and sodium bicarbonate (reduce metabolic acidosis). This patient's dietary change directly resulted in improved kidney function, improved quality of life, and reduced risk of mortality.[1]

Appropriate Protein Consumption for the Elderly

A plant-based dietary approach with its high nutritional value and lower protein values may resolve issues of compliance with restrictive "traditional" low-protein diets in elderly patients with kidney disease. Though protein restriction may retard the need for renal replacement therapy, high protein intake is believed to contribute to preserving nutritional status in elderly patients or in patients with high comorbidity. Mediating between conflicting requirements can be a challenge, but Fois et al. detail a feasibility study (N=131) in which all patients attained the goal of appropriate protein reduction intake for advanced kidney disease using a stepwise approach to a high-nutrient diet.[118] The 131 patients [median age (range)= 74 (24–101)] had multiple comorbidities upon entering the study at an advanced kidney disease unit in Le Mans, France. Twenty-two (17%) chose to comply with

a plant-based diet and showed improvements in Charlston Comorbidity Index (CCI) and eGFR. All patients attained the goal of protein reduction intake of at least 0.2 g/kg/day in ≥ 3 months of follow-up, and note that each decrease of at least 0.2 g/kg/day of protein is associated with a reduction in the deterioration of kidney function. Good compliance was found in 74%, regardless of diets, indicating that treatment with low-protein, plant-based diets should not be a barrier to compliance. Even in a population with high comorbidity, a personalized approach to reduced protein intake is feasible, including with diabetic patients and in elderly individuals.[118]

Conclusion

Studies indicate that the benefits of plant-based diets can be applied to all populations to address kidney dysfunction, even in the elderly at advanced stages. Plant-based diets have been demonstrated to be safe and useful in preventing and treating all chronic diseases, including type 2 diabetes, obesity, hypertension, and hyperlipidemia, which are common comorbidities of CKD. The utility of plant-based diets for CKD has become increasingly apparent.[1,119–121]

The research discussed here has indicated a reduced risk of albuminuria, uric acid crystallization, stone formation, improved eGFR markers, and reduced acid and waste loads in individuals using lower-protein plant-based diets. Shifts towards plant-based proteins, reduced animal proteins, and reduced overall protein consumption show great promise for improving CKD outcomes, including halting renal function decline, reducing the need for dialysis, and ultimately saving lives. Though plant protein consumption is consistently associated with reduced renal load, more evidence is needed to demonstrate the long-term benefits of plant-based diets on individuals with CKD or end-stage renal disease.[2,65] Overall, existing evidence indicates that diets rich in fruits and vegetables can reduce the dietary acid load and offer an exciting approach to treating CKD by reducing kidney damage, slowing disease progression, and, most importantly, helping patients improve their quality of life.[91]

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APPENDIX 1 Kidney Disease and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Chewcharat, 2020[40] **Systematic Review and Meta-Analysis (crossover and parallel RCTs)** Adults predialysis CKD (stage 3–5) patients
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 1,459 participants across 17 studies Age range: 42–79 yrs BMI range: NR Follow-up of at least 3 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Restricted protein diet (RPD) plus ketoanalogues (KAs) to low-protein diet (LPD) (12 trials), 5 trials comparing RPD plus KAs to regular protein diet (5 trials). 9 of these 17 studies were quantitative (8RCTs + 1Non-RCT).
Outcome(s) of interest and units	Kidney-related endpoints including changes in: • eGFR • Proteinuria • BP • CKD-MBD • Nutritional parameters and other outcomes of interest

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**RPD with KA is associated with reductions in blood urea nitrogen (BUN), while improvements were found in eGFR and proteinuria.** **Low protein diet with KAs decreased serum phosphate and raised serum calcium, while decreasing levels of parathyroid hormone (PTH).** RPD w/ KA vs. RPD w/o KA: Reduction in BUN (blood urea nitrogen). WMD (weighted mean difference) = -22.01 mmol/L; 95% CI -42.42 to -1.60 6 study arms (n=338): Improvement in eGFR (WMD = 3.14 mL/min/ 1.73 m2, 95% CI 0.68-5.61, P =.013) 4 study arms (n=280) RPD w/ KA: Lowered proteinuria (WMD = -0.86 g/day, 95% CI -1.71 to -0.02, P=.046) 6 study arms (n=204) RPD w/KAs decreased serum phosphate (WMD =-0.68 mg/dL, 95% CI -1.02 to -0.33, P=.001) but also raised serum calcium (WMD =0.50 mg/dL, 95% CI 0.21-0.80, P=.001)
Comments: Significance to clinical application	This meta-analysis provides evidence that RPD supplemented with KAs can help slow the decline of kidney function, compared to regular diet or low protein diet alone. Multiple studies reported decreases in proteinuria, improvements in eGFR, decreased serum phosphate, and PTH levels. Plant-based diets can be used as a tool to achieve low-protein intake in conjunction with KA supplementation.

First author, year, study design (bold), name of study (if applicable), sample population	Carvalho, 2019[65] Systematic Review n = 7 studies totaling 161 patients, on dietary fiber diabetic kidney disease
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 161 patients across 7 studies Mean age = 58.3 (range 20-74) yrs Mean BMI = 29.4 _ 3.4 kg/m^2 Inclusion Criteria Clinical trials on patients with diabetes mellitus (types I or II) with at least one high fiber group in the intervention (supplemental or dietary pattern)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Minimum 4-week intervention comparing high fiber diet to low fiber or standard diet in patients with either type I or type II Diabetes Mellitus (DM) n = 4 vegetarian diet n = 2 fiber supplement n = 1 DASH diet "Mean fiber intake in the intervention was 24 g/day (range: 20–27 g/day) and 16 g/day (range: 14–20 g/day) in the control group."
Outcome(s) of interest and units	Markers of decline in Kidney function: • Albuminuria • Decline in eGFR
Key Results (Bold qualitative assessment followed by quantitative results)	**Plant-based dietary interventions show little evidence of reducing decline in markers of kidney function in short-term studies on patients with DM.** Vegetarian diet and type 2 DM (n = 2): No significant difference in eGFR or albuminuria for low-fat vegan diet or lactovegetarian diet compared to control diets Vegetarian diet and type 1 DM (n =2): eGRF and albuminuria were significantly lower for the intervention group, with a mean fiber intake of 0.2 g/kg/day Fiber supplement (n = 2): Two RCTs, no effects of supplementation on eGFR, with exposures of 10 g/day fiber supplementation (from guar gum and chicory inulin) DASH diet (n=1) and type 2DM: no differences in albuminuria with the diet containing 20 g/day
Comments: Significance to clinical application	Some studies have shown effects of vegetarian diet on type I DM-related kidney disease, as shown by reduced albuminuria and eGFR in intervention groups. However, fiber supplementation has shown little effect on kidney function in individuals with DM. Therefore, fiber supplementation in and of itself has no evidence for being a viable treatment for diabetic kidney disease.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Chen, 2016[116] **Cross-Sectional Study** NHANES III n = 14,866 adults (age >= 20, eGFR < 150ml/min/1.73m^2) with data on plant protein intake and mortality
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 14,866 Age = 44.8 (15.8) 52% female BMI = 26.55 (5.2) Duration: Average follow-up 8.4 years (2,163 deaths)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Ratio of plant protein: total protein Total plant protein intake Subjects stratified by eGFR < 60 mL/min/1.73 m2 Models adjusted for "demographics, smoking, alcohol use, comorbidity, BMI, calorie and total protein intake and physical inactivity"
Outcome(s) of interest and units	• All-cause mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**Increases in plant-protein consumption were inversely associated with all-cause mortality but only in the subgroup of < 60 mL/min/1.73 m^2.** 33% increase in plant protein consumption was associated with all-cause mortality in low eGFR subpopulation (HR, 0.77; 95% CI 0.61–0.96) Compared to the lowest quartile of plant protein ratio, the highest quartile had lower risk of mortality in the eGFR < 60 mL/min/1.73 m^2 subpopulation (HR, 0.67; 95% CI, 0.46-0.96).
Comments: Significance to clinical application	Increases in plant-protein consumption may be associated with a reduced risk of mortality in individuals with compromised renal function. However, more studies are needed to validate this finding. Switching to plant-based protein sources could be an effective part of an overall strategy to lower the risk of mortality.

First author, year, study design (bold), name of study (if applicable), sample population	Gutiérrez, 2014[39] **Observational Cohort** Reasons for Geographic Racial Differences in Stroke (REGARDS)—prospective cohort n = 3972 White and Black patients, greater than 45 years of age, with CKD
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 3972 (of 30,239 total cohort) Age = 69.05 54% with abdominal obesity Overall age and BMI not reported (reported by 5 diet patterns and 4 quartiles of each) Details: Participants from the REGARDS cohort, which oversamples Black individuals and those living in the southeastern United States, referred to as the "stroke belt" or "stroke buckle"; Participants limited to those with diagnosed CKD (GFR < 60 mL/min/1.73m2) or urine-albumin-creatine ratio of 30 mg/g Duration: Mean 6.5 years follow-up (816 deaths and 141 ESRD events were observed)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Covariates adjusted for in Cox Proportional Hazards model: "Age, gender, race, geographic region of residence, energy intake, lifestyle factors (self-reported frequency of exercise per week, current smoking), comorbidities (history of heart disease and hypertension), educational achievement (< vs. ≥ high school diploma), annual family income (< vs. ≥ $20,000/year), natural log-transformed urinary albumin to creatinine ratio, and estimated glomerular filtration rate" Primary exposure of interest was a posteriori empirically derived dietary pattern scores (from factor analysis of Block 98 FFQ), with 5 groups: "Convenience" (Chinese and Mexican foods, pizza, other mixed dishes), "Plant-Based" (fruits, vegetables), "Sweets/Fats" (sugary foods), "Southern" (fried foods, organ meats, sweetened beverages), and "Alcohol/Salads" (alcohol, green-leafy vegetables, salad dressing).
Outcome(s) of interest and units	• All-cause mortality • End-stage renal disease (ESRD)

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Higher plant-based diet score was associated with reduced risk of all-cause mortality. Southern patterns were associated with higher risk of all-cause mortality. There was no significant association between any dietary pattern and ESRD in models adjusted for anthropometric and lifestyle factors.** Highest quartile of plant-based diet score had a reduced risk of all-cause mortality (HR 0.74; 95% CI 0.61-0.97) in Q4 compared to Q1, while southern dietary pattern had increased risk of all-cause mortality (HR 1.51; 95% CI 1.19-1.92). No significant associations between any dietary patterns and ESRD in fully adjusted model.
Comments: Significance to clinical application	There is limited evidence to suggest benefit to ESRD with higher scores in empirically-derived dietary patterns, though reduced risk of all-cause mortality has been observed. More research is needed to determine if there are effects of plant-based diets on improving or reducing the decline of kidney function.

First author, year, study design (bold), name of study (if applicable), sample population	Lin, 2011[72] **Observational Cohort** Nurses' Health Study (NHS)—prospective cohort from 1976 onward Female participants who participated in sub-studies of both 1. analgesic use and kidney function and 2.T2D and kidney function; participants had dietary data every 4 years from 1984-1998, urinary albumin-creatine ratios (ACR) from year 2000, and plasma creatine for estimated glomerular filtration rate (eGFR) change between 1987 and 2000
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 3121 (of 121,700 total cohort) Median age = 62 Median BMI = 26.4 97.4% white Duration: Follow-up of 16 years (1984-2000)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Covariates Adjusted for in Logistic Regression Model Age, hypertension, body mass index, physical activity (metabolic equivalents per week), energy intake, cigarette smoking, diabetes, cardiovascular disease, and ACE-inhibitor/ARB medication use Primary exposure of interest 3 empirically derived (factor analysis) dietary patterns: "Prudent (higher intake of fruits, vegetables, legumes, fish, poultry, and whole grains), Western (higher intake of red and processed meats, saturated fats, and sweets), and Dietary Approach to Stop Hypertension (DASH)-style dietary patterns (greater intake of vegetables, fruits, and whole grains)"
Outcome(s) of interest and units	• Microalbuminuria (albumin-to-creatinine ratio 25 to 354 mcg/mg) in 2000 • eGFR decline of >30% between 1989 and 2000, and "rapid" eGFR decline
Key Results (Bold qualitative assessment followed by quantitative results)	**Western pattern was positively associated with microalbuminuria while DASH score was inversely associated with microalbuminuria in crude models but not fully-adjusted models (no association for prudent pattern). DASH dietary pattern showed negative association with eGFR decline, while Western dietary pattern showed positive association with rapid eGFR decline in fully-adjusted model.** Western diet score was associated with microalbuminuria in fully-adjusted model (OR 2.17; 95% CI 1.18-3.98 for 4th vs 1st quintile of Western diet score). DASH diet score was inversely associated with eGFR decline in fully-adjusted model (OR 0.55; 95% CI = 0.38-0.80 in Q4 vs. Q1), while Western diet was significantly associated with "rapid" eGFR decline (OR 1.77; 95% CI 1.03-3.03 in Q4 vs. Q1).
Comments: Significance to clinical application	Empirically derived western dietary patterns, characterized by high meat consumption and low fruit/vegetable consumption was associated with increased microalbuminuria and decline in eGFR, while DASH diet score, characterized by high consumption of plant-based foods, was inversely associated with a separate measure of eGFR decline. This study suggests that diets characterized by high consumption of plant foods may have protective effects in reducing the decline of renal function, though more research is needed for findings to be conclusive.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Moe, 2011[115] **Crossover Trial** n = 8 nephrology patients with advanced CKD (late stage 3 or stage 4)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 8 (50% female) Age = 61 (8.4) years BMI = 32 (5) kg/m^2 Details: Subjects from nephrology clinics >18 years of age "eGFR 20 to 45 ml/min by modified four-parameter Modification of Diet in Renal Disease Equation; urine protein/creatinine ratio < 5; blood pressure < 150/95 mmHg; not taking calcium binder or supplements, vitamin D, or phosphate binders; normal serum phosphorus and calcium corrected for albumin and intact parathyroid hormone (PTH) < 100 pg/ml; medically stable; and able to give informed consent and come for all visits." Duration: Subjects randomized to 7 day vegetarian diet (grain & soy protein) or meat diet (meat & dairy protein) with washout period of 2-4 weeks
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Meat vs. Vegetarian Diet Diets differ in source of protein (meat & dairy vs. grain & soy), but matched isocalorically and for macronutrient composition "The diets were designed to be isocaloric (2200 kcal), containing 1000 mg of calcium and 3000 mg of sodium per day. The protein and total phosphorus concentration were equivalent, with a target of 1200 mg/d of phosphorus and an initial goal of 20% protein" "A subject-level random intercept was specified to account for the within subject correlation from the repeated measures. Independent variables included period (period 1 or period 2) and dietary protein source (meat or vegetarian) as fixed effects."
Outcome(s) of interest and units	• Urinary phosphorous excretion (mg/24hr) • Plasma FGF23 (pg/mL) • *"creatinine, sodium, uric acid, citrate, ammonium, protein-to-creatinine ratio, and sulfate"*
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diet led to decreases in FGF23, phosphorous excretion, plasma phosphorous, serum calcium, and higher parathyroid hormone compared to the meat-based diet.** No significant differences in plasma calcium, creatinine clearance, urine 24-hour calcium excretion. Nonsignificant decrease in phosphorous excretion in vegetarian diets compared to meat diets (change of -316 vs. -253 mg/24 hr, p = 0.07) Statistically significant decrease in plasma phosphorous (p = 0.02) and plasma FGF23 (-23 vs. +29 pg/mL, p =0.008) for vegetarians compared to meat eaters "There was a significantly higher average serum phosphorus (3.6 versus 3.3 mg/dl, P < 0.0001), calcium (9.1 versus 8.8 mg/dl, P = 0.0001), and FePhosph (24 versus 18%, P = 0.0001) and lower PTH (44 versus 52 pg/ml, P = 0.0002) with the meat-based diet compared with the vegetarian diet."
Comments: Significance to clinical application	Isocaloric vegetarian diets with the same amount of protein compared to meat-containing diets may be a useful tool in maintaining phosphate homeostasis in CKD patients. In addition, vegetarian diets showed a decrease in FGF23, which is thought to be positively associated with mortality in CKD patients. Therefore, a vegetarian diet may be a useful tool in improving health outcomes or homeostasis in CKD patients.

First author, year, study design (bold), name of study (if applicable), sample population	Brunori, 2007[41] **Randomized Controlled Trial** n = 112 Italian uremic patients (non-diabetic), > 70 years old, and GFR between 5 and 7 mL/min
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 112 Age = 78.05 (5.35) BMI not reported Subjects randomized into dialysis group or supplemented very low protein diet (sVLPD) group Duration: Median follow up of 26.5 months; median sVLPD intervention of 10.7 months

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	sVLPD (n=56) "Vegan diet with a calorie intake of 35 kcal/kg of body weight (BW) per day and a protein intake of 0.3 g/kg of BW supplemented for every 5 kg of BW with 1 tablet containing 607 mg of a mixture of the 5 ketoanalogues of amino acids and 4 essential amino acids corresponding to 37 mg of nitrogen." Patients were trained by a skilled dietitian to follow this protocol. Dialysis (n=56) Hemodialysis (HD): n=7 Peritoneal dialysis (PD): n=48 Trained by dieticians to ingest a diet providing 35 kcal/kg/d and 1.2 g protein/kg/d
Outcome(s) of interest and units	• Mortality, hospitalization
Key Results (Bold qualitative assessment followed by quantitative results)	**This study found dialysis treatment to be statistically equivalent in terms of survival compared to diet intervention. In addition, secondary analysis found a slightly superior odds of survival in the diet group compared to dialysis group, even after adjustment for statistically different mean age in each group.** One-year survival rates in the dialysis and diet groups were 83.7% (95% CI 74.5-94.0) and 87.3% (95% CI 78.9-96.5) respectively, with a test for noninferiority of diet vs. dialysis providing $p < 0.001$ Log-logistic survival regression showed superior odds of survival on diet compared to dialysis (odds of survival 2.1; 95% CI 1.02-4.83).
Comments: Significance to clinical application	sVLPD with ketoanalogues was found to be noninferior to traditional dialysis treatment, showing slightly statistically significant improvements in survival in the diet group compared to dialysis, even after adjustment for unbalanced covariates (age and cerebral vasculopathy). Given protective effects of supplemental diet, dietary intervention should be considered as an additional protective factor against mortality for those with chronic kidney disease.

First author, year, study design (bold), name of study (if applicable), sample population	Siener, 2003[52] **Controlled Clinical Trial (CCT)** Total n = 10 healthy male volunteers
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 10 males Age = 28 years (range 21-32) Weight = 78.9 +/- 11.7 kg Height = 178.7 +/- 4.5 cm BMI = 24.71 kg/m^2 (calculated) Duration: 14 days on habitual, self-selected (meat-containing) diet while told to avoid high-purine foods (SD), then 5 days on each of 3 standardized diets: western diet (WD), omnivorous diet (OD), and vegetarian diet (VD)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	<u>WD</u> "Characteristic for a WD is a high energy, alcohol and protein content and a fluid intake with beverages of 1.5 l/d." <u>OD and VD</u> OD and VD diets were isoenergetic with the same amount of "main" nutrients, both with a lower purine content compared to the WD and with constant fluid intake of 2.5 l/d. Detail on specific foods not provided.
Outcome(s) of interest and units	• Risk of uric acid crystallization, as calculated by EQUIL2 software • Uric acid excretion • Urinary excretion of various minerals
Key Results (Bold qualitative assessment followed by quantitative results)	**Risk of uric acid crystallization was greatest when participants were on SD and WD with reduced risk in prudent OD and even greater reduced risk in VD.** Risk of uric acid crystallization decreased by 85% on OD and 93% on VD compared to SD and WD. VD experienced more basic urine pH, decreased excretion of ammonium, uric acid, sulfate, phosphate, creatinine, sodium, and chloride.
Comments: Significance to clinical application	Uric acid crystallization is associated with various medical problems including kidney stones. This study shows decreases in risk of uric acid crystallization with vegetarian diet.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Kontessis, 1995[86] **Crossover Trial** n = 9 normotensive, normoproteinuric Type I diabetes patients
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 9 (2 male, 7 female) Age = 32 (range 20-48) BMI = 23.8 (range 20.6-27.8) Inclusion criteria: Nonproteinuric type I diabetic patients on insulin, no antihypertensive treatment, type 1 diabetes onset before the age of 30, normal blood pressure Duration: Subjects randomized to 4 weeks on vegetable protein diet (VPD) or animal protein diet (APD), with 1 week washout period in between diets
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Two diets were isocaloric and had the same quantity of protein and ratio of polyunsaturated/saturated fats VPD consisted of entirely vegetable-based protein (0.95 g/kg body weight/d) with supplementation of animal fats to maintain the polyunsaturated/saturated fat ratio in the APD. Phosphate and calcium tablets were supplied to those in the VPD. APD consisted of 70% animal protein and 30% plant protein (1.1 g/kg body weight/d) to allow for sufficient carbohydrate and fiber intake.
Outcome(s) of interest and units	• Glomerular filtration rate (GFR, mL/min) and renal plasma flow (RPF, mL/min) • Renal vascular resistance (mmHG*min/mL) • Urinary albumin excretion (mg/24 hr) • Plasma levels of urea, creatinine, total protein, albumin, IgG, sodium, potassium, calcium, and phosphate • Urinary excretion of urea, creatinine, calcium, and phosphate.
Key Results (Bold qualitative assessment followed by quantitative results)	**GFR and RPF were lower in VPD compared to APD, with higher renal vascular resistance in VPD. VPD experienced lower urinary albumin excretion, but no differences were observed between APD and VPD in serum concentrations and urinary excretion of minerals and nutrients.** "GFR and RPF were significantly lower with the VPD than with the APD (GFR 89.9 ± 4.1 vs. 105.6 ± 5.1 ml • min"1 • 1.73 m"2, P < 0.05; RPF 425.7 ± 22.2 vs. 477.8 ± 32.2 ml • min"1 • 1.73 m"2, P < 0.05). Renal vascular resistance was higher with the VPD than with the APD (RVR 101 ± 25 vs. 91 ± 10 mmHg • min • ml"1, P < 0.05." "The urinary albumin excretion rate (median [range]) was lower with the VPD (17.1 [4.1-44.5] vs. 10.4 [1.2-22.5] mg/24 h, P < 0.01), and the fractional clearance of albumin (θalbumin) was significantly lower with the VPD (APD 3.4 ± 1.15 X 10-6; VPD 2.0 ± 0.65 X 10-6, P < 0.05)."
Comments: Significance to clinical application	Consumption of a VPD is associated with changes in GFR, RPF, and decreased albumin excretion suggesting lower renal load with vegetable protein consumption. Given the downsides associated with protein restriction, including muscle atrophy and fatigue, this study states that protein alteration rather than protein reduction should be explored for management of kidney conditions. This may be relevant for type 2 diabetes.

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ENTERAL NUTRITION

Key Points for Practitioners

- Plant-based enteral nutrition options offer a safe alternative to standard enteral formulas and may avoid GI intolerance such as bloating, diarrhea, and lack of fiber.[31]
- Nutrition rich in plant-based nutrients is associated with better health, lower inflammatory markers,[32] and a reduction in medications needed to treat medical conditions.[33] Plant-based nutrition may improve the health of the microbiome in ill patients[6] and, thus, may lessen GI symptoms and promote gut health.[3,13]
- One pathway through which plant-based formulas may improve outcomes is the alteration of gut microbiota.[3]
- Mounting evidence supports the benefits of a whole food, plant-based diet for utility in decreasing risk for autoimmune conditions and, in some cases, improving symptoms among those currently diagnosed; thus, enteral plant-based nutrition may promote improvement in the most critical patients.[32]
- Patients may better tolerate plant-based enteral formulas in regard to food sensitivities and GI symptoms,[21,31,34] which can lead to weight gain, feeling better, and improved calorie and nutrient intake.[35]
- Whole food, plant-based diets have minimal adverse side effects and are associated with other health benefits such as cardiometabolic health, healthy weight, and longevity.[2,3,18–20,36,37]
- Physicians, registered dieticians, and pharmacists wishing to prescribe plant-based enteral formulas may need to research the various formulas available to meet the specific needs of their patients. Evaluating the dietary quality to consider nutritional components and information can be done by visiting manufacturer websites and viewing features and specs, including energy counts, fatty acids, fiber, and protein sources. It is helpful to start with establishing caloric, protein, and nutritional needs for the patient.[27] More information on a variety of brands can be found at the American Society for Parenteral and Enteral Nutrition (ASPEN) at https://www.nutritioncare.org/.
- Further studies are warranted to determine the long-term benefits of plant-based enteral nutrition and offer evidence for this promising tool in medical nutrition.[3,31]
- If patients or family members express interest in using a plant-based enteral formula, it is helpful to share ACLM patient-facing resources and tools for practical guidance on plant-based eating.

ABSTRACT | Nutrition plays an essential role in disease prevention during recovery and recuperation of acute or chronic illness. During prolonged illness or hospitalization, one can nourish and maintain nutrition via enteral and parenteral routes. Several studies have demonstrated that using enteral delivery of nutrition whenever feasible helps to keep the integrity of the gut and gut microbiome intact.

Enteral feeding provides nutrition through the mouth or a feeding tube to the gastrointestinal tract (GI) to deliver nutrients and meet caloric requirements.[1] Enteral nutrition via feeding tube can serve as either the primary or supplemental feeding source in patients unable to eat via mouth due to injury (trauma), illness (cancer/radiation), or neurological challenges (e.g., after a stroke) who may be at a disadvantage in taking in necessary amounts of micro and macronutrients needed to nourish, recover, or heal.

In the intensive care unit (ICU), tube feeding intolerance is common and may account for the failure to thrive.[2] Standard enteral formulas are often poorly tolerated and could be lacking in vital phytonutrients depending on the feeds used. Most enteral formulas widely available and covered by insurances are highly processed, low in fiber, and high in added sugars or artificial sweeteners, which are associated with gastrointestinal (GI) intolerance and nutritional deficiencies. Dietary intake affects the body's ability to heal and function and supports the gut microbiota, which is dependent on dietary fiber for energy.

Plant-based enteral formulas have demonstrated improved clinical outcomes in both children and adults regarding adherence and gastrointestinal symptoms. This could be due to the added nutritional value from fruits and vegetables, with their higher fiber content and the avoidance of artificial ingredients, including high-glycemic sweeteners and oils.[3] Nutrients found in plant-based foods such as omega-3 fatty acids and antioxidants have been shown to ameliorate inflammation and decrease the length of stay in some critically ill patients. These nutrients are found in plant-based enteral formulas. Plant-based products formulated with non-allergenic foods and of higher dietary quality should be readily available as the first line of enteral care.

Enteral Nutrition in Context

According to a Nationwide Inpatient Survey (NIS), in 2017, patients received tube feeding in over 250,000 hospital stays, of which about 25% were for children and newborns. Enteral therapy can also be administered at home and in long-term care facilities, and over 400,000 patients received this therapy at home in 2017.[4] Though there is evidence of increasing use of enteral tube feeding around the world due to improved technology and government coverage,[5,6] the absence of solid food in the diet presents potential problems for some patients. Enteral formulas that lack dietary fiber, contain highly refined sugars, or both, could lead to gut microbiome imbalance and metabolic/organ dysfunction.[7,8] Most widely available commercial enteral formulas focus on adequate calories and protein and are fortified with added vitamins and minerals. Less attention is given to phytonutrients, fermentable fiber, and omega-3 fatty acids, which promote microbiome and gut health and aid in the digestion process.[9,10] Therefore, enteral formulas with organic, whole food, and plant-based ingredients that provide optimal nutrition with fewer risks should be readily available.[11] Most standard commercial enteral formulas contain emulsifiers which have been shown to worsen colitis in animal models[12] and generally have low fiber and high sugar content, which can affect GI health, including changes in protective microbiota.[13]

Benefits of Plant-Based Enteral Feeding

Nutrition plays an important role in our gut and gut microbiome health.[3] The gut microbiome modulates health and interacts bi-directionally with the brain through the gut-brain axis, modulating mood and stress.[3,14] Standard and widely available enteral formulas are low in fiber variety and amount[15] and often high in sugars or artificial sweeteners, all commonly associated with GI side effects. Plant-based diets have demonstrated the ability to heal the gut and deliver optimal nutrition.[16–20] A 2019 pilot study (n=12) reports that a higher fiber plant-based formula (7 g/12 oz) can improve gastrointestinal issues in chronically ill children, and temporal changes to an abundance of bacterial metabolites improved in most subjects.[3] Further, clinicians surveyed have supported the use of plant-based, organic, calorically dense peptide formulas (95%) and described these positive outcomes in their patients, as well.[21]

Presently, research on plant-based enteral formulas is limited. However, mounting evidence and data show encouraging benefits of plant-based formulas over standard enteral formulas. The breadth of evidence supporting whole food, plant-based diets as beneficial in disease prevention suggests that lower cancer rates (particularly gastrointestinal and hormonal), lower mortality rates, and better control

of inflammatory, renal and cardiovascular conditions can be achieved[22–26] if whole food, plant-based formulas could be translated to tube-fed patients over conventional artificial formulas.[3] More studies are needed to examine the impact of chronic disease reversal in patients on plant-based enteral nutrition.

Nutrient-rich plant-based foods are not readily accessible to those who must rely on enteral feedings; yet, these populations are most in need of high-quality nutrition.[27] Further, studies show clear clinical benefits of utilizing nutrition support for many compromised individuals who are unable to eat; these benefits include improved wound healing, reduction in complications and length of hospital stay, and lower mortality.[4] Individuals of all ages may benefit, including children and babies.[4]

Most enteral feeding aims to resolve and meet caloric requirements in patients with eating difficulties; however, food allergies and sensitivities are of concern. These include dairy, lactose, soy, gluten, corn, nuts, and reaction to food additives[21,28] such as high fructose corn syrup. A higher subset of those needing enteral formulas is likely to have food and chemical sensitivities.[28] Reactions that may hamper healing include various GI disturbances, asthma or atopic dermatitis,[29] as well as CKD proinflammatory cytokine cascades.[30] Organic, plant-based peptide formulas can alleviate and address these issues and have been found to be well-tolerated in a 2020 review of 244 prescriptions. All patients tolerated the formulas well after two months.[21]

Mechanisms

It is common for those receiving enteral nutrition with conventional formulas, particularly children, to have gastrointestinal disturbances.[38] Those patients with a higher tolerance to feeding formulas are more likely to gain weight, improve health, and thrive.[2,39] The caloric needs of patients can be calculated with standard equations (Harris Benedict equation) or indirect calorimetry.[40] The typical range falls between 25 and 30 kcal/kg/day, while protein requirements can range from 0.8–1.2 g/kg/day.[40,41] Close monitoring and evaluation of patients for symptoms of intolerance is important, which commonly include gas/bloating, reflux, diarrhea or constipation.[27]

Diet quality is essential in driving overall health, with diets composed largely of unrefined plant foods offering greater protection against chronic disease. One major aspect of diet quality that varies across enteral formulas is fiber content, as well as antioxidants and essential vitamins and nutrients.[32]

Intrinsically linked to diet quality, a healthy gut microbiome is considered a significant factor influencing optimal health. The ongoing research showing an association of a healthy and diverse gut microbiome composition with lower risk of cardiometabolic and inflammatory conditions has grown.[3,42,43] Benefits are likely linked to decreased excess weight, though mechanisms for these diseases appear to relate to gut health, particularly with autoimmune diseases.[44,45] Modification or reversal of disease with a plant-based diet suggests that enterally-fed patients could benefit from whole food, plant-predominant formulas. A high-fiber, nutritionally dense plant-based enteral formula can alter the microbial composition within weeks, from an abundance of proinflammatory taxa to a greater abundance of healthy bacteria. For instance, a study of children (n=12) found that some patients no longer needed stool softeners or gastroesophageal reflux medications at two months.[3]

A review of enteral formulas indicated that fiber-supplemented formulas have important physiological effects and clinical benefits on patients, including normalized bowel function and reduced transit time. The level of reported fiber intake ranged from 14.0 to 34.9g/day, with a statistically significant positive relationship reported between fecal mass and fiber intake [intercept, 3.9 g; gradient, 0.98 (S.E. 0.41) g/g fiber; $z=2.4$, $P=0.02$].[9] The observed increase in dry fecal weight was significantly related to the dose (15–40g) of fiber administered ($z=6.8$, $P<0.0001$).

Although the studies reported that fiber is generally well tolerated, high doses of highly fermentable soluble fibers, such as hydrolyzed guar gum or inulin, caused increased flatulence.[46,47] Conversely, the use of a single insoluble fiber such as cellulose led to constipation and fecal impaction in 4 of 18 healthy subjects.9 In one study, supplementation with inulin led to a significant increase in the number of days with flatulence [9.9 (SD 7.4) days vs. 1.4 (SD 1.1) days; $P<0.05$] for 6 of 9 patients.[47]

Common Questions and Concerns

What are potential problems with the ingredients in standard enteral formulas?

Most plant-based enteral formulas are designed to avoid common allergens and have demonstrated easier management of food allergies or intolerance.[21] Commercial formulas contain emulsifiers which have been shown to worsen colitis in animal models,[12] and generally have low fiber and high sugar content, which can affect GI health, including changes in protective microbiota.[13] Improved outcomes for patients have been observed using plant-based enteral formulas.[13]

How can I compare the standard plant-based enteral formulas that are available?

Entirely plant-based enteral formulas are somewhat uncommon. The American Society for Parenteral and Enteral Nutrition, ASPEN, is the international authority in parenteral and enteral feeding and is involved in most guidelines regulating enteral and parenteral formulas. ASPEN maintains a comprehensive, though not necessarily exhaustive, list of formulas on their website at the ASPEN Enteral Nutrition Formula Guide. This information can be combined with specific product searches and label reading on the manufacturer's website to compare brands and ingredients.

Are there plant-based formulas that are gluten-free?

Yes, there are plant-based enteral formulas that are gluten-free and dairy-free. Checking for inclusion or exclusion of specific ingredients can always be done by reviewing product labels and ingredient lists on the manufacturer's website.

Does insurance cover plant-based enteral formulas?

Plant-based enteral formulas are beginning to be widely accepted and should be covered by most insurances, depending on the type of coverage. Barriers to access and knowledge of availability could be more of a limiting factor. In these situations, RDs or physicians could involve their pharmacist/insurance carrier to authorize use via medical necessity. Practitioners could also reach out to the manufacturer to discuss patient discount programs or other incentives.

As a physician or RD, is it easy to get them in our formulary?

Check with your institution when looking for a specific product. If a plant-based formula is not in the formulary, it is usually straightforward to contact the manufacturers for assistance in getting their product into the formulary at a particular hospital or health system. You can also reach out to your institution's nutrition and pharmacy departments.

What are the side effects or complications I need to be aware of while prescribing plant-based formula?

As with any formula, there is always the possibility of allergies or intolerance when starting with new enteral feeds. Close monitoring for signs of allergies or intolerance, such as bloating, loose stools, and excessive gas, is important when starting with any new product.

Summary of Key Studies

High-quality research examining the effectiveness of plant-based enteral formula (PBEF) compared to traditional enteral formula in clinical application is limited but promising. Studies with the strongest designs in our review can be found in Appendix Table 1.

Most research examining PBEF examines its effect on weight maintenance and gain in patients in a single-arm trial or case series. In our review, we examined the effect of PBEFs on appetite and satiation markers in a randomized controlled trial,[48] a controlled clinical trial examining the effect of PBEF on microbiome composition in chronically ill, tube-fed children,3 three cross-sectional abstracts examining patient and clinician-reported PBEF outcomes in sick populations, and chart reviews on 9 PBEF users.[21,35,49] In healthy subjects, soy-based enteral formula elicited decreased time-dependent insulin responses compared to a control formula. A soy-based formula also increased satiation and reduced calorie intake at a subsequent ad-libitum lunch meal hours later.[48] Intervention with PBEF also showed improvements in stool consistency and frequency. In addition, the added fiber of PBEF may cause changes in gut microbiota within tube-fed patients. This change was observed in the clinical trial by McClanahan et al., where PBEF users showed changes from pathogenic microbiome populations to more health-promoting and diverse microbiomes

(though changes in microbiome concentration were different based on the individual).[3] In cross-sectional studies, patients on PBEF tended to experience weight gain or maintenance in most cases. In addition, most clinicians surveyed report positive outcomes with PBEF, in addition to symptom alleviation with GERD, constipation, and diarrhea. However, these effects were observed with small sample size and require validation.

One concern of PBEF is that higher fiber content may lead to greater satiation at lower calorie intake levels in populations where the goal of nutrition is to cause weight gain. Preliminary research on PBEF has demonstrated weight gain, positive alterations in microbiome composition, improved stool frequency and consistency, and positive perceptions from clinicians and patients.[3,21,34,39,50] Weight gain may be related to higher tolerance of PBEF.[39] In conclusion, research on PBEF is limited by both quality and sample size. More research on PBEF is needed to validate improvements in outcomes compared to traditional enteral controls via blinded randomized controlled trials.

Promising Results: Improved Enteral Outcomes

Several studies indicate a higher tolerance and better health outcomes, including weight gain and improved GI symptoms when utilizing plant-based enteral nutrition. Patients have reported feeling better with improved perceived benefits, indicating the potential for plant-based enteral formulas being an effective alternative to traditional animal-based enteral formulations.[39]

Plant-Based Formula Preferred by Crohn's Patients

A small case series (n=3) found that plant-based nutritional formula was preferred by pediatric Crohn's patients over casein-based or elemental formula due to less bloating, gas, and fullness. The formula was better tolerated, which allowed them to take in more calories and gain weight, with one patient reducing inflammatory markers, as well.[51]

Plant-based Enteral Nutrition Well Tolerated and Benefit Pediatric Crohn's Patients

Three pediatric Crohn's Disease patients preferred a plant-based enteral formula over their previous one, and all experienced less bloating, gas and fullness after feeds. Two of them experienced weight gain within 3–7 months, all reported feeling better, and one had a decrease in inflammatory markers.[31]

Table 1 Orellana, 2020: Weight and BMI improvements from plant-based enteral therapy in pediatric Crohn's patients[51]

a. Anthropometrics for patients before and after plant-based nutrition initiation.

	Duration on plant-based nutrition	Weight (kg)/ Z-score Before	Weight (kg)/ Z-score After
Patient 1	3 months	60.9/0.84	62.1/0.86
Patient 2	3 months	37.6/-0.24	38.3/-0.29
Patient 3	7 months	57.9/0.24	60.4/0.41

b. Anthropometrics for patients before and after plant-based nutrition initiation.

	Duration on plant-based nutrition	BMI Z-score Before	BMI Z-score After
Patient 1	3 months	0.77	0.84
Patient 2	3 months	-0.54	-0.47
Patient 3	7 months	0.30	0.55

Breaking Insulin Resistance

Reductions in insulin and blood glucose levels were observed after only two days in a critically ill 67-year-old woman with type 2 diabetes and hypertension upon hospital admission with pneumonia following enteral treatment with an oatmeal-based formula. More specifically, this formula restricted carbohydrates to whole-grain oats (180 g) and small amounts of vegetables (60 g), indicating that short-term use of a plant-based formula may be an effective tool to break insulin resistance in critically ill patients.[52]

Assessing Improved Digestive Symptoms After 6 Months on a Pea Protein-Based Formula

A 2020 study (n=392) found that both pediatric and adult users of plant-based enteral formulas containing pea protein improved GI tolerance and health.[39] Intact pea protein formula was used by 108 (67.9%), while 71 (44.7%) reported using a hydrolyzed PP PBEF. The formula was reported to be consumed orally by 90 (56.6%); 55 (34.6%) reported using a feeding pump, 13 (8.2%) a gravity bag, and 19 (11.9%) a syringe. For 110 (69.2%), the formula was reported to make up > 50% of their nutrition; 87 (54.7%) reported being on it > 6 months. A majority of patients reported improvements in digestive symptoms, being able to consume at least 75% of their goal volume, overall nutrition, gaining or stabilizing weight, and feeling healthier.[39]

Weight Maintenance and Gain in Oncology Patients after 3.5 Months

A cohort (n=13) of adult oncology patients using a plant-based oral nutrition supplement all reported tolerating the formula well, as presented in a retrospective chart review (one also received the plant-based formula via feeding tube). The nine patients who received at least one follow-up assessment from a dietitian within a twelve-month period all gained or maintained weight (six gained, and four showed an increase in BMI). Weight gain averaged 3.5kg. These results have important ramifications, as medical treatment can be interrupted when patients experience significant weight loss, dehydration, or clinical malnourishment.[35]

Conclusion

Plant-based nutrition has been shown to promote mucosal healing, decrease inflammation, and increase healthy gut bacteria, all of which aid in healing. Research has shown that plant-based enteral nutritional formulas are well-tolerated and can be an alternative option for patients requiring enteral therapy. Benefits include less bloating, gas, and feelings of fullness.[31] Research on plant-based enteral options is promising and provides the necessary rationale for systematic evaluation in clinical trials of children and adults. Studies thus far report on the benefits of healthier enteral formula options based on whole plant foods, including weight gain, tolerance, reduced GI symptoms, and decreased inflammation. Patients, prescribers, and caregivers should have options to discuss and opt for plant-based enteral nutrition. In addition, greater attention should be placed on improved access, availability, and insurance coverage for such formulas to ensure that cost and affordability is not a barrier to better nutrition and improved health outcomes.

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APPENDIX 1 Enteral Nutrition and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Bailey, 2020[5] **Cross-Sectional Survey**
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Oncology patients prescribed plant-based enteral formulas (PBEF) in the past 12 months N = 13 (53.8% female) Age = 63.3
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Prescription of PBEF in the past 12 months and has undergone oncology treatment
Outcome(s) of interest and units	• Weight gain • Malnutrition status • PBEF tolerance

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**9 patients with one follow-up assessment from a dietitian, all either gained or maintained weight.** For those with documented weight gain, the average gain was 3.5 kg. Among those with a documented increase in BMI, documented increase was 1.53 kg/m^2 over an avg 3.5 months. Patients received an average of 44.6% of daily calories from PBEF. Averages are slightly inflated by one patient on PBEF for 12-month period, experiencing 9.09 kg weight gain and 2.8 kg/m^2 increase in BMI. Without this patient, average weight gain was 2.36 kg and 1.1 kg/m^2 increase in BMI in a 2.5 month timespan.
Comments: Significance to clinical application	PBEF demonstrates weight gain and maintenance in a small cohort of oncology patients over an average of 3.5 months. PBEF may be useful in oncology patients with certain dietary preferences or ingredient intolerances and have suggestive evidence of reliable weight maintenance and even gain when providing a sizeable amount of calories to daily intake, whether orally or via feeding tube.

First author, year, study design (bold), name of study (if applicable), sample population	Carr, 2020[4] **Cross-Sectional Survey**
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 111 de-identified prescriptions (issued from April-September 2018) collected on pediatric and adult patients prescribed plant-based, peptide formula (Kate Farms Peptide 1.5 or Pediatric Peptide 1.5) N = 92 responding health care professionals based on a national electronic survey on patient outcomes
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Clinical diagnosis with conditions requiring prescription of enteral nutrition and subsequent prescription of plant-based, high calorie peptide formula (either Kate Farms Peptide 1.5 or Pediatric Peptide 1.5)
Outcome(s) of interest and units	• Clinical outcomes based on utilization of plant-based peptide formula • Reasons for prescription of plant-based peptide formula
Key Results (Bold qualitative assessment followed by quantitative results)	**95% of clinicians surveyed described positive outcomes in patients using plant-based peptide formula, including decreased gastrointestinal (GI) symptoms of food intolerance, weight gain or linear growth, and improved nutritional status.** De-identified prescriptions were for cancer (n = 50), dysphasia (n = 24), malnutrition (n = 19), and gastroparesis (n = 18) 87% of clinicians prescribing formula to patients with GI symptoms reported that most or all of their patients experienced improved symptoms of GI intolerance after using plant-based formula.
Comments: Significance to clinical application	Survey data shows positive clinician-reported outcomes for patients prescribed plant-based, calorically dense, peptide formula. Clinician reports suggest that plant-based formulas may be both successful and effective in improving GI symptoms, supporting weight gain and linear growth, and improving nutritional status in. In addition, plant-based formulas may have useful applications in individuals with food intolerances.

First author, year, study design (bold), name of study (if applicable), sample population	Cohen, 2020[2] **Cross-Sectional Study**
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 392 Of the 392: N= 183 were formula users, 57% female, 28.2% between 21-40 yrs old; N=207 were caregivers
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Diagnosis of individuals using plant-based enteral formula (PBEF)
Outcome(s) of interest and units	• Self-perceived improved nutrition • Length of time on PBEF • Self-perceived improvement of digestive symptoms • Self-reported weight gain

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**PBEF users generally reported improved perceived nutrition, feeling healthier, improved digestive symptoms, and weight gain.** Types of diagnosis reported from surveys (from most to least prevalent): other, gastroparesis, head and neck cancer, difficulty swallowing, failure to thrive, malnutrition, other cancer, cerebral palsy, developmental delay, cystic fibrosis, ALS, brain injury, esophageal cancer, CVA (stroke), achalasia 63.8% of PBEF users used intact pea protein formula while 48.7% used hydrolyzed pea protein formula. 46.4% of respondents reported using PBEF through feeding tube. Among PBEF users, 78.6% reported feeling healthier on PBEF, while 88.5% reported that PBEF improved their nutrition. 61.8% of users reported improved digestive symptoms on PBEF. 58.4% of users reported weight gain.
Comments: Significance to clinical application	This study provides suggestive evidence that PBEF is well-tolerated, provides perceived benefits in users, and may be an effective alternative to traditional animal-based enteral formulations.

First author, year, study design (bold), name of study (if applicable), sample population	McClanahan, 2019[3] **Controlled Clinical Trial (pilot study)** Participants from the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at the Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (UPMC)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 10 chronically ill, tube-fed children who were reliant on standard enteral nutrition formula Median age = 3.5 years with range of 2-8 years Duration: 2 months
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Children reliant on standard enteral nutrition formula switched to plant-based enteral nutrition (PBEN) Controls were children aged 2-17 undergoing minor surgeries and with "no major medical problems, recent hospitalizations, or antibiotic exposure in the 3 months prior to their surgery."
Outcome(s) of interest and units	• Fecal microbial biodiversity via 16S ribosomal RNA gene seq • Fecal short-chain fatty acids (SCFA) • Bile acids
Key Results (Bold qualitative assessment followed by quantitative results)	Fecal samples collected 2 months after initiation of PBEN were more similar to healthy control samples than the baseline or 2-week samples. At baseline, intervention group microbiota were characterized as having a higher abundance of pathogenic bacteria (*Enterococcus*) while controls had microbiota more characterized by healthful bacteria (*Faecalibacterium* and *Prevotella*). Post-intervention fecal samples from the intervention group demonstrated more similarity to healthy controls. Statistically significant increase in pyruvate in fecal samples and non-significant increases in butyrate, acetate, and proprionate "Conjugated primary bile acids—taurocholic acid (TCA), tauromuricholic acid (TMCA), and taurolithocholic acid—were significantly higher in PRE fecal samples relative to 2-week and 2-month samples" ($p < 0.05$). Shift from bimodal stool (constipation and diarrhea) in intervention group at baseline, to soft, formed stool at follow-up. Of 8 patients experiencing GERD, 4 improved on PBEN, 1 worsened, and 2 showed no change.
Comments: Significance to clinical application	Intervention with PBEN shows suggestive improvements in microbiome composition, as well as increases in certain SCFA and bile acids. Switching to PBEN may also improve diarrhea and constipation and increase the frequency of elimination. "Results from this pilot study suggest that PBEN is well tolerated and could improve the health of the microbiota in chronically ill children. This trial provides a rationale for systematic evaluation of PBEN in clinical trials of children who require supplemental nutrition."

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Nepocatych, 2019[1] **Randomized Controlled Trial**
Study/analysis groups, mean age, mean BMI (SD), total N, duration	N = 17 adults aged 18-40 who are habitual breakfast consumers 64.7% female Age = 27 ± 7 years BMI = 24.6 ± 4 kg/m^2
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Participants randomly assigned to 1 of 3 liquid breakfast meals after overnight fast: "High soy protein (HSP: 486 kcals; 50 g soy; PRO: 43% CHO: 43%, FAT: 14%), low soy protein (LSP: 476 kcals; 25 g soy; PRO: 23% CHO: 66%, FAT: 11%) and control (CON: 471 kcals; PRO: 3% CHO: 84%, FAT: 13%)." Later in the day, participants were allowed to consume an ad-libitum lunch.
Outcome(s) of interest and units	• Appetite profile at 0, 60, 120, and 180 minutes after test meal [area under curve (AUC)] • Thermic Effect of food (TEF) measured at 45, 105, and 165 minutes following test meal (AUC) • Respiratory Quotient (RQ) and oxygen consumption (VO2) • Leptin and insulin blood concentrations at 30 and 180 minutes after meal consumption • Energy intake at ad-libitum lunch (adjusted for body weight)
Key Results (Bold qualitative assessment followed by quantitative results)	Participants who consumed the high soy protein breakfast had higher perceived satiety and lower energy intake than the other breakfast groups. Higher satiety and fullness for the high soy protein meal compared to the control meal, but not to the low soy protein meal Control diet elicited lower VO2 than HSP and LSP and higher RQ compared to HSP. Participants who ate HSP ate 17% and 11% fewer calories per kg of bodyweight compared to LSP and CON, respectively. No significant differences in leptin response. Statistically significant time effect for insulin between the three diets ($p = 0.003$). CON had the highest insulin response, while HSP showed the greatest decrease in leptin concentration over time.
Comments: Significance to clinical application	The addition of soy had effects on reducing hunger and increasing fullness and satiety, regardless of protein content. Higher protein content of soy meal led to reductions in energy consumption per kg of bodyweight compared to LSP and CON diets. The addition of soy to enteral formulas may have beneficial effects on weight management. However, this is only generalizable to healthy populations.

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REPRODUCTIVE CANCERS

Key Points for Practitioners

- Whole food, plant-based diets have utility both in decreasing risk for reproductive cancers as well as potentially reducing rates of reoccurrence
- Important elements of plant-based diets that seem to reduce cancer risk include the reduction or elimination of animal protein and fat, the presence of fiber, and the high concentration of antioxidants
- Whole food, plant-based diets have no adverse side effects and are associated with other health benefits such as cardiometabolic health, healthy weight, and longevity
- Existing evidence on plant-based diets and cancer can be communicated to patients to support their ability to make informed decisions about their diet and course of treatment
- With appropriate care and planning, plant-based dietary interventions are complementary to conventional cancer treatments
- When weight loss is a concern, calorie tracking or plant-based enteral formulas may be helpful
- If patients express interest in trying a whole food plant-based diet of some kind, it is helpful to share educational and support resources with them

ABSTRACT | A whole food, plant-predominant diet offers benefits for risk reduction. It also complements conventional treatment of reproductive cancers by supporting healthy weight, reducing inflammation, potentially reducing insulin-like growth factor (IGF-1), increasing glucose tolerance, and increasing consumption of antioxidants to prevent oxidative damage. Reducing consumption of meat and dairy, saturated fat, and animal protein; increasing fiber consumption; maintaining normal hormone levels; and altering the gut microbiota also offer benefits of a whole food, plant-based (WFPB) diet to reduce cancer risk. Practitioners can support patients in adopting a plant-based diet by providing dietary prescriptions and educational resources for successful dietary transitions and maintenance.

Reproductive Cancers in Context

Cancer is characterized by uncontrolled cell growth and proliferation,[1] and it is the second leading cause of death in the US.[2] Cancer types are typically named for the organs or tissues of origination.[1] For women, reproductive cancers include cervical, ovarian, endometrial (uterine), vaginal, vulvar, and breast cancers,[3] of which only cervical cancer has an early detection screening test. Although breast is the most common reproductive cancer among women, ovarian is the deadliest, with a 5-year survival rate of only 44%, as early detection is difficult. Only 15% are diagnosed in stage 1, where the survival rate is 92%. More than 20,000 cases in the U.S. were diagnosed in 2020.[4] Fallopian tube cancer can occur but is very rare.[5] For men, reproductive cancers primarily include testicular, penile, and prostate cancers.[3] Survival rates for the last two male cancers are 98% and 95%,[6] respectively. This paper will focus on the most common reproductive cancers in the US, including breast, endometrial, prostate, and testicular cancers.

Causes and Risk Factors

According to the American Cancer Society, common causes of cancer include smoking and tobacco use, diet and physical activity, exposure to the sun and other types of radiation, as well as certain viruses and other infections.[7,8] While some risk factors are unmodifiable (sex, age, adult attained height, or genetics), other risk factors are potentially modifiable.[8] These are primarily related to lifestyle and include smoking, alcohol consumption, diet, and physical activity. Dietary risk factors include red and processed meat consumption, underconsumption of fruits and vegetables, dietary fiber, and dietary calcium.[8]

Some reproductive cancers have known causes with high attributable risks,[8] while others are less certain. For instance, the sexually transmitted human papillomavirus (HPV) is the known cause of cervical cancer, and the increased risk of this cancer is linked to early sexual behavior, multiple sexual partners, and exposure to other sexually transmitted infections.[9] Conversely, the causes of breast[10] and endometrial[11] cancers are less certain and likely multifactorial with strong associations established, while risk factors include hormonal, lifestyle, and environmental factors, age, comorbidities (e.g., obesity, type 2 diabetes), and the patient's personal and family health histories. While the causes of prostate and testicular cancers are also unknown, risk factors include age, race, and family history.[12,13] Obesity is an additional risk factor for prostate cancer,[12] and undescended testicle and abnormal testicle development are additional risk factors for testicular cancer.[13]

Treatment and Outcomes

Despite medical advances and successful treatments, cancer is a leading cause of death in every country globally and is the first or second leading cause of death before age 70 in nearly 60% of all countries.[14] Common cancer treatments include invasive surgeries, chemotherapy, and radiation. Less common treatments involve targeted immunotherapy, laser, hormonal, and other treatments, including some experimental.[15] Treatment options and prognoses vary by the type of cancer, stage, tumor size at diagnosis, the site(s), and extent of metastasis.[16] Further, individuals respond differently to treatments, and patient comorbidities can reduce or complicate the efficacy of treatment options. It is also important to note that many available treatments are costly and can cause unpleasant or fatal side effects. Therefore, the best way to avoid the risks involved in treatment and the debilitating and deadly outcomes associated with cancer is through prevention and risk reduction.

Prevention and Early Detection

According to the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR), an estimated 30-50% of all cancer cases are preventable through healthy lifestyle practices and avoidance of carcinogens, pollution, and long-term infections.[17] In addition to the avoidance of tobacco, the 2018 WCRF/AICR recommendations for cancer prevention focus on evidence-based modifiable lifestyle factors, including healthy weight, physical activity, and consuming a diet rich in whole grains, vegetables, fruits, and beans. Recommendations discourage using supplements for cancer prevention and state to limit consumption of fast and other processed foods high in fat, starches, added sugars, red and processed meats, sugar-sweetened drinks, and alcohol. Finally, mothers are recommended to breastfeed their babies if possible, as breastfeeding has been shown to protect against cancer. Further,[18] those diagnosed with cancer are encouraged to follow the recommendations above.[17]

Greater adherence to the 2007 WCRF/AICR recommendations is associated with lower risk of total cancer as well as of breast and colorectal.[9] For cervical cancer, the best form of prevention is HPV vaccination. Regular testing can also identify and treat pre-cancerous changes to prevent the most common form of this cancer from developing.[19] According to both the Mayo Clinic[20] and American Cancer Society,[21] there is no known way to prevent testicular cancer[13,21,22] due to the nonmodifiable risk factors mentioned above, though the following factors can add risk: age, cryptorchidism, family and personal histories, race, and HIV.

Reproductive Cancer Prevalence, Incidence, and Disparities

Reproductive cancers are more common in developed nations and regions defined by a Western lifestyle (Europe, North America, the Caribbean,

and Oceania). Although incidence in high-income countries is greater, low- and middle-income countries have higher mortality rates from these cancers due to inadequate access to early detection from screenings and treatment.[23,24] Within the US, disparities in the prevalence and mortality rates of reproductive cancers can be attributed to geography and race/ethnicity.[25] The prevalence, incidence, and known disparities of common reproductive cancers are outlined in the table below.

Table 1 Prevalence, incidence, and disparities related to the most common reproductive cancers

Cancer Type	Prevalence and incidence*	Regions with highest rates	Known disparities or noteworthy differences
Breast	Most commonly diagnosed cancer[14] Most common cancer among women worldwide[26] with 2,261,419 (2020) new cases annually (2020)[14] Most common[27] and second deadliest cancer in US women,[28] with ~43,600 annual deaths, (2021)[14]	Europe (20 countries including Iceland), Oceania (Australia, New Zealand, and Samoa), and North America (U.S. and Canada) had the 25 highest rates in 2018[26]	In the US, Black/African-American women are more likely to die from breast cancer even though their rates of this cancer are similar to those of white women.[25]
Cervical	Eighth-most common cancer overall and fourth most common cancer for women worldwide[14] 604,127 new cases in 2020 worldwide[14]	Africa had the 20 highest rates of cervical cancer in 2018[29] Highest incidence and mortality in low and middle-income countries[23] due to limited access to HPV vaccines and screening[24] ~80,000 diagnosed per year, and > 60,000 women die from the disease[30]	Lower rates of HPV vaccine in US adolescents in nonmetropolitan areas and less screening in US women with low incomes[31] Hispanic/Latino and Black/African-American women have the highest rates of cervical cancer in the US, with death most likely in Black/African-American women.[25]
Endometrial	15th most common cancer overall and sixth most common cancer in women worldwide[32] 380,000 new cases annually worldwide (2020)[33]	Europe, North America, and the Caribbean	More new cases in US women compared to other gynecologic cancers[28] The 5-year survival rate for endometrial cancer is 81%. The 5-year survival rates for white and Black women with the disease are 84% and 63%, respectively.[34]
Ovarian	18th most common cancer overall in 2018 and eighth most common cancer in women[35] 313,959 new cases annually worldwide[36]	European countries (especially those in eastern Europe), southeast Asia, Fiji, and Japan[35]	More deadly than endometrial cancer in US women (6.7 vs 4.9 deaths per 100,000 women in 2014–2018) despite being less common[28] The 5-year survival rate for women with all types of ovarian, fallopian tube, and peritoneal cancers is 49%[37]
Prostate	4th most common cancer overall and second-most common cancer worldwide for men (2018 age-adjusted statistics)[38] Most common[39] and second deadliest[28] cancer for US men overall 1,414,259 new cases in 2020 worldwide[36]	European, Oceanic, and Caribbean countries[38]	Black/African-American men have the highest rates of prostate cancer mortality among all US population groups.[25]

** this excludes all forms of skin cancer*

Testicular cancer is relatively rare compared to other cancers, but it is the most common cancer among American males between 15 and 35 years old.[13,16] Penile cancer which is highly HPV-related (>60%)[40] is another rare cancer in North America and Europe,[41] yet this cancer comprises 20% of cancers in African, Asian, and South American men.[42]

Dietary Risk Factors for Cancer

A poor diet alone may not cause cancer; however, some specific food items, food groups, and dietary patterns are known risk factors. Included among the known and probable human carcinogens identified by the International Agency for Research on Cancer and the US National Toxicology Program are alcoholic beverages, processed meat, and Chinese-style salted fish. Probable carcinogens include red meat and very hot beverages (above 65 degrees Celsius). In addition, epidemiological studies suggest that diets rich in animal foods (particularly with high amounts of saturated fat like fatty meats and dairy) and diets high in processed/refined foods may be associated with a higher risk of several cancers, including cancers of the breast and prostate. Evidence from specific analyses and systematic reviews is provided below.

Several studies have assessed associations between individual foods or food groups and reproductive cancers. A 2021 systematic review and dose-response meta-analysis included 75 studies assessing the association between breast cancer risk and various food groups, including red meat, processed meat, fish, poultry, egg, vegetables, fruit, dairy products (overall, milk, yogurt, and cheese), grains/cereals, nuts, legumes, soy, and sugar-sweetened beverages.[43] From among these, higher intakes of red and processed meat and milk above 450 grams per day increased breast cancer risk. A 2019 systematic review and meta-analysis also reported evidence with low to very low certainty that reducing processed meat consumption by three servings per week was associated with small decreases in prostate cancer mortality and incidence of breast cancer.[44] Further, a 2014 systematic review of 46 studies assessing associations between nutrients, foods, or food groups and advanced prostate cancer risk found consistent evidence that diets habitually high in saturated fat, well-done meats, and calcium increased the risk of advanced prostate cancer.[45]

Studies have also explored associations between overall dietary patterns and reproductive cancers. Though conclusions are limited by potential recall bias, a 2018 review of 17 case-control studies that examined associations between dietary patterns and risk of breast cancer[46] found that the unhealthy dietary patterns most associated with higher breast cancer risk consistently included saturated fat and red and processed meats. Some also included sugar-sweetened beverages, candy, refined grains, and fried foods. Compared to many other populations, Asians tend to consume more plant-sourced foods and fewer animal proteins, and they also have relatively low rates of breast cancer. A 2007 study exploring dietary patterns and breast cancer incidence in Shanghai found that postmenopausal Chinese women following a “Western” dietary pattern high in shrimp, chicken, beef, pork, candy, and desserts had significantly higher odds of breast cancer than those following a more traditional dietary pattern centered around tofu, cauliflower, beans, bean sprouts, and green leafy vegetables.[47] Correspondingly, dietary patterns high in processed meat and fatty dairy products are conducive to the development of prostate cancer through a variety of mechanisms, further discussed below.[48]

Benefits of Plant-Based Diets for Reproductive Cancers

Diets high in vegetables and fiber (fiber only comes from plant-food sources) are associated with a lower incidence of many forms of cancer, including the two most common reproductive cancers—breast and prostate. Overall healthy dietary patterns rich in whole grains, vegetables, fruit, and beans are recommended by the WCRF/AICR to prevent and reduce the risk of developing certain cancers[49] as the 2018 systematic review mentioned above found: healthy dietary patterns protective against breast cancer consistently included vegetables, while some also included fruits, legumes, lean protein (fish, lean meat, low-fat dairy) and whole grains.[46] Specific dietary patterns that generally follow the WCRF/AICR recommendations include the following:

- Mediterranean-style diet with high consumption of cereals, fruit, vegetables, legumes, fish; high monounsaturated/saturated fatty acids (MUFA/SFA) ratio; low consumption of dairy

products, including milk and meat; and moderate alcohol consumption[50]

- Prudent diet consisting of fruits, vegetables, whole grains, legumes, nuts, fish, and low-fat dairy products rather than refined or processed foods, red meats, high concentrated sweets, eggs, and butter[51]
- Dietary Approaches to Stop Hypertension (DASH) diet, rich in vegetables, fruits, and whole grains and includes fat-free or low-fat dairy products, fish, poultry, beans, and nuts while limiting foods high in saturated fat, such as fatty meats and full-fat dairy products[52]
- Vegetarian diets characterized by an avoidance of meat and fish but may include dairy only (lacto-vegetarian) or dairy and eggs (lacto-ovo-vegetarian)[53]
- Vegan diets (strict vegetarian) that center on whole plant foods, characterized by an avoidance of all animal-sourced foods
- Whole food plant-based (WFPB) diet focused on natural, whole, unrefined, or minimally refined plant food ingredients and excludes animal ingredients such as meat, milk, and eggs.[54]

Several studies support the use of these and similar dietary patterns to help reduce risk or improve prognoses related to reproductive cancers.

In a cohort study of women from Northern Italy with breast cancer, those who adhered more strongly to a Mediterranean-style diet showed significantly better 15-year survival (63.1% survival) compared to those with low adherence (53.6%).[50] Among women in the study over age 55 at diagnosis, the risk of breast cancer mortality was significantly lower for those with high versus low adherence to the Mediterranean diet. In India, where lifelong vegetarian diets are widely practiced, a 2018 study found that Indian women who followed a long-term lacto-ovo-vegetarian diet had lower odds of breast cancer than non-vegetarians and those vegetarians who avoided eggs.[53] A 2002 study on Indian women who migrated to England found that lifelong vegetarians showed lower odds of breast cancer with higher intakes of vegetables, pulses (e.g., lentils), and fiber.[55] Comparatively, in a 2018 cross-sectional study, odds of HPV infection, a potential cause of cervical cancer and tumors, were found to be related to dietary patterns.[56] Here, women following a Western dietary pattern had higher odds of high-risk HPV infection, and women on a prudent diet had lower odds of high-grade cervical intraepithelial neoplasia than those not following these diets.

A recent eight-year prospective cohort study assessed dietary patterns associated with site-specific cancers and found that prostate cancer risk was reduced in men following a prudent diet. As adherence increased, prostate cancer risk decreased significantly.[57] Those with the strongest adherence to this dietary pattern characterized by a high intake of grains, vegetables, and fruits showed a significantly reduced risk of prostate cancer compared to those who adhered least strongly.[57] Epidemiological evidence linking diet to testicular cancer has shown inconsistent conclusions.

Results of some studies have shown an increased risk of testicular cancer with higher consumption of milk, cheese, and dietary fat, while other studies found no association.[58]

Mechanisms

A variety of biological mechanisms that increase or decrease cancer risk have been identified, and many though not all, are related to body composition, as described below.

Excess Weight and Obesity

Perhaps the strongest evidence linking diet to cancer is the effect of diet on excess weight and obesity, which are known risk factors for many cancers, including breast and endometrial. According to the National Cancer Institute, obesity may increase the risk of reproductive cancers, as described further here.[59] Obesity often accompanies low-grade inflammation, which can cause DNA damage over time and, subsequently, lead to cancer. In the case of female reproductive cancers, increased fat tissue results in excess amounts of estrogen, which are linked to cancers of the breast, endometrium, and ovaries. Obesity is also associated with increased blood insulin levels and insulin-like growth factor 1 (IGF-1), which can promote prostate and endometrial cancers, among others. Fat cells also produce hormones that can stimulate or inhibit cell growth, such that increases in body fat are associated with

cell proliferation, while people with normal weight tend to produce more hormones with antiproliferative effects. In addition to hormones, fat cells also affect other cell growth regulators (e.g., mammalian target of rapamycin, or mTOR, and AMP-activated protein kinase). Finally, obesity can alter breast tissue makeup, immune response, and oxidative stress, among other possible mechanisms.[59]

Evidence from the third expert report of the WCRF/AICR revealed an increased risk of weight gain, overweight, or obesity with consumption of sugar-sweetened drinks and a probable increased risk with a Western-style diet and fast foods.[60,61] A probable decreased risk of excess weight was found with dietary fiber consumption and a Mediterranean-type dietary pattern. Plant-based diets offer many advantages for healthy weight loss, in achieving a normal weight, and maintaining it.

Inflammation

Greater adherence to the 2007 WCRF/AICR recommendations was found to be associated with lower levels of biomarkers indicating oxidative stress and inflammation in premenopausal women.[62] Another systematic review of 12 case-control studies found a positive association between an elevated inflammatory capacity of the diet as measured by the Dietary Inflammatory Index (DII) score and a higher risk of gynecological cancers among obese patients, particularly ovarian and endometrial. In contrast, components found in plant-based diets can reduce inflammation, including flavonoids, isoflavones, and other phytochemicals, as well as omega 3 fatty acids (particularly found in walnuts along with accompanying polyphenols, vitamin A, and other antioxidants), have been shown to reduce incidence of cancer from chronic inflammation effectively.[63–67] These plant nutrients appear to suppress carcinogenesis through multiple pathways, including the ability to decrease or suppress activation of the protein pathway involved with cytokine production and activation of the NFκB transcription factor that may be a key link between inflammation and carcinogenesis.[68]

Insulin-like Growth Factor (IGF-1)

IGF-1 is a type of growth factor and cytokine[69] that stimulates the growth of many cells in the body. Elevated blood levels of IGF-1 may increase risk of cancer. The predominance of plant-based diets in Asian countries appears to account for lower rates of some cancers and may be explained by lower circulating levels of total IGF-I and higher levels of IGFBP-1 and IGFBP-2.[70] Vegan men had 9% lower serum IGF-1 concentration compared with meat-eaters in one study[71] and 13% lower levels among women who adopt a vegan diet in another.[72] These concentrations suggest that the lower protein intake in the vegan diet may reduce serum IGF-I and increase serum IGFBP-1 and IGFBP-2 levels.[72]

Reactive Oxygen Species and Antioxidants

Elevated rates of reactive oxygen species (ROS) that promote tumor development and progression have been detected in almost all cancers. In part, ROS comprises free radical oxygen intermediates, which can cause damage to cells and tissues due to their instability from unpaired electrons.[73] To stabilize these free radicals, tumor cells express increased levels of antioxidant proteins suggesting a delicate balance of intracellular ROS levels in cancer cell functionality.[74] Antioxidants are naturally occurring compounds in plant foods that act as free radical scavengers and reducing agents, among other functions in the body,[75] thus preventing some of the free radical damage known to be implicated in cancer development. Plant-prominent diets contain lower levels of ROS and high levels of antioxidants, whereas Western-style diets contain high levels of ROS and low levels of antioxidants.[76] Dietary nutrients, including folate, carotenoids, and vitamin C, rich in vegetables and fruits, are significantly associated with reduced overall mortality (range 33–50%) after breast cancer diagnosis.[77]

Total Protein and Animal Protein Consumption

Protein consumption has been demonstrated to affect cancer promotion in animal models, with consumption levels predicting risk profiles in humans.[78] In rat model experiments, alternate levels of the dairy protein casein fed to rats successfully turned on preneoplastic foci growth using a high-protein diet (20% calories coming from the protein) and then turned off the growth with a low-protein diet (5% casein). This suggests that low-protein

diets inhibit lesion development, whereas high-protein diets encourage it. The carcinogen-activating CYP27A1 enzyme can be highly responsive to increases in casein.[79] Results of these animal models are supported by the comprehensive ecological study, the China–Cornell–Oxford Project conducted in 1983–1984, which found varying mortality rates for a wide variety of cancers and other chronic diseases throughout rural China,[80] with such associations confirmed by more recent work.[81] At that time, the breast cancer rate in China was positively associated with dietary fat intake, plasma cholesterol, and circulating estrogen activity.[82,83] This relationship is further supported for overall cancer mortality when examining cancer incidence among individuals 50–65 years, with a 75% overall mortality increase and 4-fold increase in cancer death over the next 18 years.[84] Associations were attenuated or abolished if the proteins were from plant foods.[84]

Meat and Dairy

Diets rich in animal foods appear to be associated with increased risk of many cancers, though some mechanisms are unclear.[85,86] Increased risks for specific reproductive cancers are associated with higher consumption of specific foods. Some studies, including the UK Women's Cohort Study (N=35,372), found that red and processed meat are associated with increased breast cancer risk in premenopausal women (HR=1.32, 95% CI: 0.93–1.88).[87]

In the Nurses' Health Study II, higher red meat intakes were strongly related to elevated risk factors among n=1021 cases of breast cancer among premenopausal women (26-46 years old) with cases of estrogen and progesterone receptor positive (ER+/PR+) breast cancer (n=512). For this population, when compared to eating <3 servings of red meat per week, the increased relatives risks for additional servings were: 1.14 (0.90-1.45) for > 3 servings per week to <5 per week, 1.42 (1.06-1.90) for > 5 per week to <1 per day, 1.20 (0.89-1.63) for >1 per day to <1.5 per day, and 1.97 (1.35-2.88) for > 1.5 per day (test for trend, P=.001).[88]

Data show that a diet high in dairy fat is associated with increased plasma phytanic acid concentration, which may play a role in cancer development.[89] Phytanic acid is a branched-chain fatty acid produced in the milk and meat of ruminant animals that appears to increase prostate cancer risk in higher intakes.[89,90] This fatty acid oxidation pathway is upregulated in prostate cancer tumors, and the enzyme crucial in phytanic acid metabolism is also consistently overexpressed in prostate cancers.[91]

Dairy intake is positively associated with breast cancer risk, according to several studies. Recently, data from the Adventist Health Study (N=52,795) indicated that women consuming 1/4–1/3 cup of milk increased their breast cancer risk by 30%. One cup per day increased risk by 50%, and two to three cups per day were associated with an 80% increased risk.[92] Conversely, soy foods rich in isoflavones have been associated with reduced risk of breast cancer among North American women, as well as increased prevention and all-cause mortality and prevention in large cohort studies.[92,93] In a Danish population of postmenopausal women (N=24,697), higher increase of breast cancer was associated with intakes of red and processed meat, poultry, and fish, with the risk increasing by 9, 15, and 23 percent respectively, (IRRs of 1.15 (95% CI, 1.01–1.31) and 1.23 (95% CI, 1.04–1.45) per 25 g increment in intake).[94]

Meat and dairy consumption are also positively associated with increased risk of prostate cancer and mortality.[95–98] Other risk factors associated with meat-eating include heme iron, nitrates/nitrites in processed meats, and cooking methods that may create mutagens.[96] Risks associated with dairy intake include high saturated fat consumption,[99] high calcium which can decrease vitamin D levels,[100,101] and increased IGF-1 levels.[102,103]

Hormone Changes

Dietary modification can induce significant improvement in estrogen metabolism to decrease morbidity and mortality from cancer. Though the hormone estrogen is inherent in a broad spectrum of physiological functions in women, including regulation of the reproductive system, modulation of bone density, brain function, and cholesterol mobilization, unsustained exposure to exogenous estrogen is a well-established risk factor for various cancers, as it influences progression of both estrogen-negative and estrogen-positive tumors.[104–106] Changing to a vegetarian diet significantly decreases the amount of circulating estradiol, indicating that plant-predominant

diets might mediate influences on estrogen activity due to their high-fiber and low-fat concentrations.[107,108]

This is likely due to weight loss and dietary fiber's ability to intercept and shuttle circulating estrogens out of the bloodstream to be excreted.[109] Further, vegetarian diets appear to increase concentrations of sex-hormone-binding globulin which keeps sex hormones inactive.[110–112] In women, a Western diet has been shown to induce changes in hormonal activity, which may increase incidence of both coronary heart disease and breast cancer.[113]

Estrogen triggers proliferation of endometrial cells during the menstrual cycle, and such cell division over many years tends to increase the risk of cancer development by stimulating the division of uterine or breast cells that have DNA mutations, and also by increasing the chances of developing new, spontaneous mutations from carcinogens or radiation.[114] In men, Ornish 2005 has demonstrated that intensive lifestyle changes may affect the progression of early, low-grade prostate cancer.[115]

Fiber

Fiber acts in several ways to protect against cancer development; first, by controlling harmful weight gain by filling up the stomach with water and non-digestible carbohydrate (fiber), resulting in both satiation and low energy density. Excess weight is associated with both breast cancer and prostate cancer risk.[116,117] High-fat, low-fiber diets are associated with higher blood testosterone levels in men (due to increased production as well as decreased excretion), and higher testosterone levels increase risk for prostate cancer.[118] The fiber in plant foods reduces cholesterol absorption, which is a precursor to estrogen, and cholesterol intake, as dietary cholesterol comes from animal tissue.[119] High-fiber diets also reduce risk of hormonal cancers by improving insulin sensitivity, as fiber mitigates the absorption of glucose into the bloodstream allowing control of insulin and avoiding insulin resistance.[120] High-fat diets are associated with insulin resistance as well as breast cancer.[121]

Gut Microbiome Composition

The immune system maintains homeostasis and protects against invading pathogens (viruses, bacteria, fungi, and toxins) by engulfing and purging invaders and producing antibodies against them.[122] It is the gut microbiome that regulates the immune system and protects against disease, as well as against autoimmune reactions to healthy tissue. Short-chain fatty acids (SCFAs) produced by gut microbiota protect the mucosal lining of the gut allowing it to maintain tight junctions and prevent "leaky gut," which controls inflammatory proteins from entering circulation. This protects against all cancers[123–125] and specifically breast carcinogenesis.[126,127] Trillions of supportive gut bacteria from ~ a thousand species live in the gut to support local gut homeostasis and systemic health. Together, they can be considered an organ in itself with many functions, some yet undiscovered.[128] Dietary patterns alter and control gut microbiome composition.[129] An imbalance of bacteria can lead to uncontrolled processes, including inflammation and cancer development. The standard American diet promotes unhealthy bacteria that decrease SCFAs, increase insulin resistance risk, and potentially fuel estrogen-responsive cancers. In contrast, whole plant foods which contain fiber promote gut microbiota which increases SCFA and protects the gut lining to decrease inflammation and lower risk of hormonal cancers.[130,131]

A Selection of Key Studies: Plant-Based Diets and Reproductive Cancers

Much research has examined the effects of plant-based diets on reproductive cancers, and especially breast cancer. Data from 10 studies with the most rigorous designs from our literature search are presented in Appendix Table 1 below. Of these studies, five were systematic reviews, meta-analyses, or both. Two studies were randomized controlled trials (RCT), and three were observational cohort studies. Four studies examined the relationship between plant-based diets and overall cancer risk,[132–135] five studies examined breast cancer risk,[133,136–140] two studies examined endometrial and ovarian cancer risk,[141] and three studies examined prostate cancer risk.[136,139,142] We found no studies examining the relationship between a plant-based diet and testicular cancer.

Of studies examining overall cancer risk, *a posteriori* derived (observational) plant-based dietary patterns were associated with a reduced risk of overall cancer incidence. An earlier study found that vegan and vegetarian diets were associated with a reduced risk of all-cause mortality and mortality from cancer. However, our analyses found some risk of publication bias in the reviewed articles.[135]

When examining breast cancer risk, one study found no reduced risk of breast cancer associated with vegan or vegetarian diets.[136] However, one study, the California Teacher's Study examining the relationship between *a posteriori* derived dietary patterns and breast cancer incidence, found that individuals who adhered most strongly to a plant-based diet had a reduced risk of breast cancer incidence compared to those who were nonadherent.[137] An examination of the Adventist Health Study-2 found possible but unsubstantiated links between vegan and vegetarian diets and reduced risk of breast cancer.[138] One study examining the relationship between diet and cancer outcomes post-diagnosis found that high intakes of saturated- and trans-fatty acids were associated with greater risk of all-cause mortality and non-breast-cancer mortality, and high protein consumption was associated with reduced risk of breast cancer recurrence and mortality from cancer. In addition, soy intake was associated with reduced breast cancer recurrence in this study.[139] Another study found a reduced risk of breast cancer with higher serum carotenoid concentrations; however, participants assigned to a high-carotenoid diet and the control diet showed no difference in cancer risk.[140]

Finally, when examining prostate cancer, one study found no association between vegan and vegetarian diets and risk of prostate cancer, though a protective effect for overall cancer incidence was observed in cohort studies, and no increased risk from plant-based diets was observed.[136] Another study found increased risk of cancer-specific mortality in those who consumed whole milk and chicken with the skin on, but not in red and processed meat. That same study found reduced cancer-specific mortality with high consumption of cruciferous vegetables and mixed associations with tomato products.[139] One RCT found reduced need for traditional prostate cancer treatments like radical prostatectomy and radiotherapy with a lifestyle intervention including a low-fat diet, stress reduction, and increased exercise.[142] Another randomized controlled trial by Ornish et al. confirmed these findings, showing a decrease in PSA and other factors, demonstrating a slowing of prostate cancer progression with a plant-based diet and lifestyle intervention.[115] These randomized controlled trials suggest that wholistic lifestyle changes, including the adoption of a plant-based diet, would offer benefits and protection if incorporated into the standards of care.

Common Questions and Concerns

Are plant-based diets safe for cancer patients?

Yes, in fact, the American Cancer Society and American Institute for Cancer Research encourage the consumption of plant-based diets,[17,49] as they are associated with lower overall risk[134,143] and contain cancer-fighting phytochemicals and fiber.[17] They recommend avoidance of processed meats, red meat, and added sugars which are associated with cancer risk.[144,145] For those in treatment, optimal nutrition provides phytochemicals to support healing and recovery and avoid recurrence.[115,146] Foods that provide these nutrients include vegetables, whole grains, legumes, and fruits. These foods can control inflammation, dampen the growth of abnormal pre-cancerous cells, and help the body function as best as possible. It is important to work with practitioners to avoid any foods that may interact with chemotherapy which may trigger adverse reactions from food intolerance.[17]

Do plant-based diets provide enough protein for cancer patients?

Yes. Legumes are a rich source of protein, dietary fiber, iron, zinc, folate, and potassium and are low in saturated fat, making them a healthier option than meat and dairy.[17] Consumption of soy products is associated with lower risk of recurrence and higher survival rates among breast cancer patients.[147,148] Including beans, whole grains, nuts, and seeds in the daily diet should provide more than enough protein for most patients,[149] and working with a knowledgeable dietitian can help in planning a health-promoting diet with adequate protein for patients.

Will eating a plant-based diet cause weight loss in cancer patients?

Weight loss in cancer patients is not uncommon, particularly during chemotherapy or radiation treatments.[150] For those with overweight or obesity, a plant-based diet will likely lead to weight loss and improved weight maintenance,[17] which is associated with lower risk of reproductive and gastrointestinal cancers.[17] But for those who need to build or maintain weight and muscle mass, this dietary pattern can provide the necessary protein to fulfill requirements as long as enough calories from whole foods are consumed.[151] Concentrating on higher fat foods containing higher protein levels can help, particularly nuts, seeds, nut butters, and tofu.[17,152] Eating throughout the day instead of a set three meals may allow the consumption of more calories throughout treatment.[153] Whole food, plant-based enteral formulas may help when eating is difficult or with nausea.[151,154]

How can patients be encouraged to eat plant-based foods?

Patients trust their physicians for wellness advice and recommendations more than any other person.[155] Practitioners can provide steps towards dietary improvement or therapy based on their readiness for change, starting with simple suggestions and avoiding overwhelming the patient with a big dietary overhaul.[155] They can offer resources like those provided by ACLM at lifestylemedicine.org, including meal plans, shopping lists, and nutritional information. Emphasizing the many benefits of healthy plant-predominant eating, including better health outcomes in general, leading to lower healthcare costs, can motivate patients. Lastly, health professionals who model good lifestyle behavior will inspire their patients to make healthy food decisions.[156]

Do plant-based diets have any adverse interactions with chemotherapy or radiation treatments?

Plant-based diets may pose certain challenges during cancer treatment, but they can be resolved through planning, as it may be harder to maintain body mass and keep from losing too much weight during cancer treatment on a plant-based diet. Patients may benefit from a personal weight-management plan or suggestions from an oncology dietitian. Malnutrition can impair the body's response to treatment, and thus, the National Cancer Institute recommends a diet assessment early on and monitoring at all phases of recovery.[150] Citrus fruits, pineapple, and tomatoes may irritate the mouth during chemotherapy, particularly if mouth sores are present.[153] Digestive issues may demand adjustment of fibrous foods. For constipation, high-fiber foods like peas and whole grains may help, and for loose bowels, high sodium and potassium foods may help, including broth, bananas, peaches, or apricot nectars; also bland, low-fiber foods such as rice noodles, boiled potatoes, farina, white bread, canned fruits or well-cooked vegetables may be well-tolerated.[150]

Promising Results—Plant-Based Diets as Part of Medical Treatment

Further research on the effects of plant-based diets as part of cancer treatment is merited. The following encouraging results from the Prostate Cancer Lifestyle Trial (PCLT)[142] indicate that prescribing a plant-based diet as part of care may offer meaningful benefits for patients.

The Prostate Cancer Lifestyle Trial (PCLT)[142] found that patients with early-stage prostate cancer choosing active surveillance might be able to avoid or delay costly and invasive conventional treatment for at least two years by making changes in their diet and lifestyle (N=93 men; mean age 66 ± 8 years with biopsy-proven prostate cancer; Gleason score <7, PSA 4–10 ng/mL). Intervention patients were prescribed a low-fat, plant-based diet. After two years of follow-up, a total of 27% of control patients and only 5% of intervention patients had been treated with conventional prostate cancer treatment (radical prostatectomy, radiotherapy, or androgen deprivation, $P < .05$). The experimental patients also had greater improvements in cardiovascular health parameters than did control patients. These findings are noteworthy because avoiding the need for conventional treatment even after cancer diagnosis can translate to improved quality of life and reduced healthcare costs.

Conclusion

Current research indicates that lifestyle factors play a pivotal role in cancer development and health promotion. In particular, whole food, predominantly plant-based diets offer a variety of benefits for cancer prevention, and their use as part of cancer care may aid conventional treatment. Focusing on a healthy, plant-predominant diet can be a key component of cancer treatment to support health and optimal outcomes.

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APPENDIX 1 Reproductive Cancers and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Rinninella, 2020[139] **Systematic Review** Duration: N/A
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Studies of adult (≥18 years old) patients diagnosed with breast, gastrointestinal (gastric, pancreatic, colorectal), gynecological (uterine, cervical, ovarian, endometrial, vulvar), lung and urological (prostate, bladder) cancers where studies examined associations between diet and cancers; n=29 prospective cohort studies; Overall age and BMI NR
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Post-diagnosis dietary patterns or components including low-fat diet, Modified Mediterranean Diet Score, healthy quality diet, high fiber consumption from vegetables, high-quality protein consumption, western diet, and saturated fat consumption
Outcome(s) of interest and units	• Overall survival (OS) or all-cause mortality (ACM) • Cancer-specific mortality (CSM) • Death from a cause other than specific cancer • Cancer progression • Disease-free survival (DFS) • Cancer recurrence and recurrence-free survival (RFS)
Key Results (Bold qualitative assessment followed by quantitative results)	**Many studies showed beneficial associations between ACM, cancer recurrence, and CSM with adherence to plant-based diets. Detrimental associations were found for these outcomes with saturated fats, trans fats, and sugar-sweetened beverages.** Breast cancer: Multiple studies suggest increased risk of all-cause and non-breast cancer mortality with high consumption of saturated and trans fats, and high-fat dairy products. Higher intake of protein was associated with reduced risk of breast cancer recurrence and CSM. Prostate cancer: Higher adherence to Mediterranean diet post-diagnosis, increased consumption of vegetable fats, and lower carbohydrate consumption were all associated with decreased ACM. Higher saturated and trans fat intake was associated with higher ACM. High consumption of whole milk and chicken with skin but not red and processed meat was associated with greater risk of CSM. High cruciferous vegetable consumption was associated with decreased cancer progression, while studies on tomato products have shown both decreased risk of progression and null findings.
Comments: Significance to clinical application	This review provides substantive evidence that increased consumption of plant-based diets is associated with reduced all-cause mortality after cancer-diagnosis. Plant-based diets were associated with reduced cancer recurrence and certain cancer-specific mortality. Saturated, trans, and animal fats were associated with increased all-cause mortality and cancer recurrence. Based on this, avoiding Western dietary patterns post-cancer diagnosis may improve mortality and recurrence outcomes. In addition, increased consumption of fiber from all sources, omega 3 fatty acids, vegetables, plant-fats, and nuts should be recommended. These recommendations fit within the scope of many plant-based diets, such as Mediterranean, prudent diet, vegan, and vegetarian diets.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Bella, 2017[132] **Meta-Analysis** Duration: N/A
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Observational studies that explored associations between dietary patterns and cancer incidence; n=7 studies with n=501,034 total individuals analyzed and n=8,177 cancer cases; Overall age or BMI NR
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Dietary patterns including plant-based diets (high in fruits, vegetables) and western-style diets (high in processed foods, meat, and other animal products) Adjusted for variables potentially related with cancer incidence, including gender, body mass index, smoking status, physical activity, energy intake and hormonal and parity status in women
Outcome(s) of interest and units	• Cancer incidence (all cancers)
Key Results (Bold qualitative assessment followed by quantitative results)	**Adherence to plant-based diets was associated with reduced odds of cancer incidence compared to both meat-based and mixed diets. Women had lower odds of cancer incidence if they adhered to a plant-based diet compared to a mixed diet.** Adherence to meat-based diet was associated with higher odds of cancer compared to plant-based diet (OR=1.64; 95% CI: 1.02, 2.63). In the comparison between plant-based and mixed dietary patterns, the odds of developing cancer were lower in those following a plant-based derived dietary pattern (OR=0.88; 95% CI: 0.92, 0.95). Women showed decreased odds of cancer in plant-based groups compared to mixed-diet groups (OR=0.91; 95% CI: 0.83, 0.99).
Comments: Significance to clinical application	This article suggests there is likely a reduced risk of cancer incidence with plant-based diets as compared to meat-based or mixed diets. This study showed a reduced risk of cancer for women with plant-based vs mixed diets. These results suggest an overall decrease in cancer risk with plant-based diets. Therefore, it may be prudent to recommend plant-based diets, or a reduction in animal sourced foods, for those with high environmental and genetic risk for developing cancer.

First author, year, study design (bold), name of study (if applicable), sample population	Godos, 2017[136] **Meta-Analysis** Duration N/A
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Studies comparing vegetarian, semi- and pesco-vegetarian diets to non-vegetarian diets in their risks of breast, colorectal, and prostate cancer; n=9 cohorts with n=686,629 total individuals (n=3,441 cases of breast cancer; n=1,935 cases of prostate cancer); Overall age and BMI NR
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet (eating meat < once per month); Semi-vegetarian diet (eating meat > once per month but < once per week); Pesco-vegetarian diet (consumption of fish > once per month); Non-vegetarian diet (eating meat > once per week)
Outcome(s) of interest and units	• Breast cancer incidence • Colorectal cancer incidence • Prostate cancer incidence
Key Results (Bold qualitative assessment followed by quantitative results)	**This study showed no benefit of vegetarian diet in reducing risk of breast cancer or prostate cancer. Semi-vegetarian and pesco-vegetarian diets had lower risk of colorectal cancer than non-vegetarian diet.** Compared to non-vegetarian diets, no variation of vegetarian diet showed lower risk of breast cancer (pure vegetarian RR=0.96; 95% CI 0.88, 1.05) or prostate cancer (pure vegetarian RR=0.83; 95% CI 0.63, 1.10); Semi-vegetarian and pesco-vegetarian showed reduced risk of colorectal cancer incidence (semi RR=0.67; 95% CI: 0.53, 0.83; pesco RR=0.86; 95% CI: 0.79, 0.94).
Comments: Significance to clinical application	This meta-analysis of 9 prospective cohort studies found no association between diet and risk of breast or prostate cancers. As plant-based diets have benefits in heart disease and management of type II diabetes, recommendation of plant-based diets for those at risk of cancer will likely not cause harm.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Penniecook-Sawyers, 2016[138] **Cohort; Adventist Health Study-2 (AHS-2)** Mean follow-up of 7.8 y (393,554 py)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Women in the AHS-2 cohort who did or did not develop breast cancer (BC); n=50,404 women (out of n=62,511 women from total cohort); Age=35-110 Cases (n=892): BMI =27.58 Non-cases (n=49,512): BMI =27.38
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Primary habitual dietary pattern reported over the last 1 year including non-vegetarian, vegan, lacto-ovo-vegetarian, pesco-vegetarian, and semi-vegetarian. Stratified by race (Black vs non-Black) and pre- or post-menopausal status; Adjusted for race, height, physical activity, family history of cancer, mammography after age 42 y, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children, breastfeeding, education, smoking, alcohol, BMI
Outcome(s) of interest and units	• BC incidence
Key Results (Bold qualitative assessment followed by quantitative results)	**Semi-vegetarians had a significant increase in BC risk in the post-menopausal group. No other significant associations were found between dietary pattern and BC risk including in subgroup analyses by Black and non-Black races. Vegans showed the lowest risk of breast cancer compared to all other dietary patterns in this study.** Non-statistically significant results were found for vegans with lower risk of BC compared to non-vegetarians (HR=0.78; 95% CI: 0.58, 1.05) and for vegans and semi-vegetarians with the lowest risk of BC in the premenopausal group (HR=0.77, 95% CI: 0.55-1.06 and HR=0.73; 95% CI 0.53, 1.06). Semi-vegetarians had a statistically significant increase in risk of BC in the post-menopausal group (HR=1.96; 95% CI: 1.12, 3.42).
Comments: Significance to clinical application	This study of breast cancer incidence in a low-risk population found no significant reductions in breast cancer risk in overall analyses and the premenopausal subgroup. The lack of statistical significance with nearly all associations was likely due to the small number of cases observed over the average 7.8 years of follow-up. The specificity of the study group, the low number of cases, and the lack of statistical significance make generalizability of this research difficult. However, further research on the potential benefits of vegan diets for reducing breast cancer risk is warranted.

First author, year, study design (bold), name of study (if applicable), sample population	Song, 2016[135] **Cohort; Nurse's Health Study (1980-2012) and Health Professionals Follow-up Study (1986–2012)** Total 3,540,791 py of follow-up
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Females from the Nurse's Health Study and males from the Health Professionals Follow-up Study; n=131,342 total medical practitioners Animal Protein Group (n=131,342; 64.7% women): Age=49 (9); overall BMI NR Nurse's Health Study (n=1,980; females) Health Professionals Follow-up Study (n=1,986; males)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Animal and plant protein consumption; healthy vs. unhealthy lifestyle habits group; Adjusted for age, multivitamin use, smoking status, pack-years of smoking, body mass index, physical activity, alcohol consumption, history of hypertension diagnosis, glycemic index, and intake of whole grains, total fiber, fruits, and vegetables; Mutual adjustment was conducted for animal protein and plant protein analysis
Outcome(s) of interest and units	• All-Cause mortality • CVD mortality • Cancer mortality • Other mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**Plant-protein consumption reduced risk of all-cause mortality, but there was no association between cancer mortality and plant- or animal-protein consumption.** 13,159 cancer deaths occurred during the study. Significant associations were found between plant-protein consumption and reduced risk of all-cause mortality (HR=0.90; 95% CI: 0.86-0.95), CVD mortality (HR=0.88; 95% CI: 0.80-0.97), and other mortality (HR=0.86; 95% CI: 0.79-0.92). Animal protein consumption was associated with increased risk of death from CVD (HR for highest vs. lowest quintile=1.08; 95% CI 1.01-1.16).

Appendix continued

Comments: Significance to clinical application	This study examined sources of dietary protein, where the effect size from exposure was likely small. No association between plant- or animal-protein consumption and risk of death from cancer was found, so no recommendation can be made for cancer specifically. Despite this, diets higher in plant protein were associated with lower risk of all-cause mortality, CVD mortality, and other mortality. Therefore, to reduce risk of mortality from these causes, diets higher in plant protein sources are recommended.

First author, year, study design (bold), name of study (if applicable), sample population	Jiang, 2015[141] **Meta-Analysis** Duration: NA
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Participants with or without endometrial cancer (EC); n=16 studies (6 cohort and 10 case-control) with n=7,556 participants with EC and n=563,781 without EC; Overall age and BMI NR
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Categories of animal fat, plant fat, and total fat where 11 studies examined total fat, 5 examined plant fat, and 6 examined animal fat Comparisons of highest quantile to lowest quantile.
Outcome(s) of interest and units	• EC incidence
Key Results (Bold qualitative assessment followed by quantitative results)	**No associations were found between all types of fat and EC.** There was no significant dose response for total fat and EC (30 g/d increase: RR=0.97; 95% CI: 0.94-1.01). No significant associations with EC for plant-based fat (RR=1.05; 95% CI: 0.94-1.18) or animal-based fat (RR=1.17; 95% CI: 0.92-1.36) where there was some evidence of heterogeneity in animal-based fat measures of association.
Comments: Significance to clinical application	This meta-analysis found no pooled evidence of associations between any type of dietary fat and EC incidence. More research needs to be conducted on very low-fat diets as compared to moderate and high fat diets, modified by proportion of animal/plant fat to assess the clinical implications of more varied fat consumption.

First author, year, study design (bold), name of study (if applicable), sample population	Link, 2013[137] **Cohort; California Teacher's Study Cohort** 14 years (1995-2009)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Women with no current or previous diagnosis of breast cancer; n=91,779 (out of 133,497 total); Mean (IQR) age=50 (42, 60); Mean (IQR) BMI=23.7 (21.3, 27.3)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Five habitual dietary patterns were identified: plant-based (high in fruit and vegetables); high-protein, high fat (high in meats, eggs, fried foods, and high-fat condiments); high-carbohydrate (high in convenience foods, pasta, and bread products); ethnic (high in legumes, soy-based foods, rice, and dark-green leafy vegetables); and salad and wine (high in lettuce, fish, wine, low-fat salad dressing, and coffee and tea) Stratified by age at baseline; Adjusted for race/ethnicity/ birthplace, family history of breast cancer, age at menarche, parity/age at first full-term pregnancy, average daily caloric intake, physical activity, socioeconomic status, history of a benign breast biopsy and its interaction with time-dependent age, BMI, height, menopausal status/hormone therapy use, and the other four dietary patterns
Outcome(s) of interest and units	• Breast cancer incidence; breast cancer incidence by hormone receptor site: **estrogen receptor** (ER+/-) and **progesterone receptor** (PR+/-)
Key Results (Bold qualitative assessment followed by quantitative results)	**Higher adherence to the plant-based diet was associated with a reduced risk of breast cancer and ER-PR tumors. Higher adherence to the salad and wine diet was associated with an increased risk of breast cancer and ER+PR+ tumors. No other associations were found between dietary patterns and breast cancer risk.** 4,140 incident cases of breast cancer were recorded during the study follow-up; High vs low adherence to plant-based diet (RR=0.85; 95%CI: 0.76, 0.95; P for trend=0.003); High vs low adherence to the salad and wine diet (RR=1.12; 95%CI: 1.01, 1.25; P for trend=0.011); Plant-based diet associated with reduced risk of ER-PR- tumors (RR=0.66; 95% CI: 0.48, 0.91 for highest vs lowest quintile; P-trend=0.03); Salad and wine pattern increased risk of ER+PR+ tumors (RR=1.29; 95% CI: 1.12, 1.49 for highest vs lowest quintile; P-trend=0.001).
Comments: Significance to clinical application	In this study, habitual dietary patterns were associated with breast cancer risk. However, the plant-based diet score was adjusted for alcohol intake, while alcohol was inherent in the wine and salad dietary pattern. This suggests that higher consumption of plant-based foods with abstention from alcohol may reduce risk of breast cancer, as alcohol consumption likely increases breast cancer risk. Recommendation of plant-based diets with reduced alcohol consumption should be recommended for those at high risk of breast cancer.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Huang, 2012[134] **Systematic Review and Meta-Analysis** Duration NA
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Cohort studies examining cancer incidence in vegetarians vs non-vegetarians; n=7 studies with n=124,706 total participants; Age and BMI for subjects NR
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegetarian diet, including lacto-ovo-vegetarian diet and vegan diet
Outcome(s) of interest and units	• Overall cancer incidence • All-cause mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diets were associated with reduced risk of all-cause mortality and pooled cancer mortality; however, there was a risk of publication bias in both outcomes.** A vegetarian diet was not significantly associated with all-cause mortality (RR=0.91; 95% CI: 0.66, 1.16) but was associated with a lower overall risk of cancer mortality (RR=0.82; 95% CI: 0.67, 0.97).
Comments: Significance to clinical application	This review found a slight reduction in cancer and all-cause mortality was associated with vegetarianism. Vegetarian diets pose little to no risk to the individual and have consistently shown other health benefits; therefore, plant-based diets can be safely recommended for chronic disease prevention.

First author, year, study design (bold), name of study (if applicable), sample population	Rock, 2009[140] **RCT; Women's Healthy Eating and Living Study (WHEL)** 6 years of follow-up for carotenoid measures and median 7.2 years for breast cancer events
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Women from the WHEL diagnosed with early-stage breast cancer; n=3,043; Age=51.3 (8.8); BMI=27.3 (6.0)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Daily dietary goals of 5 vegetable servings, 16 oz of vegetable juice or vegetable equivalents, 3 fruit servings, 30 g fiber, and 15-20% energy intake from fat; counseled via phone conversations to keep individuals on track with dietary goals; Stratified on years since diagnosis to randomization (0-1, 1-2, 2-3, and >3 y); Controlled for age at randomization, clinic site, tumor hormone receptor status, tumor type, chemotherapy, oophorectomy, smoking status, plasma cholesterol, and BMI
Outcome(s) of interest and units	• AUC of carotenoid concentrations over the course of follow up (serum carotenoids taken at 1, 2 or 3, 4, and 6 years) • Time to a second breast cancer event (recurrence or new primary breast cancer)
Key Results (Bold qualitative assessment followed by quantitative results)	**Regardless of study group assignment, there were significant associations between higher serum concentrations of carotenoids and decreased risk of breast cancer.** The intervention group increased serum carotenoid concentrations by 66% but showed no reduced risk of breast cancer development (HR=1.06; 95% CI: 0.89-1.27). Study participants with the highest serum carotenoid concentration had decreased risk of breast cancer incidence (HR=0.67; 95% CI: 0.54-0.83) after adjustment for covariates. The same was true for a subgroup with ER-positive tumors (HR=0.7; 95% CI: 0.54-0.91) but not those with ER-negative tumors (HR=0.7; 95% CI: 0.46-1.08).
Comments: Significance to clinical application	This study found reduced risk of breast cancer occurrence in participants with medium and high serum carotenoid levels compared to those with the lowest levels. This study's findings were inconclusive due to a potential for residual confounding. The study did not control for socioeconomic status or physical activity, and factors present before the intervention that may account for the lack of decreased breast cancer risk in the intervention group despite increased levels of carotenoid intake.

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Frattaroli, 2008[142] **RCT; NA** 1 year, with post-intervention follow-up at year 2
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Patients with early-stage prostate cancer with Gleason score <7 and PSA 4-10 ng/mL; n=93; Age=66 (8) Intervention (n=44) Control (n=49)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan diet (supplemented with soy, fish oil, vitamin E, selenium, and vitamin C) with limited consumption of simple carbohydrates, and <10% calories from fat; moderate aerobic exercise (walking 30 m, 6 d/wk), stress management techniques (gentle yoga-based stretching, breathing, meditation, imagery, and progressive relaxation for a total of 60 m/d), weekly support group to enhance adherence to intervention
Outcome(s) of interest and units	• Receipt of standard prostate cancer therapy: radical prostatectomy, radiotherapy, androgen deprivation, chemotherapy; other events; prostate (noncancer) events; cardiac events; other cancer events; "all other events"
Key Results (Bold qualitative assessment followed by quantitative results)	**Those in the intervention group experienced reduced rates of typical prostate cancer treatment and avoided radical prostatectomy and radiotherapy.** Thirteen control participants underwent some form of standard prostate cancer therapy compared to two intervention participants (P=0.005). Eight controls and one intervention participant underwent radiotherapy (P=0.034). Five controls and no intervention participants underwent radical prostatectomy (P=0.058).
Comments: Significance to clinical application	This study provides evidence that a plant-based intervention involving stress reduction and increased exercise has significant beneficial effects in reducing prostate cancer progression. Such interventions should be strongly suggested for management of early-stage prostate cancer.

First author, year, study design (bold), name of study (if applicable), sample population	Ornish, 2005[115] **RCT; NA** 12 months
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Men electing not to undergo conventional treatment for stages T1 or T2 prostate cancer with Gleason score <7 and serum PSA 4-10 ng/mL; n=93 Intervention (n=44): Age=65 (7); Weight=80 (13.6) Control (n=49): Age=67 (8); Weight=80 (11.3)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-fat, vegan diet with no animal products and minimal added oils, ~10% calories from fat, low in simple carbs, and supplementation with soy (1 serving of tofu/d plus 58 g/d fortified soy protein powder beverage), fish oil (3 g/d), vitamin E (400 IU/d), selenium (200 mcg/d) and vitamin C (2 g/d); stress management training and suggested 30 m of moderate aerobic exercise
Outcome(s) of interest and units	• Change in prostate-specific antigen (PSA), weight, total cholesterol, LDL, HDL, LNCaP growth and apoptosis (cancer cell growth and apoptosis in cultured serum from study subjects)
Key Results (Bold qualitative assessment followed by quantitative results)	**Intervention participants who underwent intensive lifestyle change had significant improvements in PSA, total cholesterol, LDL cholesterol, weight, and reduced cancer cell growth in vivo compared to controls.** Intervention group experienced decreased weight (-4.5 kg; P<0.001), PSA (-0.25 ng/mL; P=0.016), total cholesterol (-32 mg/dL; P<0.001), LDL (-30 mg/dL; P<0.001), and LNCaP growth (-69.94% FBS; P<0.001). Measures of PSA increased in control group while LDL, total cholesterol, and weight stayed consistent with baseline. Six control patients and zero intervention patients withdrew to undergo conventional treatment due to progression of prostate cancer.
Comments: Significance to clinical application	This study provides strong evidence that intensive lifestyle change, including reduced intake of animal fat and total fat with increased consumption of plant-based foods, reduced stress, and increased exercise can be beneficial in slowing the progression of markers of prostate cancer in elderly men.

NR=not reported; py=person-years

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AUTOIMMUNE DISEASE

Key Points for Practitioners

- Whole food, plant-based (WFPB) diets have utility both in decreasing risk for autoimmune conditions and, in some cases, improving symptoms among those currently diagnosed.[86,118,119,126]
- Two major mechanisms by which the diet may play a role is through decreasing inflammation and by affecting the gut microbiome.[118,127–129]
- WFPB diets have no adverse side effects and are associated with other health benefits[130] such as cardiometabolic health,[131–133] healthy weight,[86,134] and longevity.[135]
- Some evidence suggests that either or both gluten-free[84,86,136,137] or raw food versions of plant-based diets[120,138] may offer additional support.
- Existing evidence on plant-based diets and autoimmune conditions can be communicated to patients to support their ability to make informed decisions about their diet and course of treatment.
- If patients express interest in trying a WFPB diet of some kind, it is helpful to share ACLM patient-facing resources and tools with them.[139–141]

ABSTRACT | Healthy immune function is necessary to fight against viruses and diseases, yet when the immune system is poorly regulated, healthy cells can become the target of the immune system's robust defenses. Such is the case with autoimmune diseases, which encompass type 1 diabetes, inflammatory bowel diseases, rheumatoid arthritis, and nervous system diseases like multiple sclerosis, among many other disorders. Autoimmune conditions are becoming increasingly common in the United States and are currently among the most common disease category affecting millions of Americans each year. One potential explanation for the increase is the rise in the obesity state, which can interfere with the body's ability to regulate immune responses such as inflammation. Diet has strong associations with obesity, inflammation, and the immune system, and there is now ample evidence indicating that diets high in plant foods (e.g., fruits, vegetables, whole grains, legumes, nuts, and seeds) have beneficial effects on weight loss, markers of inflammation, and symptoms associated with autoimmune dysfunction. Unlike traditional pharmaceutical treatments that can be costly and produce unpleasant side effects, treatments involving dietary changes are cost-effective, safe, and have strong potential to improve multiple health outcomes beyond the targeted autoimmune diseases. With these benefits in mind, clinicians can consider plant-based dietary patterns as a component of the current treatment regimens for patients with autoimmune diseases.

Autoimmune Disease in Context

Autoimmune disease, or autoimmune inflammatory (AI) disease, refers to some 80 to 100 or more related diseases[1,2] that occur as a result of an overreactive immune system. Here, the body attacks healthy cells, tissues, or organs that it mistakes for foreign bodies, which results in the production of antibodies and creates a chronic inflammatory state.[3] With so many potentially autoimmune-related diseases, prevalence and incidence rates are difficult to calculate; however, the National Institutes of Health (NIH) estimates that 23.5 million Americans are currently affected by autoimmune diseases, while the American Autoimmune Related Diseases Association (AARDA) estimates a much higher 50 million.[2] Globally, it is thought that roughly 4% of the world's population is affected by at least one autoimmune disease,[4] and the prevalence of these conditions continues to rise.[5,6] Different autoimmune diseases affect different organ systems. For instance, in people with Type 1 diabetes, the endocrine system is attacked, which inhibits hormonal production of insulin. In Crohn's disease and other inflammatory bowel diseases, the digestive system is targeted. It is the musculoskeletal system under attack in rheumatoid arthritis, and autoimmune conditions can also affect the central nervous system (multiple sclerosis), as well as the skin and connective tissues (e.g., psoriasis).[7,8] Autoimmune diseases also affect certain populations disproportionately. In the United States, 78% of autoimmune cases occurred in women, according to a 2004 report from the Centers for Disease Control and Prevention (CDC).[8] Women of African, Hispanic, Asian, and Native American descent have been more likely to develop lupus, for example, than Caucasian women, and African American women have also been shown to develop this disease at a younger age than Caucasians.[7,9] Autoimmune diseases are known to have a genetic basis so tend to cluster in families, but individual family members may experience different autoimmune diseases.[7,9] While genetics are largely implicated in the development of many autoimmune diseases, T regulatory cells seem to play a central role in autoimmune dysfunction related to pro-inflammatory cytokine secretion,[10,11] and circumstantial evidence links certain autoimmune dysfunctions to preceding infections.[12–14]

Diet and Autoimmune Diseases

Though it is generally agreed that genetic factors predispose individuals to the development of autoimmune disorders,[15,16] research (including twin studies) reveals that environmental factors and diet play a predominant role in the manifestation of these diseases.[17] There is a higher prevalence of autoimmune diseases in Western societies where lifestyle may contribute through modern cleanliness, and sterilization practices reducing exposure to beneficial pathogens.[13,18,19] Western dietary practices are also implicated, characterized by high intakes of energy, cholesterol, protein, saturated fat, added sugar, and salt with low intakes of fiber and antioxidants. Such a diet is associated with increased risk of autoimmune diseases through directly increasing inflammation[20,21] and indirectly increasing insulin resistance and obesity.[22,24] Non-Western countries that have experienced relatively lower rates of autoimmune disease like Japan and India are now seeing increased incidence, possibly associated with changing environmental and lifestyle factors[25] such as diet.[26,27,28] Though there is limited evidence that autoimmune diseases are directly linked to diet, this may be due to the challenge of detecting causal relationships in otherwise heterogeneous populations.[10] Studies on individual nutrients have often born conflicting results.[10,29] With these challenges in mind, the remainder of this chapter will focus on existing evidence relating dietary factors to the conditions listed in Table 1, presently classified as an autoimmune disease.

Table 1 Dietary factors related to autoimmune conditions

Condition	Dietary Risk Factors*
Type 1 diabetes	• Short duration of infant breastfeeding[30,31] • Early introduction to breast milk substitutes, cow's milk formula,[30] and other dairy products[31] • Increased consumption of cow's milk or formula milk from age 6-9 mo[32] • High consumption of milk (4+ times/day) at age 1 yr[30] • Late introduction of gluten (> age 6 mo),[30] though evidence is inconsistent[33] • Early exposure to cereals,[32] eggs, root vegetables[33–35] • Low fiber[36,37] • Dietary intake lower in linoleic acid, niacin, and riboflavin, and higher in total sugars[38] including sugar-sweetened beverages[39]
Crohn's, ulcerative colitis, and other inflammatory bowel diseases	• Poor adherence to a Mediterranean-style diet[40] • Short duration of breastfeeding as an infant[41] • High consumption of ultra-processed foods (including soft drinks,[42] refined sweetened foods,[43] salty snacks, processed meat)[44] and consumption of fast food[45] • Low-fiber[26,46–48] • Diet high in protein[45,49] (especially animal proteins[50] including meat and fish[51]) • Low intake of omega 3 and high intake of omega 6 polyunsaturated fatty acids[41,50] • High intake of fats and oils,[43] total fat,[43,45] and several types of fats[43] (especially saturated fats)[50] • High intake of monosaccharides (simple sugars)[43,45,50] • Insufficient intake of vegetables or fruits[45,48] • Low fruit consumption in children[52]
Rheumatoid arthritis (RA)	• Red meat[53–55] • Salt[55–58] • Excessive food intake and obesity[59–61] • Low polyunsaturated fatty acids[62] • Magnesium supplementation[63]
Multiple sclerosis (MS), with possible implications for other nervous system disorders	• Dairy consumption[64,65] (particularly cow's milk[65–67]) • Animal fat[68] • Meat[69] • Excess energy intake/obesity[70,71]
Celiac disease	• Primary risk factor is the high-risk HLA genotype,[72,73] but symptoms develop only in the presence of gluten consumption[74,75]

Lupus	• Intestinal dysbiosis[76]**
	• Healthy gut microbes may flourish with adequate intake of these nutrients:[76]
	  • Vitamin D[77,77]
	  • Vitamin A[79–81]
	  • Omega 3 polyunsaturated fatty acids
	  • Polyphenols[82]

Psoriasis, seborrheic dermatitis, and eczema	• Low adherence to Mediterranean-style diet[83]
	• Low consumption of legumes, fish, and extra virgin olive oil[83]
	• Higher consumption of dairy products[83]
	• Psoriasis improvements have been found with:
	  • Gluten-free diet and healthy eating patterns including oral vitamin B12, vitamin D, selenium, and omega-3 fatty acids in fish oils[84]
	  • Frequent fresh fruit consumption (more than once daily)[85]
	  • A diet regimen rich in mono- and poly-unsaturated fatty acids (especially omega 3s), fruits, vegetables, and fiber, with reduced intake of saturated fats, simple carbohydrates, and sweetened drinks[86]

**Risk factors are often found together. Other interplaying risk factors include smoking, alcohol, lack of breastfeeding, and lack of exercise.[31,87–89]*
*** Intestinal dysbiosis and the interplay between gut microbiota and immunity is a noted risk factor for most if not all autoimmune diseases[90,91]*

A Note on Parkinson's Disease

The National Parkinson's Foundation clarifies that Parkinson's disease (PD) is not categorized as an autoimmune disease at the time of this writing, as the cause is still unclear. Therefore, it is not included in this table and the summary of key studies to follow, though PD may be included in some research mentioned here. The etiology of PD appears to be multifactorial, with potentially genetic as well as environmental factors at play. A recent study (2020) adds increasing evidence that PD is at least partly an autoimmune disease as it involves recognition by T cells of specific epitopes derived from the PD-associated protein α-synuclein.[92,93] The researchers report that signs of autoimmunity can appear in PD patients years before their official diagnosis. Regarding interventions for PD patients, researchers have found improvements in the Unified Parkinson's Disease Rating Scale (UPDRS), modified Hoehn and Yahr Staging Scale (HY), and UPDRS sub scores III and II with a plant-based dietary intervention.[92]

Benefits of Plant-Based Nutrition for Autoimmune Disease

Ample evidence suggests that plant-based diets are protective against autoimmune disease and have the potential to produce improvements in symptoms. Plant-derived antioxidants have an anti-inflammatory effect by controlling free radicals leading to oxidative stress and pro-inflammatory cytokines involved in the pathogenesis of autoimmune diseases.[11,94] Further, omega-3 fatty acids, particularly EPA and DHA found in algae and algal oil, decrease C-reactive protein levels and other inflammatory mediators and have elicited an anti-inflammatory effect in lupus patients.[95,96] DHA and EPA have also demonstrated protection against free radicals and cardiovascular alteration by reducing specific antibodies (anti-dsDNA) and interleukins (IL-1α, IL-1β, IL-2) as well as TNF-α.[96,97] Studies show their role in regulating proteinuria and blood pressure, as well.[96,97] Other sources of omega-3 fatty acids include fish, flaxseed, olives, and olive oil.[98]

Much research indicates that consumption of a Mediterranean-style diet that focuses on fiber-rich plant foods has been associated with reduced risk of rheumatoid arthritis (RA)[99] and Crohn's or inflammatory bowel diseases,[100] though results for RA are mixed. One recent large prospective cohort did not find clear associations between iron or meat and RA,[101] though several other studies have.[54,55,99]

A recent population study (N=280) found that adherence to a plant-based Mediterranean diet was associated with disease activity improvements in lupus patients, with greater dietary adherence exerting a more beneficial effect.[102]

Low-fat, plant-based diets have been found to lessen symptoms of multiple sclerosis and reduce or eliminate the need for medications.[103–105] In contrast, diets that include animal foods have been shown to impair the management of chronic inflammatory autoimmune diseases.[53,54,106–108] Obesity and metabolic dysfunction predispose individuals to inflammation and, therefore, autoimmune diseases.[70,71,109] Diets higher in whole or minimally processed plant-source foods can be instrumental in maintaining a healthy weight or achieving a healthy weight if overweight or obese. Large population studies have shown that following or transitioning to a healthy plant-based diet from diets containing more animal foods is associated with less weight gain over time.[110,111] Another study showed lower baseline BMIs in vegetarians of any kind (i.e., vegan, lacto-vegetarian, lacto-ovo-vegetarian) compared with non-vegetarians. In a longitudinal follow-up, risk of obesity was 7% lower for each additional year that an entirely plant-based vegan diet was followed compared to a non-vegetarian diet.[112]

Dietary interventions using whole plant-based foods, particularly foods rich in prebiotics (i.e., cereal grains, legumes, fruits, and vegetables),[113–115] possibly accompanied by customized medically supervised fasting,[116–118] may help control and limit symptoms for certain autoimmune conditions and lessen or eliminate the need for pharmaceuticals.[119–124] This dietary approach may offer a safe and effective intervention[125] for this cluster of diseases that have no curative treatment in traditional medicine.

Mechanisms

There are many mechanisms by which plant foods improve autoimmune conditions. Several nutrients found in them have demonstrated a protective and anti-inflammatory effect for autoimmune disorders, including polyunsaturated fats and antioxidants, while harmful effects have been found with foods such as red meat and salt.[55] A few of the foremost mechanisms linking diet to autoimmune diseases are highlighted below.

Inflammation and Oxidative Stress

Apart from normal physiological inflammation, prolonged inflammatory responses can lead to significant tissue and organ damage and are associated with many chronic diseases, especially autoimmune diseases.[142] Abnormal immune response by T cells and other immune cells as well as epigenetic mechanisms have been implicated in the development and progression of autoimmune diseases,[10,142] and diet is known to be associated with inflammatory regulation in both healthy populations and those with autoimmune diseases.[143] In particular, both observational and interventional studies have shown anti-inflammatory effects with the Mediterranean dietary pattern when compared to typical North American or Northern European dietary patterns.[143] Similarly, the "Western diet" (characterized as high-fat and cholesterol, high protein, high sugar, and with excess salt intake, and frequent consumption of processed and "fast foods") has been shown to be a possible promoter of autoimmune diseases. This dietary pattern leads to excessive accumulation of white adipose tissue, subsequently producing systemic inflammation through the release of pro-inflammatory mediators such as TNF-α, IL-6, leptin, resistin, and C-reactive protein, and by impacting T cell response.[10] A number of clinical trials have demonstrated that a low-fat vegan diet contributes to improved symptoms of rheumatoid arthritis (RA), sometimes when coupled with fasting. A randomized controlled trial (N=66) using a gluten-free, vegan diet reduced inflammation and improved the colonic microbiome, particularly lactobacilli, producing potentially atheroprotective and anti-inflammatory changes, including decreased LDA and oxLDL levels, as well as raised anti-PC IgM and IgA levels.[136,144,145]

Being in a chronic state of inflammation increases risk of cellular damage in the body through the overproduction of reactive oxygen species. This process ultimately leads to oxidative stress and damage to biomolecules (e.g., proteins, DNA);[146] therefore, in addition to inflammation, oxidative stress is characteristic of many AI diseases, including lupus. The anti-inflammatory activity of omega-3 fatty acids can inhibit pro-inflammatory cytokines and C-reactive proteins. Thus, whole fruits and vegetables with intact oils can improve oxidative stress, while evidence suggests that omega 6 fatty acids in oils from processed foods are pro-inflammatory.[147–151] Furthermore, many plant-based foods, such as kale and berries, are rich sources of antioxidants which are known to combat oxidative stress.[152]

Gut Microbiome

The role of intestinal microbiota in modulating inflammation has only recently emerged.[153–156] Dietary imbalances may induce dysbiosis and introduce proinflammatory cytokines that are associated with autoimmune diseases.[157–159] As evidence of this dysbiosis, several studies have shown vastly different microbial compositions in the gastrointestinal tracts of individuals with and without inflammatory bowel disease. Those with this disease have shown restriction of biodiversity and imbalanced bacterial composition compared to healthy individuals. With this change in composition also comes a distinct change in microbial functions, including fecal tryptic activity, oxidative response, or lipid and glycan metabolism pathways.[160] Similarly, patients with systemic lupus erythematosus have shown restricted diversity of gut microbiota, and this is associated with increased gut permeability ("leaky" gut) and impaired gut barrier leading to less protection against pathogens in this population.[161] Interactions between bacterial communities and the host can also result in epigenetic modifications that have been associated with insulin secretion and emerging conditions leading to type 1 diabetes.[137] The gut may also play a key role in rheumatoid arthritis, where intestinal barrier permeability can allow endotoxins to enter the bloodstream.[162] This may explain elevated antibodies and pro-inflammatory T cells in RA patients.[163–165] Diet is a key factor in shaping the composition of intestinal microbiota and establishing microbiota homeostasis. Subsequently, diet plays a role in

stabilizing the integrity of the gut mucosal barrier, which helps modulate gut immunity.[137] Specifically, diets containing sufficient quantities of non-digestible carbohydrates, such as dietary fibers and resistant starches, which are present only in plant foods, enable gut microbes to produce short-chain fatty acids (SCFAs). These SCFAs confer beneficial effects such as reducing mucosal inflammation in the GI tract, strengthening the epithelial defense barrier to avoid pathogenic infections, and preventing insulin resistance and diabetes.[137]

Fiber

Increasing fiber-filled plant food improves glycemic control through normalizing beta cell function in the pancreas and allowing the body to overcome insulin resistance.[166] This is especially crucial for individuals with Type 1 diabetes and those with AI diseases accompanied by obesity where glycemic control may be compromised. Evidence supports that nutrient-dense diets high in fiber can improve glycemic load control and disease outcomes in these populations, especially when paired with exercise.[167,168,169] For instance, studies comparing animal protein (that has no fiber) and plant protein (which contains fiber) suggest that a diet rich in plant protein may favorably affect glycemic control.[170–175] Potential mechanisms explaining this benefit include the following: high intake of fiber and magnesium, elimination of oxidation produced by heme iron intake, increased intake of antioxidants (e.g., carotenoids) and other nutrients, weight loss, and the favorable amino acid profiles of plant proteins.[176–178]

Dietary Fats

Diets high in fat, especially those high in long-chain saturated fatty acids, have pro-inflammatory effects in many organs throughout the body.[179] Studies have shown that when some or all of these long-chain fatty acids (found in animal-sourced foods) are replaced with medium-chain saturated fatty acids (found in coconut or palm oils) in the diet, incidence of spontaneous colitis can decrease, and there is some protection against chemically-induced gut inflammation due to the attenuation of pro-inflammatory cytokines and immune cell oxidative stress.[179] Diets higher in unsaturated fatty acids, especially polyunsaturated fatty acids (PUFAs), along with fiber from whole plant food have been associated with decreased risk for MS as well as RA.[66,180] Among PUFAs, omega 3 fatty acids, found in plant and marine oils, have been correlated with decreased production of pro-inflammatory cytokines through decreased alkaline phosphatase and bile duct injury.[179] Intake of omega 3 fatty acids at a ratio of 1 part to 3 parts omega 6 fatty acids has shown the most benefit, and studies have suggested that even partial replacement of omega 6 with omega 3 (ratio of 10) or medium-chain triglycerides can improve experimental colitis.[179] Dietary patterns with higher omega 3 to omega 6 ratio, including Mediterranean-style, vegetarian, and vegan diets, have demonstrated improvements in some RA disease activity such as pain score, morning stiffness, physical function and vitality, and measures of inflammation (e.g., CRP).[181] Other studies have shown that a dietary pattern low in calories and protein but high in fiber, PUFAs, vitamins, minerals, and polyphenols (e.g., whole food, plant-based diet) has the potential to modulate the inflammation and immune functions of systemic lupus erythematosus.[121] In this dietary pattern, the PUFAs specifically can reduce levels of inflammatory mediators, C-reactive protein, lymphocyte proliferation, macrophage-mediated and cytotoxic T-cell-mediated cytotoxicity, synthesis of proinflammatory cytokines, and chemotaxis from monocytes and neutrophils.[121] Despite the growing evidence in support of diets higher in PUFAs to reduce inflammation, several randomized controlled trials have shown no effect from omega 3, omega 6 or overall PUFAs on inflammatory bowel diseases (including Crohn's Disease and ulcerative colitis) or their associated long-term inflammatory status.[182]

Polyphenols and Flavonoids

Polyphenols are bioactive molecules found in plants (especially fruits, vegetables, legumes, cereal grains, olives, cocoa, tea, coffee, and wine), and flavonoids are a class of polyphenols that are especially abundant in fruits and vegetables. These compounds protect against chronic degenerative ailments in humans and have numerous health-promoting benefits, including anti-inflammatory and antioxidant properties.[183] For autoimmune diseases like type 1 diabetes, RA, and MS, polyphenols have a potential role in prevention and treatment by regulating signaling pathways, suppressing inflammation, and

limiting demyelination.[123] Polyphenols can modulate immune effects by inhibiting autoimmune T cell proliferation and downregulating pro-inflammatory cytokines (interleukin-6 (IL-6), IL-1, interferon-γ (IFN-γ)). Beyond suppressing inflammation, polyphenols can elevate antioxidant enzyme gene expression and secretion of anti-inflammatory mediators. In inflammatory bowel diseases, polyphenols can be effective in management strategies due to their ability to modulate the expression of pattern recognition receptors and inflammatory responses in the intestinal epithelial and immune cells.

Furthermore, polyphenols can influence the gut microbiota as a probiotic, supporting the maintenance of intestinal homeostasis and reducing inflammation.[123] In patients with MS, studies assessing individual flavonoid compounds have shown positive therapeutic effects alone and when combined with anti-MS therapeutic agents. Here, flavonoid compounds had anti-inflammatory effects on peripheral blood mononuclear cells (PBMCs) by reducing PBMC proliferation, reducing production of TNF-α and IL-1β from PBMCs, and inhibiting NFkB which reduced MMP-9.[184]

Common Questions and Concerns

Is there a link between diet and autoimmune disease?

It seems that the autoimmune response occurs from a cascade of events leading to inflammation, and that diet may be a trigger for susceptible individuals.[99] Accumulating evidence shows that dietary factors are implicated in risk for autoimmune diseases,[99] and a Western-style diet might increase risk.[10,53] Diets high in whole plant foods (fruits, vegetables, whole grains, seeds, beans, and nuts) and low in refined carbohydrate (sugar and flour), and saturated and trans fats (meats and dairy) appear to be protective against systemic inflammation and help to control the inflammatory response.[97,99] There does not appear to be harm in moving towards an unrefined, WFPB diet for those experiencing autoimmune diseases, whereas there appears to be a link between animal and refined foods and the inflammatory response.[53,94] Attention may be needed to avoid dietary triggers or allergic reactions to some foods or nutrients, such as gluten, for those with celiac disease. Celiac disease seems to be the exception to autoimmune diseases and diet in that there is a clear causal connection to gluten.[185] Note also that those suffering from one autoimmune disorder, particularly celiac disease, are at higher risk for developing others.[186] This could be due to damage done to the mucosal barrier of the intestinal lining that protects against an autoimmune reaction to pathogens entering the blood.[75,186,187]

Will a plant-based diet reduce inflammation from the autoimmune reaction?

A plant-based diet of whole grains, legumes, fruits, and vegetables that is low in or void of red meat shows potential to reduce the risk of the autoimmune response, probably due to its anti-inflammatory properties. It may be that the dietary fiber in plant foods helps to stimulate the growth of certain gut microbiota, particularly but not exclusively Bifidobacterium and Lactobacillus, which hold anti-inflammatory properties and work to improve symptoms, including inflammation and to limit joint pain.[188–190]

Can't non-digestible (insoluble) fiber make IBD symptoms worse?

Though dietary fiber intake supports gut health and can control inflammation, it may be hard to determine if dysbiosis is the cause or consequence of IBD. For those with flare-ups or active IBD, Crohn's, or ulcerative colitis, undigested fiber may worsen symptoms for some with a sensitivity to it. Further, incomplete fermentation due to the dysbiotic state may result in a buildup of pro-inflammatory metabolites, including succinate,[191] that may irritate an already sensitive bowel. It may be helpful to limit intake to only the fibers with clear evidence of anti-inflammatory effects. Some evidence indicates that limiting or avoiding insoluble fiber (brown rice and whole grains) and concentrating on soluble fibers might be most beneficial for IBD patients.[192] Soluble fiber is more readily fermentable by gut microbes into the short-chain-fatty-acid butyrate. Fruits are the highest source of soluble fiber, and some research suggests long-term intake of fiber from fruits reduces risk of developing Crohn's disease but not ulcerative colitis.[193] Higher amounts of soluble fiber from whole fruits, vegetables, beans and oats may help some individuals, though certain foods may be triggers for others.[194] Fruits with skin and seeds, raw green

vegetables, cruciferous vegetables (broccoli, cabbage and cauliflower), whole nuts, and grains may be triggers for some. Eliminating all dairy and limiting fat intake may help.[127] It may be difficult to zero in on triggers, particularly with diets that include animal protein and sugar. Working with a knowledgeable lifestyle medicine-trained dietitian or healthcare professional may be helpful.

Can a plant-based diet help patients with AI diseases lose excess weight to address AI symptoms?

Excess adipose tissue propagates inflammation and can exacerbate certain symptoms associated with AI diseases and common comorbidities, such as hypertension and metabolic syndrome, and can reduce a patient's response to some medical treatments.[117,195,196] Therefore, maintaining a healthy weight and reducing obesity and overweight in AI patients can be an effective treatment to reduce, alleviate, or lower the risk of developing some AI symptoms.[197,198] Plant-based diets can be effective for preventing weight gain,[111,199–201] maintaining a healthy weight,[199] and achieving healthy weight loss.[111,199–202] This is largely due to the high fiber and water content of plant-based diets—especially those centered around whole, minimally processed foods—which allows most people to eat until satiated without overconsuming calories.[203,204] Furthermore, the higher nutrient-density of plant-based foods can improve nutrient status and lead to improved symptoms for patients with various AI diseases.

Does a plant-based diet provide enough protein for patients at risk of muscle-wasting due to their AI disease?

Some AI diseases, such as MS and inflammatory bowel diseases, are characterized by loss of muscle mass which can lead to lower functionality and quality of life. In these patients, a higher intake of dietary protein in conjunction with daily exercise and regular resistance training or high-intensity training may be necessary to sustain a healthy muscle mass.[205–207] A well-executed plant-based diet can provide plenty of protein for all patients, including those with higher protein needs. Legumes, in particular, provide high amounts of protein as well as dietary fiber, iron, zinc, folate, and potassium, and they are low in saturated fat, which makes them a healthy alternative to animal-based protein sources such as meat and dairy.[208] A daily diet that includes beans, whole grains, nuts, and seeds can provide adequate protein for most patients,[209] but patients with higher protein needs may benefit from working with a knowledgeable dietitian to plan a health-promoting diet with adequate protein.

Do plant-based diets have any adverse interactions with AI treatments (since some drugs can interact with nutrients like B12 and folate)?

Several possible drug-nutrient interactions have been identified for various AI disease treatments.[210,211] Folic acid absorption can be impaired in psoriasis or rheumatoid arthritis patients receiving methotrexate. Supplementation is common for these patients.[210,211] Plant-based diets are typically high in folate since it is present in vegetables, fruits, nuts, beans, and grains. Excellent sources of dietary folate include spinach (and other leafy green vegetables), black-eyed peas, asparagus, brussels sprouts, broccoli, peas, and kidney beans.[212] Psoriatic or RA patients taking ciclosporin should be advised to avoid the consumption of grapefruit juice, as this juice increases the bioavailability of ciclosporin by more than 60%.[210,211]

Any patients taking systemic retinoids should be advised to avoid food sources rich in vitamin A, particularly liver, to reduce risk of hypervitaminosis A. Retinoids can also induce hyperlipidemia, so dietary patterns that are low in saturated fats and high in omega-3 fatty acids are recommended to significantly lower serum triglycerides.[210] Plant-based diets are naturally lower in saturated fatty acids than diets including meat and dairy products and can include adequate omega-3 fatty acids from sources such as chia seeds, Brussels sprouts, algal oil, hemp seeds, walnuts, and flaxseeds.[213] For other possible drug-nutrient interactions related to treatments for AI diseases, patients should be advised to consult with their pharmacist.

Summary of Key Studies

Multiple studies have examined the association between various versions of plant-based dietary interventions and improvement of autoimmune conditions, including rheumatoid arthritis (RA) (7 studies), multiple sclerosis (MS) (2 studies), and hypothyroidism (1 study). Key data are presented in Appendix Table 1.

Types of interventions included in these studies are the anti-inflammatory diet (AID), vegan diet, gluten-free vegan diet, living-foods diet, fasting followed by vegan diet, and prudent diet limiting saturated fat with slow reintroduction of low-fat animal foods. The follow-up duration for most of these studies ranged from one month to one year, with one study following participants up to 34 years.[214]

In patients with RA, a gluten-free vegan diet prompted reductions in various immunoglobulins and improvement in American College of Rheumatology 20% (ACR20) score.[136] In a systematic review of studies on patients with RA, an intervention of fasting followed by gluten-free vegan diet resulted in statistically significant decreases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen and tender joint count (SJC and TJC), morning stiffness, patients' evaluation of pain, and an improvement in patients' global evaluation.[181] At one year of follow-up in another study of RA patients, there was no difference between vegetarian and control diets in ESR, SJC, TJC, but intervention participants reported significant decreases in subjective measures including pain, morning stiffness, and patients' global evaluation compared to controls.[215] In addition, studies that classified patients as "responders" tended to find more responders, or people with improvement in disease metrics, in plant-based interventions than controls.[136,181,215,216] Plant-based interventions demonstrated reductions in tender and swollen joint counts (TJ and SJ), improvement in global assessments of disease progress, duration of morning stiffness, grip strength, and scores on health assessment questionnaires (HAQ).[128,136,138,215–217]

The body of work on the impact of plant-based dietary interventions in patients with MS is less clear. One plant-based dietary intervention yielded no significant improvement in number or volume of brain lesions at 12 months of follow-up.[218] Another long-term intervention study by Swank et al. found that among those diagnosed with MS who had low disability scores at baseline, 95% in the intervention group remained only mildly disabled at a follow-up of 30 years. The intervention group was assigned to a prudent dietary pattern, with the primary goal of minimizing saturated fat intake rather than limiting all animal food. Therefore, the findings in this study may only be generalizable to mostly plant-based diets with the inclusion of low saturated fat animal products.[214]

Finally, a 2013 study using data from the Adventist Health Study-2 (AHS-2) cohort (n = 65,981), described a lower incidence and prevalence of Graves' disease, one form of hyperthyroidism, in people following vegan diets, compared to omnivorous, lacto-ovo-vegetarian, semi-vegetarian, and pesco-vegetarian diets, even after controlling for BMI and demographic variables. The researchers speculated that the inflammatory properties of animal products could explain the lower risk in vegans.[219] However, these findings may be subject to reverse causation due to lack of a temporal component in data. In addition, none of the associations found between diet and hypothyroidism were statistically significant.[219]

For medical treatment, a plant-based dietary intervention may be a valuable tool for physicians to suggest to patients dealing with RA, MS, and PD symptoms, though more high-quality research must be done to solidify the effects of diet on symptoms and progression of autoimmune diseases. Most statistically significant findings are from subjective assessments from patients, making assessments vulnerable to placebo effects or response bias.

Promising Results—Case Reports of Success with Dietary Treatment

For many AI diseases outlined here, research on associations with diet and/or nutrition is still in the early stages of exploration and needs further development through more robust studies to establish any strong conclusions. Despite this, current evidence provides support for the risk reduction and health benefits of plant-based diets in populations with various AI diseases primarily due to the strong links between diet and inflammation, immunity, and obesity. While several interventional and cohort studies have been outlined above, numerous case studies offering more dramatic examples of improvements in symptoms using diet and lifestyle interventions are also worth noting and are highlighted below.

Myasthenia gravis (MG)

In a case study reported by Yiaslas et al., a 65-year-old male veteran with multi-morbidities reversed his severe atherosclerotic heart disease, obesity, and the autoimmune disorder, Myasthenia gravis (MG), which is a neuromuscular dysfunction causing weakness in the skeletal muscles.[220] After fifteen weeks on the Heart Disease Reversal Program (HDRP), which centers on a WFPB diet, this patient eliminated his angina, lowered his total cholesterol by 23% (-24 mg/dL), and lowered LDL cholesterol by 42% (-16 mg/dL). After nine months on a WFPB diet, his musculoskeletal pain completely resolved, and he lost 20% of his body weight (50 pounds), along with improving type 2 diabetes and glycemic control metrics more than expected if he were following the American Diabetes Association diet guidelines.[172] The patient reported that after two previous heart attacks and a drug-induced coma to control his MG flare-ups after surgery, he could manage and live with his disease. Nine years later, however, he decided to participate in an Esselstyn-style heart disease reversal program (HDRP) at his Veterans Hospital at Mather Field, which he says "saved [his] life." The HDRP consists of 3 components: adoption of the WFPB diet, physical activity promotion, and stress management training.

Type 1 Diabetes

Type 1 diabetes (T1D) is an inflammatory autoimmune disease that leads to permanent degeneration, including retinopathy, nephropathy, neuropathy, foot complications, high blood pressure, and a lifetime dependence on insulin. T1D is considered irreversible, and life expectancy for individuals with T1D is estimated to be 8–13 years less than healthy non-diabetic peers.[221] Despite this, compelling evidence shows how nutrient-dense diets high in fiber allow for glycemic load control and can improve disease outcomes, especially if accompanied by exercise.[167,168,169] Fuhrman and Ferreri reported on three T1D cases who began following a nutrient-dense, plant-rich (NDPR) diet focused on vegetables, legumes, nuts and seeds, and lower-sugar fruits at different stages of T1D disease progression.[169] The case reports document how insulin therapy can be lowered, delayed, or avoided altogether in T1D patients, with the potential to improve glycemic control, as well as cardiovascular risk factors. Results suggest that the earlier a WFPB diet intervention is initiated, and the younger the patient, the higher the potential to reverse the course of T1D and slow or prevent further destruction of beta cells. In support of this, a patient who began a NDPR diet upon diagnosis at age 3 required no insulin therapy up to at least three years after diagnosis. This patient also showed a steady decline in autoantibody levels during follow-up. Another child who began a NDPR diet several months after diagnosis required only a low dose of insulin and showed a favorable HbA1c with more consistent blood glucose readings. After one month of initiating nutritional therapy, a 45-year-old male patient was able to reduce insulin requirements thirteen years after initiating insulin therapy, from approximately 70–100 units/day to 16 units of Lantus/day plus 4 units of Humalog/meal. His C-reactive protein level reduced from 4.5 to 0.2 mg/l. This patient continued to exercise regularly and weighed 149.6 lb. (67.9 kg) with approximately 10–11% body fat at the time of reporting. He mostly avoids meat, dairy, white flour products, white rice, added sugars, processed and fried foods, indicating high success in controlling his disease even without dietary perfection. These cases concur with other studies demonstrating benefits to eating this way for better control of T1D, including a boost in insulin sensitivity, more predictable blood glucose levels, reduced risk of diabetic neuropathy, kidney protection, and more energy.[166,168,222]

Lupus

Lupus is an autoimmune dysfunction causing Inflammation that can affect many different body systems, including joints, skin, kidneys, blood cells, brain, heart, and lungs. Lupus is difficult to diagnose, but the most common form is systemic lupus erythematosus (SLE). Up to 60% of SLE patients develop nephritis, a complication that causes significant morbidity and mortality.[223] Goldner (2019) reports two case studies of patients who reversed symptoms of SLE, including nephritis, into remission after adopting a customized WFBP eating regimen high in raw leafy and cruciferous vegetables and rich in omega-3 polyunsaturated fatty acids, antioxidants, and fiber.[224] To increase patient compliance with this diet, Goldner suggests blending specific whole plant foods into smoothies to enable patients to ingest enough nutrients from them. In the case report,

a 24-year-old female patient achieved increased kidney function (measured by the glomerular filtration rate, eGFR) from 14 to 27 ml/min in 6 weeks on her regimen, with energy and joint pain levels also significantly improved. Dialysis was no longer needed, nor was her scheduled renal transplant. Five months after beginning her regimen, the patient was considered in full remission and tapered off all medications. The second case was a 41-year-old male with SLE who first tried a Paleo dietary pattern to control his symptoms and consumed large amounts of meat 3–4 times daily. On this diet, his symptoms rapidly worsened, developing into nephritis. He had edema in bilateral lower extremities and alopecia, and his eGFR was 61 ml/min, which put him in stage II chronic kidney disease. He first adopted a WFPB diet on his own and felt better, but he optimized recovery with Goldner's regimen, which consisted of 454 grams of leafy and cruciferous vegetables, fruits, chia or flaxseed, and 3.8 liters of water per day through green smoothies. Both cases displayed rapid deterioration upon deviating from the raw, WFPB intervention diet, indicating there may be even greater benefits for disease management and reversal using raw nutrients in this illness due to the availability of certain nutrients, enzymes, and changes in food structure.

High consumption of meat appeared to bring on additional loss of kidney function in Goldner's second case, which may indicate that higher protein intake, or meat intake in particular, is not optimal for SLE-related nephritis. Nephrologists who advise patients to increase animal protein intake should reconsider this advice and could alternatively recommend a highly anti-inflammatory diet that is also high in antioxidants and fiber.

Rheumatoid Arthritis

The inflammatory autoimmune condition, rheumatoid arthritis (RA), attacks the joints by causing inflammation and damage to the tissue. It can also affect other tissues throughout the body and cause problems in organs such as the lungs, heart, and eyes.[225] Specific causes of RA are unknown, and the primary treatment includes medications that can be costly and have side effects. However, some evidence suggests that dietary intake can impact the severity of RA symptoms. For instance, saturated fat may be linked to worsened RA symptoms, while monounsaturated fats are associated with improved outcomes.[94,136] Other research suggests that dietary fiber can improve the diversity of gut microbes which may significantly impact RA progression as described above.

McDougall et al. (2002) reported using a very low-fat vegan diet over four weeks for 24 patients with RA and found significant improvements in RA symptoms (joint pain, stiffness, swelling, and function; $p < 0.001$).[136] On this diet, patients decreased intake of fat (69%), protein (24%), and energy (22%), and significantly increased intake of carbohydrates (55%). All measures of RA symptomatology decreased significantly ($p < 0.05$) except for duration of morning stiffness ($p > 0.05$). Weight also decreased significantly ($p < 0.001$). At 4 weeks, non-significant decreases were found for C-reactive protein (-16%, $p > 0.05$) and RA factor (-10%, $p > 0.05$), while erythrocyte sedimentation rate was unchanged ($p > 0.05$).[163] Treatment using a WFPB diet to mitigate inflammation and weight alone makes it a valuable tool to consider for RA and inflammatory diseases in general.

Conclusion

The studies reviewed here indicate the value and effectiveness of using WFPB dietary intervention to control and, in some cases, potentially reverse autoimmune disorders. Compared to other tools available to practitioners, dietary interventions are inexpensive, have few side effects, and come with co-benefits such as weight maintenance, cardiovascular improvements, improved brain function, decreased fatigue, and the establishment of lifestyle improvements. These diseases merit further rigorous research, and more randomized controlled studies comparing the effects of plant-based diets to other dietary interventions in populations with autoimmune diseases are needed. In conclusion, several studies to date have reported lower risk of autoimmune diseases and improvement of symptoms with a WFPB diet.

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APPENDIX 1 Autoimmune Diseases and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Philippou E, 2020[181] **Systematic Review (SR)** Total number of studies N=70
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Number of studies with plant-based interventions included: N = 10
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Inclusion Criteria: Human studies on patients with RA Any nutrition, dietary supplement, or fasting intervention compared to other dietary intervention, placebo supplement, or no control group Must study symptoms of RA, laboratory / clinical / radiological signs of RA and/or remission of RA
Outcome(s) of interest and units	• Risk of developing RA • Prevalence of RA • Progression or regression of RA • Clinical outcomes for RA progression or regression
Key Results (Bold qualitative assessment followed by quantitative results)	**5 subtotal fast (100-300 kcal for 7-10 days) followed by gluten-free vegan diet for 3.5 months, followed by a lacto-vegetarian diet (4/5 of these studies are a series done by the same author in the same time period, 1991-1994).** Reported statistically significant decreases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen and tender joint count (SJC and TJC), morning stiffness count (MS), patient's visual analogue scale (VAS) evaluation of pain, and an increase in patient's global evaluation. 1 year post intervention showed no difference between intervention and control in ESR, SJC, TJC, but significant decreases in VAS for pain, MS, and patient's global evaluation for intervention compared to control. 2 Uncooked Vegan Diet: Reported no significant effects within or between groups for any RA measures 1 Low-Fat Vegan Diet: Reported no effect within group for ESR and CRP but significant decreases from baseline for SJC, TJC, MS, VAS
Comments: Significance to clinical application	Evidence from trials examining fasting followed by gluten-free vegan diets and trials in low-fat vegan diets suggest that these interventions can bring moderate improvements in RA symptoms in both subjective and objective measures. However, in some cases, fasting may be unsustainable. Physicians should consider dietary modification for patients with RA symptoms as one lifestyle modification that can potentially improve RA symptoms.

First author, year, study design (bold), name of study (if applicable), sample population	Yadav V, 2016[218] **RCT** Subjects recruited from Oregon Health & Science University with MS duration less than 15 years, age between 18-75 years, and documented clinical relapse or active disease identified by MRI. Study subjects allowed to be on DMT.	
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Diet n= 32 Age = 40.8 (8.86 BMI = 29.3 (7.42)	Wait-Listed n= 20 Age = 40.9 (8.48 BMI = 28.4 (6.76)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Low-fat vegan diet "…starchy plant foods (beans, breads, corn, pastas, potatoes, sweet potatoes, and rice with the addition of fruits and non-starchy vegetables). Approximately 10% of calories were derived from fat, 14% from protein and 76% from carbohydrate. Meat, fish, eggs, dairy products and vegetable oils (such as corn and olive oil) were prohibited." Both groups were recommended to exercise at least 30 minutes per day.	
Outcome(s) of interest and units	• Primary outcome was the number of brain lesions observed at follow up • Secondary outcomes were number of enlarging lesions, change in lesion volume, and change in brain volume, all in 12 months	
Key Results (Bold qualitative assessment followed by quantitative results)	**Intervention group saw improvements in fatigue, though no improvements in counts of brain lesions was observed.** After controlling for fatigue at baseline, intervention group saw improvements in the Modified Fatigue Impact scale (MFIS) by 0.06 points per month (t=−3.88; Padj=0.0010) and the Functional System Score (FSS) by 0.23 points per month, (t=−3.85; Padj =0.0011).	

Comments: Significance to clinical application	Though low fat, plant-based diets may help with weight management and blood markers such as cholesterol or LDL, there is little evidence to suggest that a low-fat, plant-based diet provides protection, slows the progression, or can reverse multiple sclerosis (MS).

First author, year, study design (bold), name of study (if applicable), sample population	Tonstad S, 2013[219] **Observational Cohort Study** Subjects were members of the Seventh-Day Adventist Church in the United States and Canada. Total n = 106891

Study/analysis groups, mean age, mean BMI (SD), total N, duration	Prevalent Hypothyroidism		Incident Hypothyroidism	
	No	Yes	No	Yes
	n = 61,744	n = 4237	n = 40,028	n = 882
	Age = 56.3 yrs	Age = 62.6	Age = 56.6	Age = 58.8
	BMI = 27.2	BMI = 28.2	BMI = 26.8	BMI = 26.9

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	**FFQ at baseline and classification of vegetarians (no animal products), lacto-ovo vegetarians (dairy/eggs > 1 time per month but no meat), semi-vegetarians (red meat/poultry > 1 time per month and < 1 time per week), and omnivores.** Salt added to food queried as well Analysis adjusted for salt intake and weight
Outcome(s) of interest and units	• Prevalence: Defined as self-reported diagnosis of hypothyroidism by a doctor in the past 12 months via questionnaire • Incident disease (bi-annual Hospitalization History Questionnaires (HHQs) initially administered two years after the baseline questionnaire • In HHQ 3, administered in 2008, subjects were asked for the first time whether they had been diagnosed with hypothyroidism.
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegan diet group had the lowest odds ratio for incidence and prevalence of hypothyroidism, though no results are significant.** Vegan diet OR for incidence of hypothyroidism: 0.78 (0.59-1.03) compared to omnivores; vegans had the lowest odds ratio of all diet groups (though not statistically different from other diet groups) Vegan diet OR for prevalence of hypothyroidism: 0.89 (0.78-1.01)
Comments: Significance to clinical application	This study has severe limitations. The outcome was assessed by non-objective measures including a type of self-reporting. Caution should be used when interpreting the prevalence data due to potential for reverse causation. Incidence data shows lower odds of hypothyroidism but does not reach statistical significance. Overall, no definitive conclusions can be reached from this study due to design limitations. Results suggested a possible protective effect from a vegan diet, but more research is needed to be conclusive.

First author, year, study design (bold), name of study (if applicable), sample population	Elkan AC, 2008[136] **RCT** Total n = 66 patients with RA according to ACR criteria

Study/analysis groups, mean age, mean BMI (SD), total N, duration	Intervention:	Control:	Duration:
	n = 38	n = 28	Follow-up at 3 and 12 months
	Age = 49.9 (46.6-53.3)	Age = 50.8 (46.2-55.5)	
	BMI = 24.1 (22.3-25.9)	BMI = 23.8 (21.6-26.0)	

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Vegan The vegan diet contained vegetables, root vegetables, nuts, and fruits. As gluten was not permitted, the diet contained buckwheat, millet, corn, rice, and sunflower seeds. Unshelled sesame seeds in the form of sesame milk were a daily source of calcium. 10% protein, 60% carb, 30% fat Control/Non-Vegan Diet 10% to 15% protein, 55% to 60% carbohydrate, and no more than 30% fat, of which saturated fat was not supposed to make up more than 10% of the total energy intake. Five or more daily servings of fruits and vegetables recommended. Increasing intakes of starch and other complex carbohydrates by eating potatoes, bread, and cereals and selecting whole-grain products as often as possible also recommended.

Appendix continued

Outcome(s) of interest and units	• Disease Activity Score for 28 joints (DAS28): number of swollen joints number of tender joints • Patient's assessment of global disease activity (high responders classified as decrease in score of 1.2, and total score below 3.2) • European League Against Rheumatism score (EULAR) • ACR20 • Stanford Health Assessment Questionnaire (HAQ): Score from 0-3, 3 representing highest degree of disability • Oxidized LDL and antibody determinations
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegan diet intervention showed significant improvements in HAQ score, DAS28, oxidized LDL, anti-PC IgA at 3 months, and DAS28, HAQ score, CRP, cholesterol, LDL, and LDL/HDL at 12 months** Stats for intervention effect at 12 months: DAS28 from 5.3-4.3 ($p < 0.001$) HAQ from 1.4-1.0 ($p = 0.001$) CRP from 13-5 ($p = 0.008$) Only significant decrease for controls was anti-PC
Comments: Significance to clinical application	Gluten-free vegan diet intervention improves markers of DAS28 and HAQ score, suggesting benefits of intervention to joint swelling and damage caused by rheumatoid arthritis. Mean DAS28 response would be classified as medium responders to treatment, with an average decrease in score of 1.0 point. In summary, this study suggests that intervention in RA patients with gluten-free vegan diet helps improve various RA symptoms.

First author, year, study design (bold), name of study (if applicable), sample population	Hafström I, 2001[216] **Randomized Controlled Trial (RCT)** Analysis Intention-to-treat (ITT) Valid Compliant Completer (VCC) Total n = 66 patients between 20-69 years with rheumatoid arthritis (RA) according to American College of Rheumatology criteria (ACR)		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	ITT Vegan n = 35 non-Vegan n = 26 age = 49.5 (9.6)	VCC Vegan n = 22 non-Vegan n = 25 age = 50.8 (11.9)	Duration 9 months BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Gluten-Free Vegan Diet "[Vegan Diet] contained vegetables, root vegetables, nuts and fruits. As gluten was not permitted, the diet contained buckwheat, millet, corn, rice and sunflower seeds. Unshelled sesame seeds in the form of sesame milk was a daily source of calcium." Well-Balanced Non-Vegan Diet "well-defined nonvegan diet. This implies a variety of foods from all food groups according to previously described recommendations"		
Outcome(s) of interest and units	• American College of Rheumatology (ACR20) response criteria • Antibodies against food-related antigens Immunoglobulin G (IgG) and IgA antibody levels against gliadin and b-lactoglobulin • Radiographic assessment: radiographs of hands, wrists, and feet were evaluated at enrolment and after 6 and 12 months, using modified Larsen score • Number of erosions was calculated as well as the number of eroded joints		
Key Results (Bold qualitative assessment followed by quantitative results)	**The intervention showed suggestive evidence that gluten-free vegan diet is superior to control diet in improving ACR20 metrics. In addition, there was suggestive evidence for reduction in various immunoglobulins.** 9/22 VCC Vegan patients (40.9%) categorized as responders by ACR20 standards 1/25 VCC patients (4.0%) categorized as responders by ACR20 standards Significant reductions in IgG anti-gliadin and anti-b-lactoglobulin levels from baseline were noted in the vegan diet group		
Comments: Significance to clinical application	Adherence to diet was similar between both groups. Vegan gluten-free diet may be a useful tool in improving RA symptoms and decreasing blood concentrations of immunoglobulins associated with gluten intolerance.		

Appendix continued

First author, year, study design (bold), name of study (if applicable), sample population	Nenonen MT, 1998[138] **RCT** Total n = 43 patients with chronic and active RA according to ARA criteria	
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Intervention group N = 22 Age = 49.1 (7.1) BMI =25.5 (4.1)	Control group N = 21 Age = 55.6 (10.8) BMI = 23.5 (3.5)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Living food vegan diet Control group followed usual diet	
Outcome(s) of interest and units	Disease improvement index was calculated from the changes in the following six variables: • ESR • Number of swollen joints • Number of tender joints • Rheumatic pains on a VAS • HAQ • Global patient estimate A decrease or increase of 20% or more was estimated as significant and the number of significantly changed variables was calculated for each patient.	
Key Results (Bold qualitative assessment followed by quantitative results)	**Intervention group shows improvements in number of people with swelling, pain, morning stiffness, and overall impression of disease compared to controls.** For subjective measures of RA disease, intervention group had a significantly higher number of participants reporting positive change compared to the control group in rheumatic pains, swelling of joints, morning stiffness, and general impression of their disease symptoms. After the intervention period, the intervention group had a significantly higher number of people reporting a negative change in rheumatic pains, swelling of joints, and morning stiffness. Disease Activity Score did not significantly improve over the course of the study.	
Comments: Significance to clinical application	This trial shows evidence of improvement of individual symptoms and indices form a living-food diet. However, overall disease activity score for individuals in the intervention did not show significant changes from baseline. There is limited evidence to suggest a living food vegan diet to treat RA symptoms.	

First author, year, study design (bold), name of study (if applicable), sample population	Peltonen R, 1997[128] **RCT** Total n = 43 adults diagnosed with chronic and active RA according to ARA criteria in Steinbrocker's functional classes II and III	
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Living food intervention: N = 22 Age = 49.1 yrs BMI = 25.5	Control: N = 21 Age = 55.6 yrs BMI = 23.5
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Uncooked living food vegan diet, rich in lactobacilli. It does not contain any animal products, raffinated substances or added salt. The items may be soaked, sprouted (seeds, grains), fermented, blended or dehydrated. Control group instructed to continue their usual diet	
Outcome(s) of interest and units	A disease improvement index (0–6) was calculated for each patient. The index was based on changes in six disease activity parameters: • pain VAS (scale 0–100) • Finnish version of HAQ • Number of tender joints • Number of swollen joints • Subjective evaluation of improvement (scale 0–5) • ESR Patients with >20% improvement in 5/6 categories was categorized as a high responder.	

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Living food diet changed CFA content at 1 month, while five patients in the test group were high responders, with higher mean improvements in RA symptoms.** Living food diet significantly changed CFA content of test group compared to control group ($p < 0.001$). Fecal flora were significantly different between high responders and low responders in the test group at 1 month ($p < 0.001$) and post-diet ($p = 0.029$), though there was already dissimilarity at baseline ($p = 0.129$). Five patients in the test group and no patients in the control group were classified as high responders, with improvement indices of 3.1 and 2.0 ($p = 0.027$), respectively.
Comments: Significance to clinical application	Living food vegan diet was associated with significant changes in CFA makeup compared to baseline and across groups. There were significant differences in disease improvement between groups. **This study suggests that a living food vegan diet could improve RA symptoms compared to omnivorous diet at one month of follow-up.**

First author, year, study design (bold), name of study (if applicable), sample population	Kjeldsen-Kragh J, 1994[215] **Non-Randomized Controlled Clinical Trial (CCT)** Total n = 53 patients with "classic or clinical" RA Two-year follow-up		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Vegetarian Diet n = 27 Age = 51.3	Control Diet n = 26 Age = 55.1	BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	**Main comparison: diet responders between vegetarian and omnivorous groups** Diet responders are classified by: number of swollen joints, Stanford Health Assessment Questionnaire (HAQ) index (12), pain score on a visual analogue scale, number of tender joints, patients' global assessment and erythrocyte sedimentation rate (ESR).		
Outcome(s) of interest and units	• Diet adherence after follow-up • Erythrocyte sedimentation rate (ESR) • Hemoglobin • Platelet count • White blood cell (WBC) count • Albumin • Pain on visual analogue scale (VAS)		• Duration of morning stiffness • HAQ • Global assessment • Grip strength • Tender Joints • Ritchie's Articular Index • Swollen joints
Key Results (Bold qualitative assessment followed by quantitative results)	**There were more "diet responders" in the vegan group than in the control group. In addition, diet responders keep benefits of the intervention after 1 year in pain, morning stiffness, HAQ, global assessment, tender joints, Ritchie's Articular Index, and swollen joints.** More responders on the vegetarian diet than on the omnivorous diet (45% vs. 8.7%) ($p = 0.014$)		
Comments: Significance to clinical application	Those who followed the vegan diet intervention were more likely to experience improvement in RA symptoms, maintain diet adherence, and retain benefits of the intervention after 1 year.		

First author, year, study design (bold), name of study (if applicable), sample population	Kjeldsen-Kragh J, 1991[217] **RCT** Study population: see Kjeldsen-Kragh 1994[215] Total n = 53		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Diet group: N = 27 Age = 53	Control group: N = 26 Age = 56	BMI not reported
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Dietary Exposure During the first 3-5 months, the patients were asked not to eat food that contained gluten, meat, fish, eggs, dairy products, refined sugar, or citrus fruits. Salt, strong spices, and preservatives were avoided-likewise alcoholic beverages, tea, and coffee. After this period, the patients were allowed to reintroduce milk, other dairy products, and gluten containing foods in the way described above. The patients who did not use cod liver oil supplemented the diet with vitamin D during the first 4 months. Control group The patients in the control group had a four week stay at a convalescent home and were asked to eat ordinary mixed food throughout the study		

Appendix continued

Outcome(s) of interest and units	• Joint count included Ritchie's Articular Index, the number of joints that were tender or painful on movement, and the number of swollen joints. • Three determinations of grip strength were made for each hand with 'Vigorimeter.' • At baseline, all patients had hand, wrist, and forefoot radiographs taken, and these were done again in patients who completed the study. • Pain scores with 10 cm visual analogue scale (VAS) • Haemoglobin, ESR, platelet count, white blood cell count, C-reactive protein, and serum albumin were initially measured at each clinical evaluation.
Key Results (Bold qualitative assessment followed by quantitative results)	**Intervention group saw decreases in ESR, CRP, white blood cell count, and decreases in number of tender joints, Ritchie's Articular Index, number of swollen joints, pain, duration of morning stiffness, and increased grip strength and score on health assessment questionnaire. Intervention did better than control group on all disease indices.** ESR ($p < 0.001$), CRP ($p < 0.0001$), and white blood cell count ($p < 0.0001$) were all significantly decreased in the diet group. After 1 month, patients saw decreases in the number of tender joints ($p<0.0002$), in Ritchie's Articular Index ($p<0.0004$) in the number of swollen joints ($p<0.04$), in pain ($p<0.0001$), duration of morning stiffness ($p < 0.0002$), increased grip strength ($p<0.0005$), and score on health assessment questionnaire ($p<0.0001$).
Comments: Significance to clinical application	This randomized controlled trial suggests that a vegan diet omitting gluten, citrus fruit, caffeine, preservatives, and strong spices may improve RA symptoms.

First author, year, study design (bold), name of study (if applicable), sample population	Swank RL, 1990[214] **Observational Cohort Study** Subjects were MS patients who maintained contact with "the clinic" between December 1948–April 1954 (Montreal Neurological Institute, Veterans Administration hospitals in Canada and Northern New York State)
Study/analysis groups, mean age, mean BMI (SD), total N, duration	"Good" Dieters Minimum disability n= 23 Age = 31.0 Moderate disability n= 25 Age = 31.8 Severe disability n= 24 Age = 34.2 "Poor" Dieters Minimum disability n= 6 Age = 30.8 Moderate Disability n= 33 Age = 34.4 Severe Disability n= 33 Age = 37.1
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Prudent diet: elimination of saturated fats and trans fats, with primary protein sources of skinless chicken and fish, added cod liver oil, and fruits, vegetables, legumes and nuts
Outcome(s) of interest and units	• "Rates of Deterioration and Death" both calculated with non-MS related deaths and without
Key Results (Bold qualitative assessment followed by quantitative results)	**In patients who were only mildly disabled at baseline, removing deaths from heart disease and stroke, 95% of participants remained mildly disabled at 30 years.** Deaths from all causes and from MS were lower with good dieters compared to bad dieters ($p = 0.0026$ and $p < 0.0001$).
Comments: Significance to clinical application	This trial shows that prudent dietary habits of increasing consumption of polyunsaturated fatty acids, plant foods, fish, and chicken and eliminating the consumption of saturated fatty acids were associated with lower all-cause mortality and progression of MS-related disability.

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LONGEVITY

Key Points for Practitioners

- Globally, populations that traditionally consume largely whole food, plant-based diets are where we find the longest expected average life spans, as demonstrated by the regions dubbed the "Blue Zones."[3,41,42]
- Both an increased consumption of unrefined plant foods and a decreased consumption of animal and highly processed foods seem to contribute towards increased longevity and reduced mortality.[3,41,42,53]
- Whole food, plant-based diets are associated with lower mortality and other intermediate health benefits such as improved cardiometabolic health outcomes.[1,54]
- Existing evidence on plant-based diets and longevity can be communicated to patients as part of wellness counseling.
- Adherence to a healthy dietary pattern such as the Mediterranean and MIND diets is associated with slower rates of decline in cognitive performance, lower risk for cognitive impairment, and
- Overall lower risk of AD and dementia.[55–58] Overall, plant-based diets can support a higher quality of life as individuals age.[37]
- If patients express interest in trying a whole food, plant-based diet of some kind, it is helpful to share ACLM patient-facing resources and tools for practical guidance on plant-based eating.

ABSTRACT | As the number of centenarians increases globally due to improved living standards and access to quality healthcare, efforts to improve quality of life through modifiable health behaviors are even more relevant for the lifestyle medicine (LM) practitioner. Avoidance of the chronic diseases that plague our society today prolongs life and circumvents premature mortality[1–7] while also making living better, not just longer, possible. Research indicates that a plant-based diet is the cornerstone of healthy longevity and potentially the most important prescriptive tool to help patients achieve a longer life and better quality of life as they age.

Longevity in Context

Medical and health professionals have two fundamental purposes: to sustain life and to relieve suffering. If they are successful, the net effect is an increase in human longevity and quality of life. Recent research has indicated that genetic predisposition likely accounts for only 15–30% of longevity;[8] for instance, the Danish Twin Study established that only 20% of the average person's lifespan is dictated by genetics. Other research suggests that under 10% of lifespan is driven by genetics.[9] Thus, environmental and lifestyle influences play a large role in determining lifespan.[10] In 2020, life expectancy from birth was 78.9 years for the total US population. In 1860 it was 39.4 years and had risen over the past 160 years largely due to the dramatic decrease in infant and child mortality rates in the late 19th and early 20th centuries.

Additionally, medical advancements, fewer wars, and organized efforts to control the spread of infectious disease, including widespread water and sanitation infrastructure and improved living standards, all contribute to longer lifespans.[11] Today in developed countries, non-communicable diseases (NCDs) are

collectively the major cause of death, most of which are lifestyle-related.[12] Though both social inequities and the COVID-19 pandemic have made the continued rise more uncertain,[13,14] life expectancy has roughly tripled over the course of human history. However, since 1970, the main driver of these gains in industrialized countries has been a reduction in death rates from cardiovascular disease and cancer, particularly among older adults and largely due to medical interventions.[15,16]

The number of individuals 80 or older will more than triple in future decades, reaching almost 400 million in 2050.[17] This demographic shift presents clear challenges for health care systems. Though nutrition is recognized as important to overall morbidity and life expectancy, its impact on health has often been underappreciated within the medical community. A suboptimal diet is the main modifiable risk factor for NCDs, along with physical activity, alcohol, and tobacco use.[18]

Morbidity, Mortality and Diet

Both disease and longevity are associated with diet quality.[5,19] The comprehensive Global Burden of Disease Report that examined the health effects of dietary risks in 195 countries (1990–2017) found that low fruit, vegetable, and whole grain consumption and, similarly, high red and processed meat consumption are currently among the main global risk factors for chronic disease.[20] In 2017, 11 million deaths and 255 million disability-adjusted life years or DALYs were attributable to dietary risk factors. High intake of sodium (3 million deaths and 70 million DALYs) , low intake of whole grains (3 million deaths and 82 million DALYs), and low intake of fruits (2 million deaths and 65 million DALYs) were the leading dietary risk factors for deaths and DALYs globally.[20] The Global Burden of Disease study is important because nutritional studies with total mortality as an outcome are uncommon, largely because the sample size must be extremely large and the duration of follow-up long. However, mortality as an outcome has unequivocal clinical relevance.[21]

Proper nutrition, including lower consumption of refined, calorie-dense, and animal-based foods alongside higher intake of nutrient-dense whole plant foods, may help prevent almost half of the cardiometabolic deaths in the United States and, as such, promote increased lifespan due to disease avoidance.[20] Specifically, a plant-based diet has been shown to decrease risk of all-cause mortality, obesity, type 2 diabetes, and coronary heart disease while effectively improving nutrient intake. Such health-promoting diets filled with nutrient-dense, fiber-protective whole plant foods have also been shown to reduce the risk of metabolic syndrome and type 2 diabetes by about one-half. Additionally, the risk of coronary heart disease events may be reduced by an estimated 40% and the risk of cerebral vascular disease events by 29% among populations consuming a plant-based diet.[22]

Cognitive Decline

Addressing the cognitive health of older adults is key to quality of life, particularly as dementia is now the fastest-growing epidemic in developed nations.[23] Dementia, which includes Alzheimer's disease (AD) and other neurological dysfunction of the brain is now a leading cause of both mortality and morbidity globally and the leading cause of mortality in the U.S.[24] Though medical treatments have successfully reduced mortality in the last twenty years with treatment for chronic diseases such as diabetes, heart disease, and cancer, mortality from AD has increased by more than 123%.[25] A diet containing flavonoids, specifically a daily 1/2 cup of foods high in flavones and anthocyanins such as berries and dark leafy green vegetables, may lower risk of cognitive decline by as much as 20%, according to one study.[26] AD is not exclusively a genetic disease. Unlike other genetic diseases driven by chromosomal or other gene-related flaws like Down Syndrome or muscular dystrophy, AD appears to have multifactorial origins and is potentially related to the body's ability to respond to stressors, including glucose and lipid dysfunction inflammation, and oxidation.[27] Thus, a lifestyle approach to treatment is warranted to address these pathological pathways, particularly utilizing nutrition.

Elevated cholesterol and blood pressure appear to be associated with AD,[28] as is saturated fat.[29] Further, probiotics and antioxidants in plant foods can positively modulate the immune response by reducing gut inflammation and neurodegeneration.[30,31] Accordingly, adherence to healthy eating patterns, including the MIND diet, a hybrid Mediterranean-Dietary Approaches to Stop

Hypertension diet, has been associated with slower cognitive decline. In the MIND diet study, lower AD rates were observed at the highest tertiles of adherence to a plant-prominent diet (HR = 0.47, 95% CI 0.26, 0.76).[32] More research has indicated that this dietary pattern shows promise to preserve brain health and for treatment to address AD, including research examining cholesterol,[33] animal product intake,[34] and NHANES data on cognitive health and insulin resistance,[35] indicating that diet, a controllable factor in brain health, can modulate cognitive decline.

Quality of Life

Healthy dietary patterns are associated with lower disease burden and mortality rates, as measured by disability-adjusted life years (DALYs). Cohort studies such as the large European Prospective Investigation into Cancer and Nutrition–Netherlands indicate that plant-based dietary patterns are associated with lower disease burden as reflected in DALYs.[36] A 2021 Japanese review of DALYs found that vegetable consumption reduces a range of health challenges associated with mortality, including diabetes, kidney disease, and cancer. The use of medications to treat chronic disease can also add to disability and decrease life years.[37] In fact, research has found that DALYs are inversely related to the increase of drugs launched for use. On an individual level, the number of prescription medications being taken is also implicated in quality of life. Studies on vegan and vegetarians show that plant-based eaters take fewer medications, including anti-hypertensive,[38] asthma,[39] and diabetes medications.[37,40]

Quality of life comprises a complete package of health and lifestyle factors as they relate to longevity and is well-illustrated by examining populations of older adults living long and healthy lives, such as the "Blue Zones" discussed below.

The "Blue Zones"

Plant-based dietary patterns are common among longer-lived populations, illustrated by those living in "Blue Zones," a phrase coined by author Dan Buettner in his 2008 book to describe five places around the world where residents have the greatest longevity. His project aimed to find commonalities among them and found they shared particularly healthful plant-based eating patterns.[41] The original Blue Zones identified included Okinawa, Japan; Ogliastra, Sardinia; Loma Linda, California; Ikaria, Greece; and the Nicoya Peninsula of Costa Rica. Though their lifestyles differ, they all share certain lifestyle traits that enhance and prolong their lives. They include diet, built-in routine exercise, social and familial connection, and living a purposeful life. The dietary component in all Blue Zones is primarily plant-based, (95%)[42] with daily legume and local vegetable consumption, providing high levels of fiber and phytonutrients that protect against chronic disease. We will highlight three examples from the "Blue Zone" regions to identify the lifestyle practices that support longevity and illuminate their commonalities to better understand how modifiable lifestyle factors may be addressed within the scope of medical practice.

Okinawa

Among the common healthy habits are high levels of daily physical activity, positive attitude, and high consumption of fruit, wild plants, and vegetables, with minimal or no consumption of meat products. Interestingly, Okinawa, also Japan's poorest prefecture, had the highest longevity indices in the country.[43]

In Okinawa, the traditional diet was plant-based and rich in phytochemicals and antioxidants. Over half of daily caloric intake came from sweet potatoes. They also consumed high amounts of green leafy vegetables and soy products while taking in minimal fat (about 6% of the total energy intake).[21] Interestingly, in 1988, the daily intake of meat and pulses was higher than the national average, approximately 90 grams for each. This amounted to roughly 20% and 30% higher, respectively. Traditional daily intake of green and yellow vegetables was about 50% higher than the national average. However, by 1998, the global transition towards a preference for dietary meat had made its mark, and daily meat intake, as well as percent energy from fat had surpassed 100 grams and 30%, respectively, while daily intake of pulses and green and yellow vegetables had declined to the level of the national average.[43] Today, longevity in Okinawa is no longer higher than the national average, but the net result of their relatively healthier diet on a global scale, along with modern technology, keeps them as a hotspot for longevity.

The lessons learned from Okinawa had major practical implications in Japan. Until the first half of the 20th century, life expectancy at birth was very low in Japan. However, within a short span of 50 years, thanks to major investments in public health infrastructure and nutrition education, the Japanese people now have the longest life expectancy at birth in the world.[4] This example illustrates how fast change may occur and that dietary change paralleled positive shifts for public health.[21]

Loma Linda

Located in the orbit of Los Angeles is Loma Linda, California, where people live up to ten years longer than similar demographic groups in California.[4] Much of this difference in lifespan may be attributable to dietary choices, including less meat consumption and more tomatoes, legumes, and nuts.[4,6] Approximately 9,000 Seventh-day Adventists have thrived in this area following their faith's endorsement of healthy living, which discourages the consumption of meat, caffeine, and rich foods. Smoking is also discouraged, and thus low rates of lung and other cancers and cardiovascular disease exist in this community. In 1958, a series of long-term medical research projects were started by Loma Linda University to study mortality and health among the Seventh-Day Adventists.[44] From this longitudinal research, we have learned that nonvegetarian Adventists have twice the risk of heart disease than those following vegetarian diets, as well as higher risk for colon and prostate cancers.[6] Dietary factors that may be protecting them include the high consumption of tomatoes which contain lycopene. Consumption is inversely associated with prostate, colon, and other cancers, as well as cardiovascular disease.[46,47] Adventists consume higher quantities of nuts which may protect against cardiovascular disease.[48] Further, water consumption is a principle of health for the Adventists, and the Adventist Health Study indicates that those who drank 5–6 glasses of water per day had a 60–70% lower risk of heart attack compared to those who drank considerably less in both men [relative risk (95% CI)=0.46 (0.28, 0.75); p trend = 0.001] and women [0.59 (0.36, 0.97)].[49] Together, these practices may impact the overall health of the population.

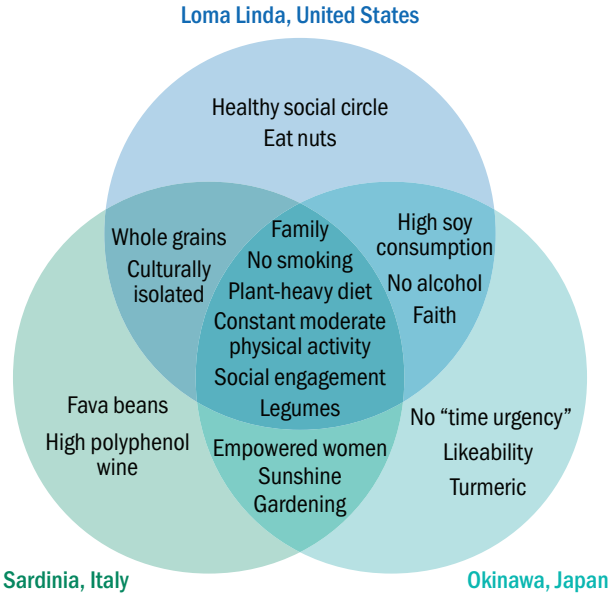

Figure 1 Blue Zones diagram of lifestyles commonalities[45]

Sardinia

The villagers of this rocky, hilly island have traditionally spent their days moving steadily to farm the land, shepherd their sheep, and tend to extended family. Though not necessarily strenuous, herders walk miles a day tending their flock.[3] Other habits include a daily glass or two of Sardinian red wine, which contains high levels of antioxidants from the brightly-colored grapes used. The grapes produce more red pigment than most as a protection against the sun and are then allowed to marinate longer than most, resulting in two to three times the level of resveratrol, a flavonoid known to be atheroprotective.[50] This compound has been shown to inhibit oxidation of low-density lipoproteins and their aggregation and to modulate cardiovascular disease.[51] It also holds anti-inflammatory properties.[51] Goat milk in this region, also a dietary staple, contains high levels of arzanol, an anti-tumor, anti-inflammatory substance found in the wild Sardinian dwarf curry that the goats graze on.[3] Their cheese made from sheep's milk contains high amounts of omega-3 fatty acids. Fava beans and chickpeas are consumed daily, and meat is reserved for Sundays or special occasions.[3]

Blue Zones Lessons

Considering these regions of healthy longevity highlights the powerful effects of diet and lifestyle on life expectancy. Though these lifelong patterns play a role in disease avoidance, improvements in biomarkers can occur swiftly for those with chronic

disease who choose to adopt these lessons. Particularly intriguing is emerging evidence that diet plays a major role in preventing age-related cognitive decline and Alzheimer's disease. It has been shown that a diet rich in fruits, grains, legumes, vegetables, nuts, and seeds may cut the risk of Alzheimer's disease by more than a half.[32]

Healthy Aging and Protein

Aging typically is associated with age-related reductions in muscle mass, function, and strength, the latter of which is termed sarcopenia. Sarcopenia results from numerous factors, one of which is inadequate dietary protein intake in older adults. Both nutrition and exercise interventions can delay this progression and enhance quality of life. Thus, recommendations for older adults emphasize sufficient, high-quality protein in their daily diet. Healthy older adults should aim to consume adequate protein: 1 to 1.2 grams of protein per kilogram of body weight daily—a 25% to 50% increase over the US recommended daily allowance.[52] Though there is no evidence indicating benefits of animal-sourced protein, it continues to be the norm. Research indicates no significant difference between animal or plant protein sources for muscle composition and size in older adults.[15] Meeting protein recommendations with plant foods is feasible and would convey a host of other health benefits. Additional benefits of more protein-rich plant foods for older adults include dietary fiber to support gut health and maintain healthy body weight, antioxidants and phytochemicals to reduce oxidative stress that contributes to aging and disease pathogenesis, and omega-3 fatty acids to support brain health.[21]

Mechanisms

Lower Rates of Chronic Disease

Avoidance of chronic diseases including obesity, cardiovascular disease, diabetes, certain cancers, and respiratory conditions is a major contributor to health and longevity, and averting risk factors can circumvent early death.[59] These risks include excessive caloric intake from the rich Western diet, which adds risk for weight gain, heart disease, and metabolic dysfunction.[40,60] Sodium in processed foods adds risk for hypertension, adding a burden to the heart and increasing risk of heart failure and stroke,[61] as do high blood cholesterol, saturated fats, and trans fats from animal foods, which appear to play a role in the development of atherosclerosis, the hardening and narrowing of the arteries, by adding fatty deposits in the blood and affecting blood flow.[54,62–65] Research indicates that a plant-predominant diet has the potential to increase life expectancy by reducing risk for chronic disease.[22] Mechanisms that lower risk factors include effective long-term weight loss for those suffering from overweight, which not only controls blood pressure and blood cholesterol[66] but improves glycemic control to avoid metabolic disorders such as diabetes. Diabetes adds the burden of cardiovascular disease risk. Further, using plant-based dietary treatment does not add potential harm from medications or polypharmacy.[22,66]

The first large study investigating diet and lifestyle related to mortality was the Seven Countries Study launched in 1958 by Ancel Keys. It established a positive correlation among dietary fat, blood cholesterol, and heart disease. With hundreds of reports published, this study established the cardioprotective effects of the Mediterranean diet and the effects of various fatty acids on serum cholesterol.66 The Mediterranean diet was first categorized here as one that is high in cereal products, legumes, fruits, and vegetables; moderate in fish; and low in dairy and meat products. Olive oil was identified as the principal fat component.[67] Adherence to this plant-predominant dietary pattern and healthy lifestyle was associated with a >50% lower rate of all-cause and cause-specific mortality [(Mediterranean diet HR, 0.77; 95% CI, 0.68-0.88), (moderate alcohol use HR, 0.78; 95% CI, 0.67-0.91), (physical activity HR, 0.63; 95% CI, 0.55-0.72), and (nonsmoking HR, 0.65; 95% CI, 0.57-0.75)].[68] Regression of cognitive decline and heart disease, as well as reversal of cardiometabolic dysfunction, has been documented in older adults prescribed a whole food, plant-based diet[5,21,22,69,70]

The Framingham multigenerational study of residents in one Massachusetts town found similar implications for mortality in that increased cholesterol and elevated blood pressure increase risk of heart disease, and diet and exercise can reduce risk.[71,72] Further, excessive caloric intake common in the Western diet overwhelms adipose storage capacity and disrupts glucose and insulin metabolism that can lead to insulin resistance and

the diabetic state.[60] This dietary pattern provides less fiber and more saturated fat, both associated with unfavorable lipoprotein concentrations and insulin control, as well as cardiovascular disease risk.[73] Cardiovascular disease continues to be the leading cause of death and disease burden in the US and worldwide despite the tremendous decline in the Western world due to medical advancement.[74–76]

Individuals consuming plant-based diets have lower rates of overweight and obesity than those whose diets include meat and refined foods.[77–80] Both obesity and diabetes have been shown to increase mortality risk by altering pulmonary mechanics, increasing inflammation, and increasing lung injury and malfunction.[81] Further, diabetes and high blood pressure are the leading causes of end-stage renal disease, which is associated with all-cause mortality.[82] The fiber and antioxidants found in plant foods could explain lower levels of systemic inflammation and oxidation found to be both cardio- and immunoprotective.[83–85]

Regarding reproductive cancers, dietary modification can significantly improve estrogen metabolism to decrease morbidity and mortality from cancer because estrogen triggers the proliferation of endometrial cells during the menstrual cycle. Over time, risk of cancer development may be increased by the division of DNA-mutated uterine or breast cells, increasing the chance of developing new, spontaneous mutations from carcinogens or radiation.[86,87] Overall, the phytochemicals in plants reduce risk for cancer, as they are anti-inflammatory and protect cells from damage.[88,89] For example, cruciferous vegetables have active components that may protect estrogen metabolism and inhibit lipid oxidation and carcinogenesis,[90,91] including lignans in flaxseed that appear to lower reabsorption of estrogen in the lower intestine.[87,92] These components found in plant foods protect against cancer.[88,93,94]

Common Questions and Concerns

Do older adults need more protein? How can they get enough on a plant-based diet?

Older individuals are slightly less responsive to anabolic stimulus to build and maintain muscle mass from the essential amino acids taken in from protein,[95,96] which means they need more protein than older adults. Adults are advised to consume 0.8 grams of protein per kilogram of body weight, or 0.36 grams per pound which averages to ~51 grams of protein per day (based on weighing 150 pounds). Experts in aging recommend that older adults consume 1.0–1.5 grams of protein per kilogram of weight, averaging ~100 grams of protein (for 150 pounds). Most American adults consume ~100 grams of protein per day, which is roughly equal to or higher than the recommendation for the older adult population; therefore, a diet consisting of 15 to 20% caloric intake from protein is easily achievable to cover their needs.[96,97] A goal for older adults' protein intake is to approach the upper end of the acceptable macronutrient distribution range (AMDR) of 10–35% of calories, and specific requirements within this range depend on individual health status and activity level.[98]

Do people need to adjust their diets as they age?

Because the basal metabolic rate slows with aging, caloric needs generally decrease, though the amount of protein needed increases slightly with age. Natural changes in physical activity and body composition slow the body down with less demand on musculature and for energy intake. Further, older adults are at greater risk for all chronic diseases, and, thus, healthy lifestyle choices like diet quality are more important.[99]

Do older adults need supplements?

Though many adults over 65 take supplements as recommended by their physicians, only a fraction actually need them to address a deficiency.[100] Ideally, adequate micronutrient intake can be achieved for older adults from a healthy diet.[101] Older adults do have some special dietary needs to maintain optimal health. Exceptions may include vitamin B12 and D. The need for supplementation should be considered under the advisement of a healthcare practitioner based on actual needs or clinical deficiencies as identified with bloodwork. Healthy bone density is important for older adults, and adequate minerals and vitamins needed for bone formation and mineral storage is necessary. Weight-bearing exercise may play a more important role for older adults who have adequate calcium, phosphorus, and caloric intakes that reflect adequate diet quality with antioxidants and phytochemicals coming from whole plant food.[102]

Do older adults need fish for healthy fats to ward off cognitive diseases like Alzheimer's?

A healthy Mediterranean or plant-based diet emphasizing fruits, vegetables, whole grains, as well as sources of unsaturated fats like flaxseed, walnuts, soybeans, and possibly fish and olive oil has been shown to ward off age-related processes that could lead to cognitive decline.[32,69,103] The benefits seen from including fish as a high source of omega-3 fatty acids could be due to the essential nutrient itself, which has anti-inflammatory properties and is important for cell signaling, not necessarily the dietary source of omega-3 fatty acid, as plant-derived omega-3 fatty acids have been shown to be protective, as well.[104,105] Omega-3 supports the healthy colonies of gut microbes, decreases risk for high blood pressure, and limits oxidative stress to avoid systemic neuroinflammation.[32,85,106] These benefits can be obtained by consuming any dietary source of omega-3 fatty acids[104] such as flax or chia seeds, walnuts, or soy products. Gut microbes have been found to play an important role in the brain and nervous system.[106–108] Though a higher intake of fish has been associated with lower risk of Alzheimer's disease,[109] it may be due to an increased ability to absorb fat-soluble antioxidants coming from fruits and vegetables in the diet, particularly carotenoids, that protect the omega-3 fatty acids in the brain from oxidation.[110] The inclusion of fish for omega-3 fatty acids is not essential, and there are several plant sources to choose from, including those mentioned above.

What if an older adult has trouble cooking or eating?

For those with chewing and swallowing difficulties, very soft, well-cooked vegetables and grains may help improve consumption to enable sufficient nutrient and fiber intake through eating. If needed, enteral nutrition can provide the calories and nutrients for older adults who cannot meet needs from dietary sources. Plant-based formulas, with their inclusion of fiber and avoidance of refined sugars, are readily available and can provide optimal nutrients and calories with few risks, thus providing a good alternative or supplement to limited eating.[111–113] These can also serve as meal replacements when cooking is not possible.

Summary of Key Studies

There is a large body of research on the relationship between plant-based diets, mortality, and longevity, especially focusing on cognitive decline. However, few studies focus on quality-adjusted life years (QALY) or quality of life, derived from following a plant-based diet compared to a standard diet. We have summarized the strongest studies from our literature review of plant-based diets and longevity in Appendix Table 1. Studies covered cognitive function (n = 2),[114,115] all-cause mortality only (n = 2)[116,117] and multiple causes of mortality (n = 5).[7,118–121]

Studies examining cognitive function and decline had mixed results. One study with participants in Quebec and France found no association between empirically derived dietary patterns and cognitive decline. Patterns defined by high plant-food consumption had higher cognitive performance at baseline, while Western-style diets showed lower baseline cognitive performance.[114] However, this may be due to differing lifestyle factors. Another study on cognitive decline found cognitive performance differed across certain diets, including the Mediterranean, DASH (Dietary Approach to Stop Hypertension), anti-inflammatory, and MIND (Mediterranean-DASH diet Intervention for Neurodegenerative Delay) diets, with the MIND diet intervention producing cognitive performance 7.5 years younger than participants' age would suggest.[115] These findings suggest that multiple plant-based dietary patterns can promote cognitive well-being into old age.

Plant-based diets showed mixed effects in various causes of mortality. For all-cause mortality, five studies showed a decreased risk of mortality associated with plant-based diet patterns,[7,116–118,121] while two studies found no significant effect.[119,120] One study found decreased risk of pancreatic, lymphatic and hematopoietic cancers,[118] while other studies found decreased risk of cardiovascular disease (CVD) and ischemic heart disease (IHD) associated with vegetarian or vegan diets.[7,119–121] Substituting carbohydrate with plant protein and fat had a risk-reducing effect,[120] while substituting with animal protein and fat had a risk-increasing effect for all-cause mortality, further supporting the link between plant-based diets and reduced risk of mortality.[122,123]

These studies show somewhat consistent disease risk and mortality reductions associated with plant-based dietary patterns, though regarding substantially large degrees of outcome heterogeneity based on race, study group, and population location emerged. In addition, men with higher plant-based diet scores seemed to confer greater benefits compared to women, suggesting that other lifestyle factors may be modifying the associations between diet and mortality risk.[1] Further research should also focus on quality of life in the form of QALYs or disability-adjusted life years.

Promising Results: Cases of Improved Longevity and Quality of Life

Healthy Aging with a New Lease on Life

An 82-year-old man with a history of polypharmacy due to coronary artery disease, myocardial infarction, ischaemic cardiomyopathy, hyperlipidemia, hypertension, and persistent atrial fibrillation who presented with memory loss, cognitive impairment, fatigue, and weakness was given an exclusively plant, whole-food diet treatment, with moderate physical activity. Results reported include a rapid reduction of hyperlipidemia and high blood pressure and discontinuation of statin, anti-hypertensive, and beta-blocker drug therapies. The patient also reported reversal of impaired cognition and symptoms associated with atrial fibrillation and ischaemic cardiomyopathy, including light-headedness, fatigue, and weakness. This case demonstrates the exciting potential of dietary and lifestyle modifications to improve cardiovascular disease symptoms and reduce polypharmacy, along with associated negative consequences in older adults, particularly memory loss, which is so important to quality of life.[124]

After suffering two strokes within months, an 85-year-old man took on a whole food, plant-based diet to avoid further neurological and cardiovascular damage. Both his neurologist and cardiologist did not expect him to survive. As an accomplished athlete in his youth (semi-pro baseball, Golden Gloves boxer, and champion racquetball until age 85), he worked out every day until his debilitating strokes. His son, who cooked him every plant-based meal during his month-long rehabilitation, commented that the meals were nurturing, but the critical factor in his return to health was eliminating the dangerous foods that got him there. Almost a year after the first stroke, the man's physical and cognitive skills improved daily. He graduated from his walker to a cane and enjoys daily scrabble games with "incredible" memory skills.[125]

Populations with Exceptional Longevity

Populations consuming plant-based diets appear to have exceptional longevity.[116] For instance, the Blue Zones uncovered areas with high rates of people living into their nineties, including many living into their hundreds.[126] Compared to the US, where life expectancy is 78.54 years (2018), life expectancy in Japan is 84.67, the longest in the world. Okinawa specifically has a very high prevalence of octogenarians. Among the 7th Day Adventist population in Loma Linda, CA, the vegetarian men and women have expected ages at death of 83.3 and 85.7 years, respectively. These are 9.5 and 6.1 years, respectively, greater than the general Californian population at the time of analysis (1985). Overall, greater adherence to a plant-based dietary pattern correlates with lower all-cause mortality, as uncovered by the EPIC-Elderly Study (European Prospective Investigation into Cancer and Nutrition),[116] the Adventist Health Study[2,7] and NHANES III data from the U.S.[5]

Conclusion

Though healthy longevity has shown to have a small genetic component, modifiable risk factors, particularly diet but also exercise, nonsmoking, and social connection, play a predominant role in longevity.[67,68,127,128] Many examples of longest-lived communities exemplify these lifestyle factors and can help guide health practitioners in caring for and advising their patients. The dietary commonalities include a rich supply of antioxidants, fiber, other essential nutrients, and phytochemicals from unrefined plant foods in various forms.

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APPENDIX 1 Longevity and Plant-Based Diets: A Selection of Key Studies

First author, year, study design (bold), name of study (if applicable), sample population	Allès, 2019[129] **Observational Cohort Study** The Three Cities Study, France (3C) The NuAge Study, Quebec (NuAge) n = 9294 community dwellers over 65 years old in Bordeaux, Dijon, and Montpellier n = 1789 community dwellers between 67-84 years old in Quebec with good mental health
Study/analysis groups, mean age, mean BMI (SD), total N, duration	3C n = 1388 Age = 75.7 (4.8) BMI = 26.1 (4.2) Mean follow-up = 4.5 years NuAge n = 1439 Age = 74.3 (4.2) BMI = 27.8 (4.4) Mean follow-up = 2.9 years
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Linear mixed models "Adjusted for age, sex, education, total energy intake, self-reported diabetes or hypertension, and self-reported history of stroke" Primary exposures of interest were empirically derived dietary patterns from factor analysis using principal component analysis • Healthy-France • Healthy-Quebec • Western-France • Western-Quebec • Traditional-France • Traditional-Quebec
Outcome(s) of interest and units	• Cognitive function at baseline and rate of cognitive decline • Mini-Mental State Examination (MMSE) used to assess cognitive function (lower score means fewer errors and higher cognitive function)
Key Results (Bold qualitative assessment followed by quantitative results)	**No dietary patterns showed significant associations with cognitive function changes over time, though Healthy-France patterns showed better cognitive scores at baseline, while Western-France patterns showed worse cognitive scores at baseline.** Healthy-France pattern was slightly significantly associated with higher MMSE scores at baseline in fully-adjusted models (β = -0.053; 95% CI, -0.089 to -0.016). Western-France pattern was associated with lower cognitive scores at baseline (β = 0.054; 95% CI, 0.006 to 0.102). No associations were seen between baseline cognitive function or change in cognitive function with Traditional-France or any Quebec dietary patterns.
Comments: Significance to clinical application	This study suggests little difference in the effects of dietary patterns in cognitive function over time. The improved cognitive scores at baseline for Healthy-France dietary patterns compared to Western-France dietary patterns may be due to confounding factors such as socioeconomic status, though this assumption must be explored to be validated.

First author, year, study design (bold), name of study (if applicable), sample population	Chen, 2019[130] **Systematic Review** n = 37 studies
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Most study participants were older adults, community-dwelling individuals, and were from North America, Australia, Europe, and Hong Kong.
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures: *"Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diet, Anti-inflammatory diet, Healthy diet recommended by guidelines via dietary index, or Prudent Healthy Diets generated via statistical approaches"*
Outcome(s) of interest and units	• Mini-Mental State Examination to determine cognitive decline and performance

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**The Mediterranean diet is the most studied diet relating to cognitive outcomes; however, beneficial effects have been seen in research on MIND, DASH, and anti-inflammatory diets.** Studies on the MIND diet were all of high quality and produced a protective effect of diet on cognitive decline. One study calculated mental health for the intervention group as being 7.5 years younger than participant's age. 9 cohort studies showed a protective effect of Mediterranean diet on cognitive decline. DASH diet research suggests mixed effects, with some studies providing protection and others showing no association between diet and cognitive decline. Research on anti-inflammatory diet found that higher intake of an inflammatory diet pattern was associated with greater cognitive decline. Healthy diet recommended by dietary guidelines provided null findings, suggesting that adherence to government-set guidelines does not necessarily provide protection against cognitive decline.
Comments: Significance to clinical application	This systematic review provides evidence that adherence to the MIND diet is likely protective against cognitive decline. In addition, there is suggestive evidence that the Mediterranean diet also provides a protective effect. An inflammatory diet characterized by high meat and processed meat consumption and added saturated fat and processed foods accelerate cognitive decline. This review provides evidence to support the recommendation of increased whole plant-food consumption and diet high in unsaturated fats to protect cognitive function.

First author, year, study design (bold), name of study (if applicable), sample population	Seidelmann, 2018[131] **Observational Cohort and Meta-Analysis** Atherosclerosis Risk in Communities (ARIC) Study n = 15,428 US adults between the ages of 45-64 at recruitment
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 15,428 Age = 54.18 (5.8) BMI = 27.7 (0.1) Duration: Median follow up of 25 years
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposure Quintile of energy from carbohydrate relative to the rest of the study population (carbohydrate quality not reported here, except to say that populations consuming high-carbohydrate diets today tend to be high in refined carbohydrates)[132,133] Covariates Adjusted for Age, sex, race, study center, education level, cigarette smoking status, physical activity level, total energy intake, ARIC test center location, and diabetes status
Outcome(s) of interest and units	• All-cause mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**Authors found a statistically significant ($p < 0.001$) U-shaped association between carbohydrate intake and mortality, with mortality at a minimum around 50-55% energy intake from carbohydrate. Hazard ratios were not presented. Meta-analysis showed that substitution of carbohydrate with animal protein and fat increased mortality, while substitutions with plant-based proteins and fats decreased mortality ($p < 0.001$).**
Comments: Significance to clinical application	Increase plant food consumption coupled with reduced animal food consumption reduces risk for mortality. Authors' Interpretation: "Low carbohydrate dietary patterns favoring animal-derived protein and fat sources, from sources such as lamb, beef, pork, and chicken, were associated with higher mortality, whereas those that favored plant-derived protein and fat intake, from sources such as vegetables, nuts, peanut butter, and whole-grain breads, were associated with lower mortality, **suggesting that the source of food notably modifies the association between carbohydrate intake and mortality."**

First author, year, study design (bold), name of study (if applicable), sample population	Dinu, 2017[119] **Systematic Review and Meta-Analysis of Observational Studies** n = 10 studies included
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Subjects were presumably healthy individuals older than 18 years of age.

Appendix continued

Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures Vegan and Vegetarian diet Omnivorous diet
Outcome(s) of interest and units	Vegetarians • All-cause mortality • Cardiovascular disease • Ischemic heart disease • Cerebrovascular disease • Cancer incidence • Cancer mortality • Breast cancer incidence • Breast cancer mortality • Colorectal cancer mortality • Prostate cancer mortality • Lung cancer mortality Vegans • All-cause mortality • Cancer incidence
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diet was significantly associated with decreased risk of cardiovascular disease (CVD), ischemic heart disease (IHD), and cancer incidence, while vegan diets were associated with reduced cancer incidence, as well.** Vegetarians • All-cause mortality (RR 0.94 (0.86, 1.04) • Cardiovascular disease (RR 0.93 (0.86, 1.00)) • Ischemic heart disease (RR 0.75 (0.68, 0.82)) • Cerebrovascular disease (RR 0.93 (0.78, 1.10)) • Cancer incidence (RR 0.92 (0.87, 0.98)) • Cancer mortality (RR 0.98 (0.86, 1.11)) • Breast cancer incidence (RR 0.94 (0.56, 1.58)) • Breast cancer mortality (RR 0.94 (0.56, 1.58) • Colorectal cancer mortality (RR 0.90 (0.76, 1.05)) • Prostate cancer mortality (RR 0.90 (0.63, 1.29)) • Lung cancer mortality (RR 0.86 (0.62, 1.19)) Vegans • All-cause mortality (RR 0.88 (0.75, 1.02)) • Cancer incidence (RR 0.85 (0.75, 0.95))
Comments: Significance to clinical application	This meta-analysis shows statistically significant protective effects for vegetarian diets in CVD, IHD, and cancer incidence. In contrast, vegan diets show protection against total cancer incidence.87, 92, 93 In addition, vegan and vegetarian populations tended to have improved risk factors for chronic diseases, such as lower BMI and blood markers associated with cardiovascular diseases. However, the use of cross-sectional studies doesn't allow for causal inference of these diets and risk factors. Ultimately, this meta-analysis provides evidence for practitioners to recommend vegan diets for reducing risk in CVD, IHD, and cancer incidence.
First author, year, study design (bold), name of study (if applicable), sample population	Appleby, 2016[118] **Observational Cohort Study Pooled from 2 Prospective Studies:** The Oxford Vegetarian Study (OVS)[134] and the EPIC-Oxford cohort[135] n = 14,916 participants between 20 and 89 in either of the two above cohorts
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Overall n = 14,916 Age at recruitment = 44.8 (14.7) BMI = 23.8 (3.3) Duration: expressed as > 1 million person-years
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Regular meat consumption, low meat consumption, fish consumption, vegetarian diet, and vegan diet were exposures of interest Covariates adjusted for: "Smoking, alcohol consumption, physical activity, marital status, and regular use of nutritional supplements, and stratified by study/method of recruitment, all possible combinations of sex, parity, oral contraceptive use, and hormone therapy use, prior diabetes, prior high blood pressure, and receipt of long-term medical treatment"
Outcome(s) of interest and units	• All-cause mortality • Mortality from the following cancers: colorectal, pancreatic, lung, breast, ovary, lymphatic, hematopoietic • Mortality from mental and behavioral disorders • Nervous system diseases • Circulatory disease • Respiratory disease • Digestive disease • Injury, poisoning, and external causes • All other causes

Appendix continued

Key Results (Bold qualitative assessment followed by quantitative results)	**Vegan and vegetarian diets were associated with decreased hazard or pancreatic and lymphatic/hematopoietic cancers, in addition to all-cause mortality in sensitivity analysis removing deaths from individuals who were known to have switched diet groups during follow-up. For all other causes of death, no association was found.** Vegetarian and vegan diet was associated with decreased hazard of pancreatic cancer (HR 0.48; 95% CI, 0.28 to 0.82) and lymphatic/hematopoietic cancer (HR 0.50; 95% CI, 0.32 to 0.79) but no other causes of death in models taking all deaths into account before age 90. Vegetarian and vegan diet was associated with decreased hazard of malignant cancer (HR 0.82; 95% CI, 0.72 to 0.94), pancreatic cancer (HR 0.47; 95% CI 0.26 to 0.87), lymphatic/hematopoietic cancer (HR 0.43; 95% CI, 0.27 to 0.70), and all-cause mortality (HR 0.92; 95% CI 0.84 to 0.99). No significant associations were found for colorectal, lung, breast, and ovarian cancers, or mental and behavioral disorders, nervous system diseases, circulatory diseases, ischemic heart disease, cerebrovascular disease, other circulatory diseases, digestive or respiratory diseases, poisoning, injury, external causes, and other causes
Comments: Significance to clinical application	This study suggests that vegan and vegetarian diets may have protective effects against pancreatic and lymphatic/hematopoietic cancers, though no other significant associations were found for any other causes of death. To confirm the associations between vegetarian and vegan diets, more research must be done examining vegan and vegetarian diets and pancreatic and lymphatic cancers. Interestingly, no association was found for vegan/vegetarian diet on heart disease mortality or all-cause mortality in the overall group. Therefore, this study suggests a largely null finding for the protective effects of vegan/vegetarian diets, though future research should explore the details of the vegan/vegetarian dietary pattern in terms of refined foods, total fat, and saturated fat consumption.

First author, year, study design (bold), name of study (if applicable), sample population	Kwok, 2014[120] **Systematic Review and Meta-Analysis** Adventist Health Study, Adventist Health Study II, Adventist Netherlands, EPIC-Oxford study, German Vegetarian Study, Health Food Shoppers Study, Japanese Zen Priest Study, Oxford Vegetarian Study n = 8 studies
Study/analysis groups, mean age, mean BMI (SD), total N, duration	Study and participant characteristics: Included studies used prospective or observational cohorts, with a total number of participants n = 183,321. Studies had to include groups of meat eaters and vegetarians, or special groups that otherwise do not eat meat.
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures: Vegetarian vs. omnivorous diets
Outcome(s) of interest and units	• Mortality • Ischemic Heart Disease or cardiac event • Cerebrovascular disease
Key Results (Bold qualitative assessment followed by quantitative results)	**Vegetarian diet was associated with decreased risk of ischemic heart disease (IHD) in both Seventh Day Adventist (SDA) and non-SDA populations. SDA studies faced large amounts of heterogeneity, suggesting widely different outcomes in different trials.** (Relative risks are comparing vegetarians to nonvegetarians) Studies • Death (RR 0.68 (0.45-1.02)) • IHD (RR 0.60 (0.43-0.83)) • Cerebrovascular disease (RR 0.71 (0.41-1.20)) Non-SDA Studies • Death (RR 1.04 (0.98-1.10)) • IHD (RR 0.84 (0.74-0.96)) • Cerebrovascular disease (RR 1.05 (0.89-1.24)) Pooled Relative Risks for all studies • Death (RR 0.87 (0.68-1.11)) • IHD (RR 0.71 (0.57-0.87)) • Cerebrovascular disease (RR 0.93 (0.70-1.23))

Appendix continued

Comments: Significance to clinical application	This meta-analysis shows significant reduction in risk of IHD in SDA populations. However, non- SDA populations showed a much more modest effect of vegetarian diet. In addition, studies on SDA populations showed a large degree of heterogeneity, suggesting results in SDA studies are inconsistent with other studies regarding the relationship between vegetarianism and heart disease, possibly due to unmeasured confounders. However, both vegetarian SDA and non-SDA populations do show a reduction in IHD risk. Therefore, vegetarian diet emphasizing fruits, vegetables, nuts, seeds, and legumes may be used in patients at risk for heart disease to reduce risk of cardiovascular events.
First author, year, study design (bold), name of study (if applicable), sample population	Martínez-González, 2014[121] **Observational Cohort Study** PREDIMED n = 7216 participants
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 7216 Age = 67 years Overall BMI not reported Average follow-up = 4.8 years
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures Adherence to pro-vegetarian food pattern, calculated by summing up scores for 5 categories of consumption of 7 different plant foods and inverse scores of 5 different animal foods. High plant food consumption contributes 5 points to adherence score while high animal food consumption contributes 1 point to adherence score.
Outcome(s) of interest and units	• All-cause mortality • Cardiovascular mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**High plant-based diet score was associated with decreased hazard of mortality from all causes and from cardiovascular causes, even after extensive adjustment for covariates.** "Age- and sex-adjusted HRs of death from any cause (95% CIs) were 1 (reference), 0.83 (0.56, 1.23), 0.75 (0.51, 1.09), and 0.52 (0.33, 0.80)" from lowest to highest category of plant-based diet adherence. Hazard ratios for only cardiovascular deaths: "0.48 (0.24, 0.99), 0.44 (0.22, 0.90), and 0.47 (0.21, 1.04)" for 3rd to 1st highest adherence to plant-based diet adherence (with lowest adherence serving as the reference group) Further adjustment for BMI, medication use, waist-to-hip ratio, diabetes, hypertension, and hyperlipidemia attenuated associations by 3-4%. However, associations retained statistical significance.
Comments: Significance to clinical application	This study found that high consumption of plant-based foods and low consumption of animal-based foods was associated with a decreased risk of mortality from all causes and cardiovascular causes in older populations after adjustment for covariates. These results suggest that early transition of individuals to more plant-based diets may be protective against all-cause mortality.

First author, year, study design (bold), name of study (if applicable), sample population	Orlich, 2013[7] **Observational Cohort Study** Adventist Health Study II n = 73,308 Seventh-day Adventist men and women		
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 73,308 Vegan n = 5,548 Age = 57.9 (13.6) BMI = 24.1 (4.7)	Lacto-Ovo n = 21,177 Age =57.5 (13.9) BMI = 26.1 (5.3) Pesco n = 7,194 Age = 58.8 (13.7) BMI = 26.0 (5.0)	Semi n = 4,031 Age = 57.8 (14.1) BMI = 27.3 (5.6) Nonvegetarian n = 35,358 Age = 55.9 (13.1 BMI = 28.3 (6.1)
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposures Vegan, lacto-ovo vegetarian, pescatarian, semi-vegetarian, and nonvegetarian diets Covariates Age, race, smoking, exercise, personal income, educational level, marital status, alcohol, region and sleep		

Appendix continued

Outcome(s) of interest and units	• All-cause mortality • IHD mortality • Cardiovascular Disease (CVD) mortality • Cancer mortality • Other mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**Heterogeneous effects of vegan diet were found in subgroup analysis of men and women. In men, vegan diet was associated with reduced risk for All-cause, IHD, and CVD mortality. In women, vegan diet was not found to be protective for any cause of mortality. In addition, pescatarian diet was associated with reduced risk of All-cause, IHD, and other mortality in the combined group, reduced risk of all-cause, CVD, and other mortality in men, and IHD in women.** Vegan diets were only associated with reduced risk of mortality in the "Other" category (HR 0.74; 95% CI 0.56-0.99), while Pescatarian diet was associated with reduced risk of All-cause (HR 0.81; 95% CI 0.69-0.94), IHD. (HR 0.65; 95% CI 0.43-0.97), and Other mortality (HR 0.71; 95% CI 0.54-0.94). In subgroup analysis, vegan diet provided protection for men in All-Cause (HR 0.72; 95% CI 0.56-0.92), IHD (HR 0.45; 95% CI 0.21-0.94), and CVD mortality (HR 0.58; 95% CI 0.38-0.89). Vegan diet was not statistically associated with reduced risk of any cause of mortality in women.
Comments: Significance to clinical application	This large cohort study of Americans shows that vegetarian and vegan diets are associated with lower all-cause mortality and some reductions in cause-specific mortality. Results appeared to be more robust in males. Therefore, the findings of this article suggest that vegan or pescatarian diet may support a reduction of risk of mortality from IHD and CVD, especially in men, though the effect is attenuated in women.

First author, year, study design (bold), name of study (if applicable), sample population	Bamia, 2007[116] **Observational Cohort Study** EPIC-Elderly Study n = 74,607 men and women 60 or older without previous heart disease, stroke, or cancer, and known survival status as of December 2003
Study/analysis groups, mean age, mean BMI (SD), total N, duration	n = 74,607 Age and BMI not reported and not directly calculable
Exposure diet or dietary intervention (Covariates adjusted for if cohort study)	Exposure: a posteriori derived plant-based diet score, grouped by tertiles; higher plant-based score means higher numbered tertile Covariates adjusted for: sex, age, diagnosis of diabetes mellitus at baseline, waist-to-hip ratio, body mass index, educational achievement, smoking status, physical activity at current work, physical activity score at leisure time, ethanol, and total energy intake
Outcome(s) of interest and units	• All-cause mortality
Key Results (Bold qualitative assessment followed by quantitative results)	**In this study of individuals, higher plant-based diet score, characterized by higher consumption of vegetables, vegetable oils, fruits, grain products, and legumes, was associated with decreased risk of all-cause mortality in adjusted random-effects models accounting for heterogeneity of country effects.** Second and third tertiles of plant-based diet score were associated with a reduced incidence of mortality compared to the lowest tertile (HR for 2nd tertile, 0.90; 95% CI, 0.84-0.98) (HR for 3rd tertile, 0.89; 95% CI, 0.79-0.99). In addition, each 1 standard deviation (SD) increase in plant-based diet score was associated with a reduced hazard of mortality (HR 0.86; 95% CI, 0.77-0.965).
Comments: Significance to clinical application	Increased consumption of food components like vegetables, vegetable oils, fruits, grain products, and legumes is associated with decreased mortality risk in older Europeans. This suggests that plant-based diets may have protective effects against common causes of death. Lack of specificity of outcomes limits generalizability.

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