Dietary Restrictions and Nutrition in the Prevention and Treatment of Cardiovascular Disease

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Abstract: **Cardiovascular disease (CVD) is the leading cause of death in many developed countries and remains one of the major diseases strongly affected by the diet. Nutrition can affect CVD directly by contributing to the accumulation of vascular plaques and also indirectly by regulating the rate of aging. This review summarizes research on nutrition and CVD incidence based on a multipillar system that includes basic research focused on aging, epidemiological studies, clinical studies, and studies of centenarians. The relevant research linking nutrition and CVD with focus on macronutrients and aging will be highlighted. We will review some of the most relevant studies on nutrition and CVD treatment, also focusing on interventions known to delay aging. We will discuss both everyday dietary compositions, as well as intermittent and periodic fasting interventions with the potential to prevent and treat CVD. (*Circ Res*. 2019;124:952-965. DOI: 10.1161/CIRCRESAHA.118.313352.)**

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According to the American Heart Association, cardiovascular disease (CVD; a classification including coronary heart disease [CHD], stroke, coronary heart failure, high blood pressure [BP], and arterial disease) annually kills >800 000 people in the United States alone; making heart disease the leading cause of death.[1] Notably, an additional 92 million Americans are living with some form of CVD or its aftereffects.[1] This epidemic is not just confined to the United States but it represents a global health crisis. In fact, 1/3 of all deaths worldwide involve heart disease.[2] Aging is the largest risk factor for CVD, yet therapies aimed at treating aging or extending health span remain largely absent from the standard of care against CVD.[3] Reversing unhealthy lifestyle choices that may contribute to both aging and CVD, including tobacco use, physical inactivity, and specific diets, are becoming progressively more integrated in the standard of care.[1] However, lifestyle interventions are focused on CVD risk factors and are not usually targeting the aging process.[4] Over a century of research on aging identified dietary interventions as the most effective in extending not only longevity but also the healthy life span or health span in a variety of organisms. Whereas the focus on a single disease can be of limited value because an intervention can reduce the risk for one pathology while increasing that for another, nutrition to extend health span represents one of the few interventions that can act on CVD without promoting side effects.

The reliance only on epidemiological studies contributes to controversy and confusion related to the type of nutrition that can reduce and possibly even treat CVD. In addition, the selection of 1 specific macronutrient as the culprit for a disease is often a misleading oversimplification contributing to frequent and confusing changes in direction. Hence, a systematic approach to extract the long-term effects of certain dietary patterns on health is needed. Thus, a method that combines multiple research areas to determine whether 1 specific nutrient, or the combination and ratios of multiple nutrients, can help us understand the role of diets in the onset of aging-related diseases and longevity.[5] This method should be based on at least the following 4 pillars: (1) basic research focused on longevity and health span, (2) epidemiology, (3) clinical studies, and (4) centenarian studies. Combined, these areas create a strong foundation that allows for the systematic evaluation of studies related to diets and their impact on healthy aging. When the common denominators from all pillars support a consistent effect of a nutrient, or the combination of nutrients (ie, diet), recommendations resulting from this process are unlikely to undergo major modifications in the near future or are determined to be detrimental. Furthermore, applying these pillars will allow us to reduce the need for genome-specific dietary recommendations and distinguish between the short-term benefits of some diets versus their effects on the long-term risk for aging-related diseases, including cancer, diabetes mellitus, and CVD.[6,7] In this review, we will focus on the role of nutrition on aging and CVDs and as a risk factor and also on the role of diets in the prevention and treatment of CVD.

Nutrition and CVD

Pillar 1: Basic Healthspan Research and Animal Models of CVD

Understanding how nutrients affect cellular function, metabolism, and health span in model organisms provides a rigorous scientific foundation to identify a dietary approach that

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CR	calorie restriction
CRP	C-reactive protein
CVD	cardiovascular disease
DII	dietary inflammatory index
FMD	fasting-mimicking diet
HDL	high-density lipoprotein
IGF-1	insulin-like growth factor-1
KD	ketogenic diet
LDL	low-density lipoprotein
NHS	Nurses' Health Study
NIA	National Institute on Aging
RR	relative risk
UW	University of Wisconsin
VLDL	very-low-density lipoprotein

will reduce and possibly help reverse CVD while contributing positively to healthy life span. Animal models of CVD, including cardiac and atherothrombotic diseases, provide important insights into the progression and pathophysiology of CVD, and they have become essential tools to evaluate new therapeutic strategies to predict or to prevent complications. Although they have limitations, mice and particularly those with genetic modifications exacerbating diet-induced CVD phenotypes are the most common choice to model the human disease. A discussion of the extensive list of mouse models used in CVD research is beyond the scope of this article and can be reviewed elsewhere.[8,9] Instead, here we focus on the use of diets to induce certain pathologies of CVD in mice and highlight the interplay between obesity, dyslipidemia, insulin resistance, and CVD.

Insulin resistance can induce not only chronic hyperglycemia but can also lead to the development of dyslipidemia: high levels of plasma triglycerides, low levels of HDL (high-density lipoprotein), and LDL (low-density lipoprotein; known as the lipid triad). This triad, along with endothelial dysfunction, contributes to atherosclerotic plaque formation.[10,11] C57Bl/6 mice are a good model to mimic obesity-induced metabolic derangements that are observed in humans, and when fed with an unrestricted high-fat diet, these mice develop hyperinsulinemia, hyperglycemia, and hypertension.[12] A/J mice maintained on a similar dietary regimen are resistant to weight gain and metabolic perturbations.[13] Feeding young male and female C57BL/6 mice with a high-fat diet (≈62% fat, 20% carbohydrate, and 18% protein) for 8 weeks induced systemic insulin resistance, but only the females developed diastolic dysfunction, reduced insulin metabolic signaling, and increased mitochondria and cardiac microvascular alterations. A similar cardiac phenotype is observed after 12 weeks on this Western diet in male mice.[14] This model mimics the greater risk for the development of heart failure in obese young women compared with young men.[15,16] Feeding male C57BL/6 mice for 8 months with a lard-based high-fat diet (60% fat, 20% proteins, and 20% carbohydrates) results in obesity, hyperglycemia, insulin resistance, hyperinsulinemia, and hypercholesterolemia—a phenotype that is further exacerbated after 16 months leading to vasoconstriction, cardiac contractility reserve reduction, heart mass increase, cardiomyocyte hypertrophy, cardiac fibrosis, and heart metabolic compensations.[17]

Mice naturally have high levels of HDL, with relatively low steady-state concentrations of VLDL (very-low-density lipoprotein) and LDL.[18] Diets to initiate atherogenesis in wild-type rodents are mostly based on the modification of dietary fat content; for example, the Paigen diet (15% fat, 1.25% cholesterol, and 0.5% sodium cholate) composed primarily of saturated fatty acids derived from cocoa butter or butter fat.[19,20] C57BL/6 mice are the most atherosclerosis susceptible strain (with males and testosterone-treated females having HDL lipid levels that are almost 2-fold higher than in females), whereas other mouse strains do not develop any lesions at all.[21,22] This variation in response to high-fat diets between different mouse strains has been mapped for quantitative trait loci: among the 27 human atherosclerosis quantitative trait loci reported, 17 (63%) are located in regions homologous to mouse quantitative trait loci, suggesting that mouse and human atherosclerosis quantitative trait loci may share specific genes.[23,24] In a study using C57BL/6 mice aimed at understanding the role of the fat source in the development of fatty streak lesions (an irregular discoloration on the luminal surface of an artery and first visible sign of atherosclerosis), dairy butter-derived fat was the most atherogenic fat source (total saturated, 67%; total monounsaturated, 22%; and total polyunsaturated, 2%). The authors concluded that the development of fatty streak lesions is proportional to plasma saturated fatty acid levels, whereas monounsaturated fatty acids are inversely correlated with this effect.[25] However coconut oil (total saturated, 95%; total monounsaturated, 4%; and total polyunsaturated, 1%) consisting of predominantly short-chain fatty acids is an exception and results in smaller lesions.[25] Notably, these studies did not include fat derived from fish or other marine organisms, which are sources of the long-chain n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid and that have been associated with cardiac health.[26,27] Research in mouse models further indicates no association between plasma lipid levels in response to the diet and atherosclerosis sensitivity. In fact, some of the most atherosclerosis-resistant strains have high total cholesterol and LDL/VLDL levels.[20] Thus, in mice, plasma cholesterol is not a reliable marker for changes in atherosclerosis risk.

The rabbit is another well-utilized model organism in CVD research that may more closely model human CVDs. When fed with a semipurified diet containing 40% sucrose, 15% fiber, 14% tallow, and 25% animal protein, but not soy protein, rabbits develop vascular lesions and display increased levels of atherosclerosis and plaque formation independent of dietary cholesterol and saturated fat.[28,29] Notably, casein is 5-fold more atherogenic than soy protein during a 6-month feeding period,[30] possibly because casein intake increases cholesterol levels, whereas soy protein decreases cholesterol levels in the serum or possibly because of uncharacterized ingredients that accompany these proteins.[31,32] Additionally, cow milk–derived lactalbumin increases atherosclerosis >2-fold

over corn- or wheat-derived protein.[33] Animal protein from 12 different sources elevated cholesterol levels compared with 11 kinds of plant-derived protein, thus making it likely that these effects translate to other animal- and plant-based proteins.[30]

Nonhuman primates represent a highly valuable model organism to determine the effects of diets on atherosclerosis because of their evolutionary similarities to humans. African green monkeys (*Chlorocebus aethiops*) fed with saturated fat–rich lard or palm oil at 35% of their daily energy intake display higher LDL cholesterol concentrations and higher levels of coronary atherosclerosis compared with monkeys fed a diet based on monounsaturated fat, high oleic safflower oil, or fed a polyunsaturated fat linoleic acid–rich diet using safflower oil.[34,35] Based, in part, on these data, the American Heart Association concludes that in >50 years of studies in nonhuman primates, saturated fat has proven to be more atherogenic than polyunsaturated fat.[36] Naturally, different monounsaturated fatty acids could have different effects on atheromas. In fact, supplementation of patients at risk for CVD with high oleic acid containing olive oil is protective against CVD and mortality.[37,38]

Rhesus macaques (*Macaca mulatta*) are the organism most closely related to humans in which dietary interventions have been studied to prevent the onset of CVD. With a DNA sequence 93% identical to humans, they develop the same diseases (such as cancer, diabetes mellitus, and CVD) that affect human health and life span. Rhesus monkeys maintained for 2 years on a calorie-dense, cholesterol- and saturated fat–rich diet designed to resemble the average American diet (containing eggs, roast beef, beef fat, American cheese, pound cake, and other typical American food choices, such as fried bacon; 25% fat, 27% protein, and 48% carbohydrates) had increased serum cholesterol levels and displayed pathological features similar to atherosclerosis in young human adults.[39] In contrast, a low-calorie and low-fat prudent diet (containing cottage cheese, salmon, turkey, baked chicken, etc; 20% fat, 35% protein, and 48% carbohydrates) low in saturated fat and high in polyunsaturated fat significantly reduced serum cholesterol levels from 383 mg/dL in response to the average American diet to 199 mg/dL in the prudent diet.[39] Macaques fed the average American diet had 46% of their intimal surface involved with pale smooth plaques and fatty streaks compared with only 7% aortic intimal surface involvement with only minor lesions in the prudent diet-fed animals. Notably, grossly discernible aortic plaques covered >6× the area in animals receiving the average American diet compared with monkeys fed the prudent diet.[39] In other nonhuman primate studies, dietary saturated fat promoted coronary atherosclerosis, whereas polyunsaturated fat reduces LDL cholesterol and coronary atherosclerosis.[34–36,39–41] The atherogenicity of saturated fatty acids appears to be linked, in part, to elevated LDL cholesterol concentrations.[42]

As an important first step to demonstrate whether the health span and longevity benefits observed with caloric restriction (CR) interventions in lower organisms may translate to organisms closely related to humans, 2 seminal studies have been conducted at the US National Institute on Aging (NIA) and the National Primate Research Center at the University of Wisconsin (UW) to evaluate how a 30% caloric restriction throughout the monkeys' life impacts their overall health, disease risk, and longevity.[43,44] The studies resulted in conflicting data on an increase in life span (monkeys in the UW study increased their life span, whereas there were no effects in the NIA study) but demonstrated remarkable disease benefits of CR in Rhesus monkeys: a major reduction of age-related disease and all-cause mortality was observed in the UW-CR group, whereas reduced incidence of cancer was shown in the NIA-CR group.[43,44] CR reduced CVDs by ≈50% in the UW study, whereas the NIA study found no differences between the CR and ad lib-fed cohorts. In agreement with the well-established role of everyday diet composition on CVD discussed throughout this review, a more in-depth look at the diets is important to help interpret these data. First, a 7-fold lower sucrose portion was fed as part of the NIA diet (3.95%) in comparison with the UW diet (28.5%).[43] Protein intake in the NIA study was based on vegan sources, including wheat, corn, soybean, fish, and alfalfa meal, whereas the UW study used lactalbumin obtained from milk whey as the main protein source. These differences raise the possibility that the lower sugar content and more plant-based protein sources used in the NIA diet compared with the Wisconsin diet may have reduced the risk for aging-related mortality factors in the control non-CR group, thus making the dietary intervention appear less effective.[43] Also, monkeys in the control group at the Wisconsin Research Facility had unlimited access to food to model a typical Western diet, whereas control animals at the NIA were fed twice a day with age- and body weight–adjusted portions. Additionally, limiting the feeding time and meal frequency may have had significant impact on aging and health.[45] Most CR feeding approaches involve a meal feeding pattern in which animals rapidly consume the provided food followed by extended fasting hours. In a recent study in male C57BL/6 mice that compared the NIA and UW diet paradigms (the NIA diet is higher in protein, 17.3% versus 13.1%; higher in fiber, 6.5% to 9.0% versus 5.0%; lower in fat, 5.0% versus 10.6%; and lower in sucrose, 3.95% versus 28.5%),[46] Mitchell et al demonstrate that the differences in these diets have no direct impact on survival; and both 30% CR and single-meal feeding enhanced longevity regardless of the diet composition in mice. Thus, it is likely that both the eating patter and dietary composition affect longevity, but the role of time-restricted feeding in health span requires additional studies particularly in primates and humans. In the following chapters, we, therefore, evaluate the impact of diet on CVD risk in humans based on the remaining pillars.

Nutrition and CVD in Humans

In humans, dietary regimens, including the composition, calorie intake, and feeding patterns, represent major factors affecting aging and chronic diseases.[47] Dietary choices alone or in combination with other lifestyle factors can alter the risk of developing CVD, in part, by affecting the low-grade chronic inflammation that is linked to cardiovascular health. Dietary patterns based on a high consumption of vegetables, fruits, whole grains, nuts, healthy oils, and fish, such as the Mediterranean diet, have anti-inflammatory properties, whereas nutritional composition/patterns collectively termed the Western diet, including high fat and cholesterol, high red meat–based protein, high sugar, and excess salt intake, as well as frequent consumption of processed and fast-foods, are

considered proinflammatory.[48–50] In addition, protein, carbohydrate, and fat all have been linked to the risk of developing CVD, thereby making dietary recommendations to aid in CVD prevention strategies inherently complicated and creating confusion among healthcare professionals, policy makers, and the population at large. Considering epidemiology, clinical studies and data from centenarians in combination with data from basic research focused on health span allow conclusions that are not final but that are based on comprehensive scientific evidence, can be considered safe, and can reduce the development of CVD and other age-related diseases.

Pillar 2: Epidemiological Studies

Animal models have clear limitations in modeling CVD, and thus identifying disease risk factors within a defined population represents a key pillar to test research in human hypotheses generated by basic healthspan science. Next, we will evaluate the role of protein, carbohydrates, and fats on CVD risk in epidemiological studies.

Protein Intake and CVD

A Swedish study of 43 396 women indicates that increasing protein intake by 10% (or 5 g of protein) while decreasing carbohydrate intake by 10% (or 20 g carbohydrates) is associated with a significant increase in CVD incidences.[51] Substituting carbohydrates mostly with animal protein, thereby changing the overall protein:carbohydrate intake ratio, is associated with poorer health outcomes.[51] Multiple other large studies suggest a positive correlation between diets low in protein and lower rates of aging-related disease. In the 26-year follow-up of the NHS (Nurses' Health Study; including 85 168 women) and the 20-year follow-up of the Health Professionals' Follow-up Study (including 44 548 men), diets high in animal-based protein and fats and low in carbohydrates are associated with higher mortality in both men and women.[52] In contrast, vegetable-based low-carbohydrate diets resulted in the lowest mortality and CVD mortality rates for both men and women.[52] In a cohort of 29 017 postmenopausal women without previous cancer, CHD, or diabetes mellitus diagnosis, nutrient density models based on mailed questionnaires were used to estimate risk ratios from a simulated substitution of total and type of dietary protein.[53] For women in the highest intake quintile, CHD mortality decreased by 30% from an isocaloric substitution of vegetable for animal protein. CHD mortality was associated with red meats and dairy products.[53] Although no association between overall protein intake levels and ischemic heart disease or stroke events was measurable, comparison of protein source groups provided further insight into the effects of animal- versus plant based-protein: an inverse correlation between plant-based protein intake and ischemic heart disease or stroke incidence in the top versus bottom quintile, as well as a negative correlation between animal-based protein intake, was detected.[54,55] In an NHS cohort of 84 136 women aged 30 to 55 years with no known cancer, diabetes mellitus, angina, myocardial infarction, stroke, or other CVD, higher intake of red meat, red meat excluding processed meat, and high-fat dairy were associated with elevated risk of CHD. Higher intakes of poultry, fish, and nuts were instead associated with lower risk.[56] Using the National Health and Nutrition Examination Survey dataset, animal protein intake was positively associated with all-cause mortality but only in subjects ≤65 years of age and not in the older ones, indicating that many studies may have been affected by the age-specific role of certain macronutrients.[57] Importantly, consuming plant-based vegetarian or vegan diets is also associated with consuming less overall dietary protein and reducing the levels of the essential amino acid methionine, which may explain part of the effects of plant-based dietary sources on disease.[58–60]

The effect of aging on function and consequently on dietary requirements is rarely discussed in the nutrition and health literature, especially in studies and reviews covering the general adult population, yet nutritional recommendations must be adapted first to specific age ranges and eventually to specific individuals. For example, for individuals aged ≥50 years from the National Health and Nutrition Examination Survey dataset, no positive association between protein intake and increased overall, CVD-, or cancer-related mortality is detected.[57] However, dividing this cohort into 2 age groups (50–65 years, ≥65 years) revealed a strong association between dietary patterns and health. In individuals aged 50 to 65 years, high protein intake (≥20% of the consumed calories derived from protein) is associated with an increase in overall and cancer-related, but not CVD-related, mortality—an effect not observed in those aged ≥65 years.[57] In fact, individuals >65 years of age who consume a low-protein diet display increased overall and cancer-related mortality compared with individuals with a moderate or high protein intake, whereas CVD mortality remained unaffected.[57] The effect of these diets on serum levels of IGF-1 (insulin-like growth factor-1) may explain the observed age-specific effects: individuals aged ≥50 years who consumed a high-protein diet also displayed higher IGF-1 levels. In contrast, IGF-1 levels were not different for subjects >65 years of age reporting high or low protein intake, although the levels were lower for all groups compared with those in younger individuals. Thus, it is possible that the benefits of a lower protein intake in the population ≤65 years are due, in part, by the low IGF-1 levels.[57] In older individuals instead the higher protein intake could help to maintain a healthy weight and preserve muscle mass and other functions thereby preventing frailty and the diseases and mortality associated with it.[61] This hypothesis is supported by results in mice: a low-protein but high-carbohydrate diet is the most effective for both longevity and metabolic health,[62–64] but old mice on a low-protein diet struggle to maintain weight and become increasingly frail.[57] The National Institutes of Health–American Association of Retired Persons Diet and Health Study cohort of half a million people aged 50 to 71 years further supports the findings above: men and women in the highest versus the lowest quintile of red and processed meat intakes had elevated risks for overall mortality, cardiovascular disease, and cancer mortality.[65] Additional studies report a positive correlation between red meat and high-fat dairy consumption and risks for developing age-related diseases, including cancer and diabetes mellitus.[66,67] These findings suggest that in addition to the high protein content, the processing of meat products (well-done red meat, frequent frying, barbequing/broiling) might also contribute to diseases and mortality.

Fat Intake and CVD

The American Heart Association recommends the reduction in dietary saturated fat to reduce the risk of CVD.[68] Populations

in East Asian and Mediterranean countries with low saturated fat intake have low rates of CVD, and many populations who have low saturated and high unsaturated fat intake display a lower incidence of CVD compared with those with high saturated/low unsaturated fat intake.[69] The Seven Countries Study of Cardiovascular Diseases was started at the end of the 1950s to compare CVD incidences related to diet differences and initially enrolled 16 population cohorts of 12 763 middle-aged men.[69] The study indicates that populations have different CVD incidence and mortality rates (CHD). These differences were strongly associated with the consumption of saturated fat and average serum cholesterol levels, with the lowest rates in Greece and Japan and the highest rates in North America and Northern Europe.[69] A strong association between saturated fat, cholesterol levels, and incidence or mortality from CHD were found, as well as an inverse relationship between high polyunsaturated and monounsaturated fat ratios and CHD mortality.[69] These findings were the basis for the nutritional guidelines that emphasized the connection between saturated fat and CVD. However, independent meta-analyses of observational studies and available clinical trials were unable to substantiate a reliable link between saturated fat and CVD,[70–73] underlining the importance of the multipillar system described earlier. A reduction in CVD prevalence and mortality could only be demonstrated when polyunsaturated fatty acids replaced saturated fat, which is more likely because of the health benefits of polyunsaturated fatty acids on the blood lipid profile, instead of any harmful role of saturated fat. In summary, saturated fats can clearly contribute to CVD, but replacing them, but especially replacing both saturated and unsaturated fats with carbohydrates and particularly starches and sugars, does not point to saturated fat as the sole CVD culprit, confirming that the historical simplistic view that a specific disease can be prevented by simply reducing 1 macronutrient at all ages is incorrect.

Carbohydrate Intake and CVD

In recent years, the attention has switched from saturated fats to carbohydrates as culprits for CVD and other metabolic diseases. In fact, high carbohydrate consumption together with high glycemic-index or glycemic-load diets (both measures quantify the glycemic burden of carbohydrate from foods) is consistently associated with the risk of CVD.[72,74,75] In a systematic review, evidence from cohort studies supports a causal association between CHD risk and protective factors (including intake of vegetables, nuts, and Mediterranean/high-quality dietary patterns) and harmful factors, including intake of trans fatty acids and foods with a high glycemic index or glycemic load.[72] The study also concludes that there is insufficient evidence for the association of CHD with the intake of saturated and polyunsaturated fatty acids, total fat, meat, eggs, and milk. A meta-analysis[76] consisting of 220 050 participants and 4826 incident cases with a follow-up from 6 to 18 years confirms the associations of glycemic index/glycemic load with CHD but also emphasizes previously reported sex differences, with positive associations more commonly observed in women[75–79]; possibly because the decrease in HDL and increase in triacylglycerol in response to high glycemic diets is greater in women than in men.[80] In addition, previous studies indicate more harmful effects of high glycemic diets in the overweight and obese even after adjusting for confounding factors, such as age, smoking, physical activity, alcohol consumption, and total energy intake.[75,76,78,79,81] Thus, body mass index (BMI) may serve as a modifier in the association of dietary glycemic load with CHD depending on the preexisting level of adiposity. The elevated insulin demand following high glycemic diets may exacerbate insulin resistance and related lipid metabolic disorders in overweight and obese subjects, thereby increasing the risk for CHD.[82]

Nutrition, Aging, and CVD

Traditionally, studies of diet and CVD risk have focused on individual foods and macronutrients. Yet, food is typically consumed in combination, not in isolation, and, therefore, comprehensive investigations are needed to understand which dietary patterns are associated with a lower risk of CVD. Dietary patterns (ie, the macronutrient ratio and its sources) impact the inflammatory potential and CVD risk.[83,84] In a meta-analysis of 13 prospective cohort studies involving 338 787 participants, greater adherence to a healthy dietary pattern (high intake of foods, such as vegetables, fruits, fish, poultry, whole grains, and low-fat dairy products) is associated with a lower risk of all-cause (relative risk [RR] estimate, 0.76; 95% CI, 0.68–0.86) and CVD (RR estimate, 0.81; 95% CI, 0.75–0.87) mortality but not significantly associated with a lower stroke mortality (RR estimate, 0.89; 95% CI, 0.77–1.02).[85] Associations between dietary patterns with recurrent CHD events and all-cause mortality were investigated in 3562 study participants with existing CHD.[84] Using multivariable-adjusted models, high Mediterranean diet scores were inversely associated with recurrent CHD events and all-cause mortality, whereas the Southern dietary pattern (added fats, fried food, eggs and egg dishes, organ meats, processed meats, and sugar-sweetened beverages predominantly observed in the southeastern United States) was adversely associated with all-cause mortality.[84] Considering eggs are a rich source of dietary cholesterol, individuals with increased risk for CVD are traditionally advised not to consume eggs.[86] This view that has been challenged because clinical trials associating egg consumption and CVD risk are not available in individuals at risk for heart disease.[86] However, egg consumption has been shown to have minimal effects on cholesterol levels on the majority of subjects tested.[87]

Inflammation and CVD

Systemic inflammation is one of the important risk factors for CVDs.[88] The high consumption of vegetables, fruits, grains, nuts, healthy oils, and fish, and some bioactive components, such as polyphenols, in Mediterranean diet-like patters are associated with anti-inflammatory properties,[89–91] although certain fruits, vegetables, and grains can also have proinflammatory properties.[92] To assess the inflammatory potential of diets, score-based systems, such as the dietary inflammatory index (DII) have been developed, which measures the consumption of 45 food parameters (ie, total energy, micronutrients, and macronutrients but also bioactive components, such as flavonoids, spices, and tea) and their inflammatory effect scores on 6 inflammatory biomarkers.[93,94] In a meta-analysis of 9 prospective studies of ≈135 000 subjects, the highest DII (ie, proinflammatory diet) was associated with an increased risk

of all-cause mortality (hazard ratio, 1.22; 95% CI, 1.06–1.41), cardiovascular mortality (RR, 1.24; 95% CI, 1.01–1.51), and CVD (RR, 1.32; 95% CI, 1.09–1.60) compared with the lowest risk DII.[94] Notably, except for 1 Australian study, the analyzed study cohorts were predominantly female, which is relevant given that sex seems to be an import modifier in the relationship between DII and circulatory disorder diagnoses. Using 15 693 National Health and Nutrition Examination Survey respondents from 2005 to 2010, those subjects in the highest proinflammatory DII quartile were 1.30× (95% CI, 1.06–1.58) more likely to have a previous circulatory disorder (excluding hypertension), a diagnosis of hypertension (odds ratio, 1.19; 95% CI, 1.05–1.34), congestive heart failure (odds ratio, 1.38; 95% CI, 1.09–1.74), stroke (odds ratio, 1.56; 95% CI, 1.21–2.01), and heart attack (odds ratio, 1.48; 95% CI, 1.12–1.97) compared with those in the lowest DII quartile.[95] The associations between the DII and circulatory disorders are significant for combined circulatory disorders, congestive heart failure, heart attack, stroke, and high BP among women but not men.[95] However, these associations do not demonstrate a causal role for inflammation in CVD, raising the possibility that elevated CRP (C-reactive protein) and other markers of systemic inflammation may be a consequence and not cause of CVD. Despite a high infectious inflammatory burden (high-sensitivity CRP >3 mg/dL in 51% of the study population), the Tsimane—a Bolivian forager-horticulturalist population—have the lowest levels of coronary artery disease of any population recorded to date.[96] Their average diet consists of 14% protein, 14% fat (average estimated daily consumption of 38 g fat, with 11 g saturated fat, 14 g monounsaturated fat, and 8 g polyunsaturated fat and lacks trans fats), and 72% carbohydrates.[97]

Pillar 3: Clinical Studies

In a multicenter trial in Spain, ≈7500 participants aged 55 to 80 years at risk for developing CVD were assigned to 1 of 3 diets: a Mediterranean diet supplemented with at least 50 g extra virgin olive oil daily, a Mediterranean diet supplemented with 30 g of mixed nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds), or a control diet with advice to reduce dietary fat.[98] After a median follow-up of ≈5 years, the hazard ratio for developing a major cardiovascular event, such as myocardial infarction, stroke, and death, from cardiovascular cause was reduced to 0.69 (95% CI, 0.53–0.91) for the Mediterranean diet with extra virgin olive oil and 0.72 (95% CI, 0.54–0.95) for the Mediterranean diet with nuts compared with the control diet.[98] These results are consistent with other studies indicating CVD benefits caused by intake of monosaturated and polyunsaturated fats from olive oil, fish, and nuts, and with those showing the link between trans fats and CVD risk.[37,99]

A number of studies indicate that caloric restriction has beneficial effects on cardiac health and the prevention of CVD in humans.[100–102] Results from the Biosphere 2 project—a sealed ecological complex in the Arizona desert—provide the initial pilot results on the effects of prolonged (2 years) CR on human health.[103] Limitations in harvesting reduced the caloric intake of the Biospherians to only ≈1800 to 2000 kcal. Despite the relative calorie deficit, their diet was a nutrient-dense diet composed of vegetables, fruits, nuts, grains, and legumes, with only small amounts of dairy, eggs, and meat (≈12% calories from protein, ≈11% from fat, and ≈77% from complex carbohydrates). This caloric restriction, together with the physical labor required to maintain the biosphere, resulted in significant weight loss (≈21% for the men and ≈14% for the women). Yet, with the exception of few minor ailments, the overall health of the Biospherians was described as excellent, and only 5 off-work days of illness were recorded throughout the 2 years.[103] The longitudinal analysis of 50 variables on each crew member during the Biosphere project indicates remarkable changes in risk factors associated with CVD. Physiological (a BMI decrease of 19% for men and 13% for women; a systolic BP decrease of 25% and diastolic BP decrease of 22%), biochemical (a blood sugar decrease of 21%; cholesterol decreased 30%), as well as numerous additional changes resembling those observed in calorie restricted rodents and monkeys.[103] Additional studies extended this seminal work of Walford et al by demonstrating that long-term CR reduces markers associated with CVD in humans. A study compared 18 volunteers who had been on CR for an average of 6 years to 18 healthy individuals on typical American diets.[104] The CR cohort consumed ≈1100 to 2000 kcal/d (≈26% of calories from protein, ≈28% from fat, and ≈46% from complex carbohydrates) based on vegetables, fruits, nuts, dairy products, egg whites, wheat and soy proteins, and meat and avoided processed foods containing trans fatty acids and high glycemic foods (eg, refined carbohydrates, desserts, snacks, and soft drinks). The age-matched comparison group ate typical US diets containing nearly twice as many calories than the CR subjects (2000–3500 kcal/d; ≈18% calories from protein, ≈32% from fat, and ≈50% from carbohydrates). Volunteers in the CR group were leaner than the comparison group (BMI, 19.6±1.9 versus 25.9±3.2 kg/m^2; body fat, 8.7±7% versus 24±8%). Adhering to the CR regimen reduced total cholesterol, LDL, the ratio of total cholesterol to HDL, triglycerides, fasting glucose, fasting insulin, CRP, and systolic and diastolic BP, whereas HDL levels were higher than in the American diet group. Carotid artery intima-media thickness—a measure for atherosclerotic vascular disease—was reduced by ≈40% in the CR group compared with the control group.[104] In a 2-year CR intervention, nonobese subjects achieved ≈12% caloric restriction (19.5% during the first 6 months and 9% on average for the remainder of the study) and maintained ≈10% weight loss. CR decreased the CVD risk factors triglycerides, total cholesterol, LDL cholesterol, as well as systolic and diastolic BP.[105] CR also increased HDL cholesterol and improved insulin sensitivity (homeostatic model assessment [insulin resistance]).

Taken together, these studies confirm that many of the risk factors associated with CVD can be prevented by implementing a strict CR. However, CR is a severe intervention that requires dedicated volunteers, which makes it suitable for only a small portion of the population. In fact, a 2-year trial aimed at restricting calories by 25% was not sustainable for volunteers who averaged only a 9% reduction in caloric intake after 6 months of intervention.[105] Furthermore, several mouse studies indicate that chronic CR can impair immune function and also wound healing,[100,106,107] which may explain the minor effect of CR on longevity but major effect on diseases in the Wisconsin monkey study and the lack for longevity effects of CR in the

NIA study.[43,44] Thus, alternative preventive dietary approaches need to be utilized to translate the important findings from CR studies to the general population. Such examples can include the modification of dietary macronutrient composition, as well as dietary supplementations.

Short-term randomized controlled trials, which fail to consider the long-term health impact of nutrition, often favor the substitution of protein for carbohydrate (high-protein/low-carbohydrate diets) because of their benefits for weight management, BP reduction, and improvements in cardiometabolic biomarkers (such as blood lipid and lipoprotein profiles) and improved glycemic regulation.[108–110] Multiple studies have demonstrated that the health-beneficial effects of exchanging protein for carbohydrate are largely depending on weight loss, enhanced postprandial satiety, and energy expenditure.[111] Although high-protein and low-carbohydrate diets may improve compliance and maintenance of weight loss in overweight adults,[112] these diets do not align with the low-protein recommendations supported by biogerontology or morbidity research.[113,114] In fact, most studies in humans and animal models support a high-carbohydrate and low-protein diet as the most beneficial for health span and life span.[57,63,64]

Prospective and randomized clinical trials demonstrate that diets with low protein content enhance metabolic health, promote lean physical appearance, lower blood glucose, and decrease the risk of developing diabetes mellitus in humans.[100,115] The Lyon Diet Heart Study—a randomized, single-blinded, multiclinic secondary prevention trial—is aimed at reducing the risk of cardiovascular deaths by diet modification and recurrent myocardial infarction in survivors of a first myocardial infarction.[83] The dietary intervention group consumed a Mediterranean-based alpha-linolenic acid–rich diet (low in saturated fat, cholesterol, and linoleic acid, but high in oleic and alpha-linolenic acid) with increased intake of root vegetables and green vegetables, more fish, and less meat (beef, lamb, and pork to be replaced with poultry). After a mean follow-up of 27 months, noticeable differences in cardiac deaths between the control (16 of 303 subjects) and experimental cohort (3 of 302 subjects), as well as nonfatal myocardial infarction (17 in the control and 5 in the experimental cohort) support that alpha-linolenic acid–rich Mediterranean-based diet is efficient in the secondary prevention of coronary events and cardiac-related mortality.[83]

Periodic Fasting-Mimicking Diets in CVD Prevention and Treatment

Caveats to almost all of these diets are the required lifestyle changes and need for the continuous implementation into daily routines. Dietary intervention–based clinical trials often experience dropout rates around 15% to 40%,[116,117] emphasizing that even health-cautious or motivated volunteers are unable to adhere to these interventions for long periods and most people eventually return to their original diet and regain weight.[118,119] One way to address some of these concerns is the development of a periodic dietary intervention that can be integrated into daily routines. The fasting-mimicking diet (FMD) is a periodic, short-term, low-calorie, and low-protein dietary intervention designed to promote benefits while reducing side effects and the burden of chronic dieting. In mice, the efficacy of this periodic FMD lasting 2 to 5 days and followed by a standard diet was shown to extend longevity, reduce and delay cancer incidence, reverse pathology in type 1 and type 2 diabetes mellitus mouse models, and reduce/reverse symptoms in a mouse model for multiple sclerosis.[120–124] In a randomized crossover clinical trial that included 100 generally healthy participants, consuming the FMD for 5 days per month during 3 consecutive months[123] reduced body weight, trunk, and total body fat, lowered BP, and decreased IGF-1. A post hoc analysis demonstrated that risk factors/markers associated with CVD, such as BMI, BP, fasting glucose, triglycerides, total cholesterol and LDL, and CRP, were reduced in participants at risk for disease but not or less in subjects who were not at risk.[123] Yet larger trials are necessary to determine whether this periodic intervention can be effective in CVD prevention and treatment and also determine how the FMD can be best optimized for this purpose. Thus caution should be used when considering the combination of FMDs in support of standard-of-care treatments, particularly in subjects over the age of 70 years.

Pillar 4: Centenarian Studies

Regions of the world where people live much longer than average or those where the prevalence of centenarians reaches record high levels provide an important pillar supporting the role of lifestyle factors in healthy aging. Whether a dietary pattern or the frequent consumption of certain foods is strongly associated with one of these long-lived populations is particularly important to confirm their safety. Thus, the dietary common denominators supported by the epidemiological, basic health span, and clinical research together with centenarian studies represent a particularly strong foundation to identify effective but also safe interventions that can be adopted by the general population. Okinawa (Japan), Loma Linda (CA), certain villages in Calabria and Sardinia (Italy), the Nicoya Peninsula (Costa Rica), and Ikaria (Greece), despite their geographic differences, all have diets in common that are (1) mostly plant based, include small and infrequent portions of fish or meat and in many cases nuts; (2) low in animal-based protein and saturated trans fats; (3) high in complex carbohydrates derived from plant-based sources[125]; (4) low in sugar. The diet of these populations, at least historically, consisted of regional produce and was often consumed in 2 or 3 meals with a light meal before dark. The dietary ingredients, macronutrients levels, and meal timing for these populations are all different from those adopted by modern Western countries.[126] Studies of centenarians identify a dietary pattern, consistently associated with a low incidence and mortality from cancer and CVD and also with the lowest death rates and the greatest survival rates.[72,85,127] Notably, the Mediterranean diet does not appear to explain the effects observed in high longevity zones because a meta-analysis focused on the Mediterranean diet showed only a 10% reduction in CVD and an 8% reduction in overall mortality for people following the Mediterranean diet compared with those on other diets.[128] For example, Seventh-day Adventist vegetarians had a 12% reduction (18% men and 7% female) in the risk of all-cause mortality and a 29% decrease in CVD mortality in men compared with nonvegetarians.[129]

Nutrition and CVD Treatment

The previous sections underline the central role of nutrition on CVD incidence. However, dietary interventions are beginning

to emerge as also potentially effective therapies for certain CVDs. The potential advantage of diet-based therapies is that they can reduce inflammation and oxidative damage and potentially even reverse or partially reverse atherosclerosis. Low-carbohydrate diets, including the ketogenic diets (KDs), which are low or very low in carbohydrates (usually <50 g/d) but high in fats and often in proteins,[130] are being adopted to reverse metabolic disorders and potentially also CVD. The underlying principle of KDs is that the cause the depletion of glycogen reserves and activates the utilization of fatty acids and ketone bodies as energy sources.[131] In humans, KD-based therapies are effective in inducing weight loss (average ≤5% of body weight at 6 months).[130] However, as described earlier, low-carbohydrate diets do not seem to be effective in CVD prevention and are, in many studies, associated with increased overall and disease-specific mortality.[132] The use of KD in the treatment of cardiovascular risk factors in humans (including obesity, insulin resistance, hypertension, and hyperdyslipidemia) has not been extensively investigated and remains controversial.[133,134] In ≈100 obese patients with a mean BMI of 43 kg/m^2 and with a high prevalence of type 2 diabetes mellitus or metabolic syndrome, subjects on a low-carbohydrate diet lost more weight (−5.8±8.6 kg) than those on the low-fat diet (−1.9±4.2 kg; 95% CI between groups, −1.6 to −6.3) during the 6-month study.[135] Because KDs are high in fats, it is necessary to assess their potential effect on dyslipidemia—a well-known risk factor for CVDs. In humans, multiple trials associated KDs with significant reductions in total cholesterol, increases in HDL cholesterol levels, decreases in triglycerides levels, and reductions in LDL cholesterol levels in normal weight and obese participants.[134–139] As discussed in previous chapters, the dietary composition is important, and the reported benefits of KDs on triglycerides and HDL cholesterol levels may be attributed to low-carbohydrate diets rich in plant-based ingredients and unsaturated fats but low in saturated fatty acids.[138] A limitation of many studies focused on KDs is their relatively short duration that prohibits to evaluate long-term cardiovascular health and healthspan benefits. Similar to the periodic FMD approach, some studies indicated that a KD interval protocol over 12 months (20 days of KD, 20 days of a low-carb non-KD, 4 months of a Mediterranean normocaloric nutrition, a second 20-day KD, and 6 months of a Mediterranean normocaloric nutrition) decreased the CVD risk factors total cholesterol, LDL cholesterol, triglycerides, and glucose levels with high compliance rates.[140]

In the 1990s, a randomized controlled clinical trial was performed to determine whether regression of coronary atherosclerosis can occur as a result of lifestyle changes.[141] Patients were asked to practice mild-to-moderate exercise and stress management and to consume a low-fat vegetarian diet without caloric restriction for at least a year. No animal products were allowed except egg white and 1 cup of nonfat milk or yogurt per day (Figure). The diet contained ≈10% of calories as fat (polyunsaturated/saturated ratio >1), 15% to 20% from protein, and 70% to 75% from predominantly complex carbohydrates. Cholesterol intake was limited to ≤5 mg/d. Caffeine was eliminated, and alcohol was limited to ≤2 units per day. In subjects assigned to this Ornish diet, the risk of developing coronary atherosclerosis decreased, whereas lesion size in patients assigned to the control diet progressed.[141,142] In 2005, Dansinger et al[143] compared the effects of the Ornish diet to 3 other popular diets (Atkins, carbohydrate restriction; Zone, macronutrient balance; Weight Watchers, CR) for weight loss and cardiac risk factor reduction. After 1 year, each diet significantly reduced the LDL/HDL cholesterol ratio by ≈10% but without significant effects on BP or serum glucose. For all diets, decreasing total/HDL cholesterol levels,

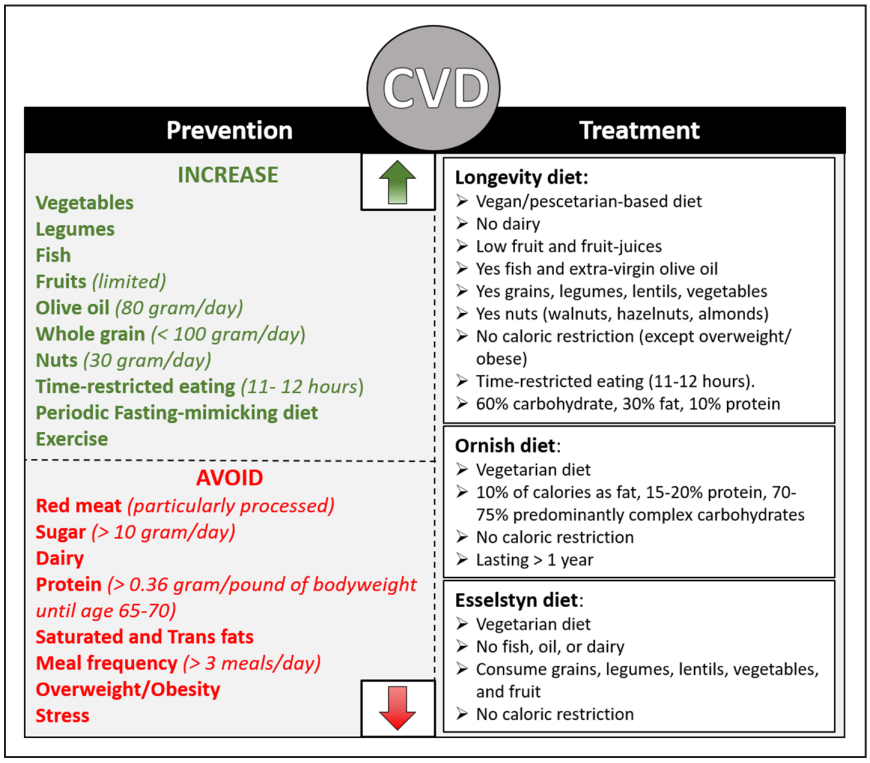

Figure. Dietary patterns associated with the prevention and treatment of cardiovascular disease (CVD).

Table. **Fasting-Based Intervention Effects on Cardiovascular Disease Risk Factors**

Intervention		Duration, mo	n (Diet Arm)	Participant Type	Risk Factor	
					Weight, kg	Waist Circumference, cm
1.5- to 3-mo interventions						
ADF	70%–75% CR on Monday, Wednesday, and Saturday; ad libitum other days	1.5	15 F	Overweight or obese	−6.0±1.2	−5.0±9.7
	>80% CR; alternated with ad libitum	2	8 F, 2 M	Overweight with asthma	−8.5±1.7	…
	75% CR; alternated with ad libitum	2	12 F, 4 M	Obese	−5.6±1.0	…
	75% CR; alternated with ad libitum	3	10 F, 5 M	Normal to overweight	−5.2±0.9	…
	75% CR; alternated with ad libitum	3	24 F, 1 M	Obese	−3.0±1.0	−5.0±1.0
IF	75% CR on 2 consecutive days per week	3	37 F	Overweight or obese	−5.0±4.4	−4.8±3.8
TRF	1 meal per day vs crossover 3 meals per day	2	10 F, 5 M	Normal weight	−1.4±3.2	…
FMD	5 consecutive days per month	3	39 F, 32 M	Normal to obese	−2.2±2.3	−3.0±4.6
				Elevated disease risk factor	−4.0±2.6 (obese)	−4.4±6.4 (obese)
6-mo interventions						
ADF	75% CR; alternated with 125% of energy needs	6	30 F, 4 M	Obese	−6.5±2.2	…
IF	75% CR on 2 consecutive days per week	6	42 F	Overweight or obese	−5.7±4.4	−6.1±4.1
CR	25% CR	6	29 F, 6 M	Obese	−6.9±2.3	…
	25% CR	6	47 F	Overweight or obese	−4.5±5.3	−3.9±4.3

(*Continued*)

CRP, and insulin was associated with weight loss but only for the minority of individuals who were able to sustain a high dietary adherence level. No single diet intervention resulted in high compliance after 1 year: 53% of subjects were able to complete the Atkins diet, 65% the Zone diet, 65% the Weight Watchers, and 50% the Ornish diet.[143] The discontinuation rates for the Atkins and Ornish diet cohorts suggest that compliance for the general population can be expected to be very low after a few years.

Similar to the Ornish diet, the Esselstyn dietary intervention tested in small preliminary studies for the treatment of CVD designed to achieve a total serum cholesterol of <150 mg/dL is vegetarian based and excludes fish, all oils, and all dairy products (except skim milk and nonfat yogurt), as well as fish, fowl, and meat.[144,145] Subjects were encouraged to eat grains, legumes, lentils, vegetables, and fruit (Figure). In a 5-year follow up,[145] in all 18 subjects that adhered to the diet (of 24 initially enrolled), CHD was either arrested or showed signs of regression. After an additional 7 years (12 years total after study initiation), 17 of the 18 subjects were able to maintain cholesterol levels <150 mg/dL.[144] Despite the observed benefits with this diet, the extremely restrictive design makes this diet an unlikely approach for the treatment of CVD in the general population. It should be noted that both, the Ornish and Esselstyn, diets overlook the benefits of nuts, plant-based fats, and fish, which are generally associated with decreased risk of heart disease[38,99,146–148] also in agreement with by dietary patterns from long-lived populations within longevity areas, with the exceptions of Seventh-day Adventists in Loma Linda, CA who often avoid fish and Okinawans who traditionally consumed low fish and oils. Further, CR-based approaches in monkeys and humans generally do not prohibit the consumption of nuts, olive oil, or fish and yet have been proven to be highly effective in reducing risk factors associated with CVD. For example, the biospherians: during their self-imposed caloric restriction, total serum cholesterol levels were reduced to ≈125 mg/dL and LDL to ≈60 mg/dL [103]; much lower than the desired 150 mg/dL total cholesterol and 80 mg/dL LDL required by the Esselstyn diet.[144,145]

Fasting-based interventions are emerging in the treatment of chronic metabolic diseases, including CVD because of various effects on cardiometabolic risk markers, such as obesity, lipid profile, and BP.[45,149] These interventions (Table) include approaches such as time-restricted eating, feeding every other day (alternate-day fasting), adopting a reduced calorie regimen twice a week (5:2 fasting), prolonged fasting, or FMDs. Alternate-day fasting involves alternating a fast day (usually ≤25% of baseline caloric intake) with a nonrestricted day; whereas the 5:2 approach requires participants to fast for 2 (usually consecutive) days followed by 5 days of normal caloric intake. Both approaches are associated with a reduction in body weight (alternate-day fasting, ≈0.75 kg/wk; 5:2, ≈0.25 kg/wk), although it remains unclear whether long-term weight loss can be sustained. Both protocols may also lower BP in prehypertense subjects if a minimum weight loss of 6% can be achieved and in addition may be useful for lowering triglyceride concentrations but with only little or no effect on total, LDL, or HDL cholesterol concentrations.[149] The conceptual framework of the time-restricted eating paradigm is based on circadian rhythms and restricts caloric intake into a 10- to 12-hour window.[126] In a study of 156 volunteers, time-restricted eating was associated with 4% reduction in body

Table. Continued

Risk Factor						References
BP, mm Hg		Cholesterol, mg/dL			CRP, mg/L	
Systolic	Diastolic	Total	HDL	LDL		
−9.7±10.2	−8.4±10.8	−12.6±43.3	8.3±19.5	−18.2±51.0	…	157
…	…	−9.3±4.0	4±1.3	−10.5±8.9	1.0±0.9	158
>−6.5	−1.5±2.5	−37.0±8.0	−2.0±3.0	−34.0±8.0	…	159
−7.0±2.0	−6.0±2.0	−26.6±6.0	−2.0±3.0	−18.0±6.0	−1.0±1.0	160
−3.0±1.0	−2.0±2.0	7.0±4.0	0.0±4.0	−1.0±6.0	−0.0±1.2	161
−4.2±3.1	…	−9.4±13.1	−0.8±5.0	−5.4±12.0	…	117
6.6±1.9	3.8±1.3	25.5±5.3	5.2±1.8	22.9±4.0	…	162
−3.8±6.8	−2.9±5.3	−9.9±19.5	−2.8±8.7	−5.7±16.8	−0.5±2.2	123
−6.7±6.9	−5.5±6.4	−19.9±25.4	0.1±3.1	−14.9±21.7	−1.7±3.1	
−3.1±8.2	−1.5±5.9	−4.3±11.1	8.4±6.3	−2.6±8.9	−0.7±1.6	163
−3.7±3.7	−7.5±4.0	−11.6±11.6	0±3.9	−11.6±11.6	−0.5±0.7	164
−3.9±8.2	−1.2±5.9	−7.6±11.2	2.2±6.5	−5.0±9.0	−0.4±1.5	163
−4.3±3.5	−5.7±3.3	−19.3±11.6	−3.9±3.9	−11.6±7.7	−0.8±0.4	164

ADF indicates alternate-day fasting; BP, blood pressure; CR, calorie restriction; CRP, C-reactive protein; F, female; FMD, fasting-mimicking diet; HDL, high-density lipoprotein; IF, intermittent fasting; LDL, low-density lipoprotein; M, male; and TRF, time-restricted feeding.

weight after 16 weeks, which could be maintained for ≤1 year.[126] Epidemiological findings support time-restricted eating because of potentially detrimental effects of late meal consumption on cardiometabolic health[150,151] but also indicate that long, daily fasting periods of ≥16 hours can lead to gallstone formation and may also increase disease and mortality.[152–154] Prolonged fasting, abstaining from caloric intake for >48 hours, might be beneficial in the treatment of hypertension: 10 to 11 days of fasting decreased systolic BP of hypertensive patients, and subjects who were taking antihypertensive medication (6.3% of the total sample) discontinued their medication.[155] Thirteen days of water-only fasting reduced systolic BP <120 in 82% of subjects with mild hypertension, and BP remained significantly lower after subjects had returned to their normal diet for 6 days.[156] However, prolonged water-only fasting is an extreme intervention; a caveat that can be circumvented by utilizing FMDs. Based on the results obtained with the FMD in generally healthy subjects, the FMD could potentially be utilized in the treatment of CVD (Figure). However, the beneficial effects on CRP, body weight, abdominal adiposity, BP, and other risk factors after 3 monthly FMD cycles[123] will need to be confirmed in larger randomized clinical trials focused on subjects with clinically diagnosed CVD and under strict medical supervision.

Outlook

Vast amounts of data on the impact of nutrition on human health are being disseminated, causing confusion among the general public and promoting diets focused on short-term effects and on one specific disease instead of healthy aging. This phenomenon underlines the need for a multidisciplinary multipillar approach focused on both basic and clinical science, as well as epidemiological studies and studies of centenarians.

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