



A plant-based diet and stroke

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1 Introduction

Stroke is a leading cause of death and disability in the United States and globally. Each year, approximately 795,000 Americans experience a stroke.^[1] Total annual costs of stroke, both direct and indirect, amount to \$33 billion. Ischemic stroke is predicted to cost more than \$2.2 trillion between 2005 and 2050.^[2] In the United States, 87% of all strokes are ischemic, 10% are due to intracerebral hemorrhage, and 3% are due to subarachnoid hemorrhage.^[1]

There are numerous risk factors for stroke, including advanced age, hypertension, diabetes, dyslipidemia, atrial fibrillation, smoking, physical inactivity, poor nutrition, family history, chronic kidney disease, obesity, coronary heart disease, sleep apnea, and depression.^[1] Several of these risk factors are modifiable lifestyle factors or are affected by modifiable lifestyle factors thus leading to the understanding that certain lifestyle choices may have a significant impact on stroke risk. The purpose of this review is to briefly examine selected evidence suggestive of nutrition, particularly plant-based nutrition, being a determinant of stroke incidence and mortality.

2 Epidemiology and etiology

Globally, high-income countries have experienced substantial declines in stroke incidence and mortality over the past two decades, including a 13% reduction in ischemic stroke incidence and 19% reduction in hemorrhagic stroke incidence.^[3] From 1998 to 2008, incident stroke among adults aged 65 and higher decreased by 40% in the United States.^[4] Gains in low-income countries, however, have been more modest. Absolute stroke incidence and mortality is significantly increasing.^[5] Largely this increase is related to the “epidemiological transition”, comprised of diet, lifestyle, and environmental changes leading to more prevalent risk factors, and, importantly, a simultaneously aging population.^[5]

Hemorrhagic stroke has traditionally been a larger percentage of strokes in the developing world, notably in Asia, as documented in Japan over the past 50 years.^[6] Contrary to the trends of other diseases of affluence (obesity, diabetes, coronary artery disease), hemorrhagic stroke prevalence in Japan decreased dramatically as the population adopted a more Western diet and lifestyle. With a 75% reduction in stroke incidence between 1970 and 1990, researchers suggested that benefits were due to a change to a Western diet, along with more common treatment of hypertension.^[6] It has been noted as well that Japan has traditionally had a very high intake of salt, and this has been decreasing over the past several decades.^[7] The most significant risk factor for intra-cerebral hemorrhage is hypertension, followed by cerebral amyloid angiopathy, or the accumulation of β -amyloid in the media and adventitia of blood vessels.^[8] Alcohol use, diabetes, tobacco smoking, and anticoagulant use are additional risk factors.^[8]

Ischemic strokes, comprising 87% of strokes in the United States, are a result of a heterogeneous collection of etiologies, separated into the following categories: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other cause of stroke, and undetermined cause.^[9] In a German population, cardioembolism was the most common etiology, followed by small vessel occlusion and large-artery atherosclerosis.^[10] In the large National Institute of Neurological Disorders and Stroke-Stroke Genetics Network, almost 17,000 cases of ischemic stroke were studied across the United States and Europe, and large artery atherosclerosis was implicated in 24%, cardioembolic in 35%, small artery occlusion in 13%, other known causes in 7%, and about 20% as undetermined/unclassified.^[11] Cardioembolic becomes a more common cause with increasing age.^[11]

3 Diet and risk factors

The INTERSTROKE study, an international case-control

study with approximately 27,000 participants, found that 90% of the population-attributable risk of stroke is associated with ten potentially modifiable risk factors (Table 1).^[12] Plant-based nutrition may reduce the likelihood of several risk factors linked to stroke risk, including hypertension, waist-to-hip ratio, diet quality, diabetes, cardiac causes, and lipid profile.

Of all the risk factors, hypertension is likely the most significant. In the INTERSTROKE study, the population-attributable risk of hypertension was 46% for all strokes (multiple studies have found that vegans and vegetarians have lower blood pressure than their meat-eating counterparts). Observational studies have found that vegetarian diets are associated with a 6.9 mmHg lower mean systolic blood pressure and 4.7 mmHg lower mean diastolic blood pressure compared to omnivorous diets. Clinical trials of vegetarian or vegan diets of at least 6 weeks duration resulted in mean decreases of 4.8 mmHg systolic BP and 2.2 mmHg

Table 1. Odds ratios associated with risk factors for all stroke in men and women over 55 years old (adapted from reference [12]).

Risk factor	OR (99% CI)
Self reported hypertension or blood pressure > 140/90 mmHg	2.55 (2.27–2.85)
Current smoking	1.70 (1.47–1.97)
Waist-to-hip ratio, highest tertile vs. lowest tertile	1.39 (1.20–1.62)
Diet (scored by modified Alternative Healthy Eating Index), highest tertile vs. lowest tertile	0.56 (0.48–0.64)
Regular physical activity	0.60 (0.50–0.72)
Self-reported diabetes or hemoglobin A1c \geq 6.5%	1.14 (1.01–1.30)
Alcohol intake, high or heavy episodic	2.14 (1.54–2.96)
Psychosocial factors (stress, depression, life events, etc...)	2.06 (1.59–2.68)
Cardiac causes (atrial fibrillation, atrial flutter, valvular disease, etc...)	2.94 (2.45–3.53)
Apolipoprotein B/Apolipoprotein A1 ratio, highest tertile vs. lowest tertile	1.79 (1.56–2.05)

Table 2. Associations of plant-based nutrition with various risk factors for stroke.

Reduced risk of hypertension ^[13,71]
Reduced sodium to potassium ratio ^[7,72]
Reduced prevalence of atrial fibrillation risk factors
Reduced risk of overweight/obesity ^[48–51]
Potentially reduced risk of obstructive sleep apnea (via lower BMI)
Reduced risk of diabetes ^[14–17]
Reduced atherosclerosis
Reduced cholesterol levels ^[18]
Reduced systemic inflammation ^[28–37]
Improved endothelial function ^[32]
Reduced TMAO ^[38–40]
Increased endothelial progenitor cells ^[41]

BMI: body mass index; TMAO: trimethylamine-N-oxide.

diastolic BP.^[13] This finding may, in part, be related to increased potassium intake (particularly if accompanied by a low sodium intake). A high sodium to potassium ratio has been associated with increased risk of stroke.^[7]

In addition to hypertension, people consuming plant-based diets have been shown to have lower risks of being diagnosed with diabetes^[14–17] and hyperlipidemia.^[18] Furthermore, patients with diabetes or hyperlipidemia who adopt a high-fiber, plant-based diet, including a healthy vegan or vegetarian diet, can often substantially ameliorate their condition.^[18–22]

In addition to diet's effect on cardiometabolic risk factors, optimal nutrition plays a central role in the pathogenesis of atherosclerosis via multiple mechanisms. Studies have demonstrated that animal protein,^[23–25] excessive added sugars^[26] and saturated fat,^[27] which are all hallmarks of a highly processed, animal-based Western diet, increase low-density lipoprotein (LDL) cholesterol. Inflammation is integral to atherosclerosis and vegetarians have been shown to have lower C-reactive protein (CRP)^[28–31] and dietary interventions rich in unrefined plant foods have been shown to reduce CRP.^[32–37] Reverse cholesterol transport is inhibited by trimethylamine-N-oxide (TMAO),^[38] a known risk factor for cardiovascular disease, which is elevated post-prandially by consumption of L-carnitine and choline^[38] and high-fat meals.^[39] Meat, dairy, and eggs are rich sources of L-carnitine and choline. This process is dependent on gut microbiota,^[40] which is sufficiently different in vegans such that vegans do not produce as much TMAO from a L-carnitine challenge (eating a steak).^[38] Interventions including plant-based diets improve endothelial function as assessed by brachial arterial flow-mediated dilatation.^[32] Finally, there is evidence that increased vegetable intake can increase circulating endothelial progenitor cells (EPC)^[41] and that low-carbohydrate, high protein diets in mice reduce the amount and function of EPC.^[42] Putting these mechanisms together, very low-fat, plant-based diets have been shown to reverse atherosclerotic lesions in clinical interventions involving patients with ischemic heart disease.^[43,44]

Though often related to atherosclerosis, cardioembolic causes of stroke are clearly distinct from atherosclerotic heart disease. Cardioembolic strokes become increasingly common with age, accounting for about 50% of all ischemic strokes above the age of 90.^[11] Several findings support the idea that diet and lifestyle affect the risk of atrial fibrillation, though this relationship is somewhat more tenuous than the relationship between nutrition and other stroke risk factors. In multiple studies, obesity has been found to be associated with a significantly increased risk of atrial fibrillation, in part due to morphological cardiac changes, including left

ventricular structural abnormalities and left atrial enlargement.^[45,46] Other atrial fibrillation risk factors include hypertension, diabetes, and obstructive sleep apnea,^[46] all of which are affected by diet and lifestyle. Perhaps the most persuasive evidence of diet's and lifestyle's impact on atrial fibrillation is the finding that loss > 10% of body weight (by facilitating significantly reduced calorie intake) among patients with atrial fibrillation results in a 6-fold greater probability of arrhythmia-free survival compared to patients who lost less than 10% of their body weight.^[47] This weight loss was accompanied by metabolic improvements, reduced left atrial volume, and reduced intraventricular septal thickness.^[47]

In addition to the benefits of plant-based diets for risk of hypertension and diabetes, as mentioned above, plant-based diets have been linked to healthier weights,^[48–51] which in turn may simultaneously reduce the incidence of sleep apnea, a disorder tightly correlated with obesity.^[52]

4 Effects of foods and dietary patterns

Various foods have been studied in relation to stroke risk, though the research is relatively limited and inconsistent. Nevertheless, fruit and vegetable consumption has been found to be protective. A recent meta-analysis shows a 21% reduction (95% CI: 0.75–0.84) in risk of stroke in highest consumers of fruits and vegetables compared to lowest consumers.^[53] The protective relationship seems to be slightly stronger with fruit than with vegetable consumption. The benefit found with fruit and vegetable consumption is consistent with several studies and meta-analyses that found an inverse correlation between the consumption of various nutrients in fruits and vegetables, including dietary folate,^[54] vitamin C,^[55] flavonol,^[56] fiber^[57] and stroke risk. Similarly, whole grains have been found to be protective against cardiovascular mortality in general.^[58]

Conversely, increased meat consumption has been shown to correlate with increased stroke risk. In one pooled analysis of just two cohort studies, for every additional meat serving (100 g) consumed per day, there was a 24% increased risk of ischemic stroke (95% CI: 1.08–1.43).^[59] In this analysis, measures of processed and red meat consumption showed trends towards increasing stroke risk but did not reach statistical significance. In a larger meta-analysis, total red meat consumption (RR = 1.14; 95% CI: 1.05–1.24), including both fresh (RR = 1.13; 95% CI: 1.04–1.22) and processed red meat (RR = 1.17; 95% CI: 1.09–1.27), was positively correlated with total stroke risk.^[60]

Some findings are weakly at odds with the proposal that a strict “plant-only” diet is best for decreasing the risk of strokes. Consuming three servings of fish per week is in-

versely correlated with total stroke (RR = 0.94; 95% CI: 0.89–0.99).^[61] Egg consumption has been found in some research to weakly trend toward lower stroke risk (RR = 0.91; 95% CI: 0.81–1.02) for an increment of one egg/day.^[62] Dairy has an inconsistent relationship to stroke, but one meta-analysis has found an inverse relationship between total dairy consumption and total stroke (RR = 0.91; 95% CI: 0.83–0.99).^[63]

Nutrition research has traditionally been focused on nutrients or single foods, but more recently overall dietary patterns have become a greater focus. The Mediterranean diet is perhaps most researched. Study subjects are given a point for adhering to the Mediterranean diet in the following nine intake categories: greater than average consumption of fruits, vegetables, grains, fish/seafood, legumes/nuts, ratio of unsaturated fats to saturated fats; lower than average consumption of meat, dairy; moderate consumption of alcohol. Generally, a Mediterranean diet is a much more plant-rich diet than is the standard American diet. In one Dutch cohort followed for 10–15 years, those with the highest adherence to the diet had an adjusted RR of incident stroke of 0.70 (95% CI: 0.47–1.05) compared to those with the lowest adherence.^[64] In a cohort of American women, maximal Mediterranean diet scores trended to lower risk of stroke (RR = 0.87; 95% CI: 0.73–1.02) compared with subjects in the lowest diet score quintile.^[65]

Similarly, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and a prudent diet have been correlated with reduced risk of stroke.^[66] Both of these dietary patterns are richer in unrefined plant foods and more limited in processed foods and red and processed meats compared to a standard American diet. Vegetarian and vegan diets have not been well researched in relation to stroke risk, but studies that have been done find no reduction in stroke incidence in populations consuming them.^[67] Generally, vegetarian and vegan diets are unlikely to yield maximal benefit, being far higher in processed foods (added fats, refined grains, and added sugars) than the whole-food, plant-based diets that have been shown to halt or reverse atherosclerotic heart disease. In addition, plant-only diets not supplemented with vitamin B12 may lead to B12 deficiency which may undermine the otherwise advantageous profile of plant-based nutrition.^[68] B12 deficiency and resulting hyperhomocysteinemia can be atherogenic.^[68] Thus patients avoiding animal-based foods should be advised to take a B12 supplement.

Very few nutritional interventions have been done, though the PREDIMED study in Spain has shown that a Mediterranean dietary intervention lasting 4.8 years with supplemented olive oil (RR = 0.67; 95% CI: 0.46–0.98) or

nuts (RR = 0.54; 95% CI: 0.35–0.84) yields a significant decrease in stroke risk among subjects at high risk for cardiovascular disease compared to a relatively high-fat control diet (37% of total calories provided by fat).^[69]

5 Nutrition and anticoagulation

Multiple anticoagulants are now in common use by patients with atrial fibrillation, including warfarin, dabigatran, apixaban, edoxaban, and rivaroxaban. Warfarin, the most common anticoagulant historically, is a vitamin K antagonist as it blocks vitamin K-dependent clotting factors. Providers have often cautioned against patients on warfarin consuming high levels of vitamin K. Unfortunately, foods high in vitamin K, including green leafy vegetables, are a particularly rich source of antioxidants and nutrients likely to benefit cardiovascular disease. An alternate management strategy, which is likely to be more beneficial, is to advise increased vitamin K intake and keep it relatively high, monitoring and adjusting warfarin closely during the period of increasing vitamin K. Patients with stable INRs actually consume more daily vitamin K compared to patients with unstable INRs, not less.^[70] It appears that having a stable, relatively higher intake is more conducive to stable INRs than near zero to moderate daily vitamin K intake. This approach allows atrial fibrillation patients, who so often have atherosclerotic heart disease, to consume green leafy vegetables.

6 Conclusions

Stroke is a heterogeneous collection of disorders with varying mechanisms; nevertheless, hypertension, atherosclerosis, or atrial fibrillation, or often a combination of all three, are key components of most strokes. Increasing intake of fruits, vegetables, whole grains and minimizing or avoiding intake of meat and processed foods has been associated with decreased prevalence of obesity, hypertension, dyslipidemia, and diabetes. Intervention studies have demonstrated benefits from very low-fat, high-fiber plant-based diets in the treatment of these conditions. In addition, this dietary pattern has been shown to have the ability to halt or reverse atherosclerosis via multiple mechanisms. Even though findings are limited and inconsistent regarding nutrition's effects on specific stroke subtypes, observational studies of stroke incidence and mortality support eating more fruits and vegetables and less meat. While interventional research is even scarcer, a Mediterranean diet has proven beneficial.

Given the demonstrable benefits of plant-based nutrition on stroke risk factors and the limited supporting observa-

tional and interventional research, further investigations of the ability of plant-based diets with minimal or no animal-based foods and processed foods to prevent stroke is strongly justified. In the absence of further research, those patients at high risk of stroke, particularly ischemic stroke, should be educated about plant-based nutrition with adequate B12 as a potentially powerful disease risk modifier.

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