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Overview

Impact of nutrition on prevention of stroke

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Abstract

Several studies demonstrated the importance of nutrition, beneficial and preventive role of Mediterranean diet in the occurrence of cardiovascular diseases, chronic neurodegenerative diseases and neoplasms, obesity and diabetes. In randomized intervention trials, Mediterranean diet improved endothelial function and significantly reduced waist circumference, plasma glucose, serum insulin and homeostasis model assessment score in metabolic syndrome. Several studies support favorable effects of Mediterranean diet on plasma lipid profile: reduction of total and plasma LDL cholesterol levels, plasma triglyceride levels, and apo-B and VLDL concentrations, and an increase in plasma HDL cholesterol levels. This effect is associated with increased plasma antioxidant capacity, improved endothelial function, reduced insulin resistance, and reduced incidence of the metabolic syndrome. The beneficial impact of fish consumption on the risk of cardiovascular diseases is the result of synergistic effects of nutrients in fish. Fish is considered an excellent source of protein with low saturated fat, nutritious trace elements, long-chain ω-3 polyunsaturated fatty acids (LCn3PUFAs), and vitamins D and B. Fish consumption may be inversely associated with ischemic stroke but not with hemorrhagic stroke because of the potential antiplatelet aggregation property of LCn3PUFAs. Total stroke risk reduction was statistically significant for fish intake once per *week, while the risk of stroke was lowered by 31% in individuals who ate fish 5 times or more per week. In the elderly, moderate consumption of tuna/other fish, but not fried fish, was associated with lower prevalence of subclinical infarcts and white matter abnormalities on MRI examination. Dietary intake of ω-3 fatty acids in a moderate-to-high range does not appear to be associated with reduced plaque, but is negatively associated with carotid artery intima-media thickness. Greater adherence to Mediterranean diet is associated with significant reduction in overall mortality, mortality from cardiovascular diseases and stroke, incidence of or mortality from cancer, and incidence of Parkinson's disease and Alzheimer's disease and mild cognitive impairment.*

INTRODUCTION

Mediterranean diet is usually consumed among the populations bordering the Mediterranean Sea, representing a model of healthy eating, favorable health status and better quality of life. It was first described in the 1960s by Angel Keys. Several studies demonstrated the beneficial and preventive role of Mediterranean diet on the occurrence of cardiovascular diseases, chronic neurodegenerative diseases and neoplasm, obesity and diabetes. Adherence to Mediterranean diet is focused on estimating adherence to the complete Mediterranean diet rather than analyzing individual components of the dietary pattern. Dietary

scores estimating adherence to Mediterranean diet are based on the characteristic components of the traditional Mediterranean diet and associated with a reduction of overall mortality and morbidity *(1, 2)*. In 1993, the International Conference on the Diet of the Mediterranean summarized the key elements of this diet as follows: abundant plant foods (fruits, vegetables, breads, other forms of cereals, beans, nuts, and seeds); minimally processed, seasonally fresh, and locally grown foods; fresh fruits as the typical daily dessert with sweets based on nuts, olive oil, and concentrated sugars or honey during feast days; olive oil as the principal source of dietary lipids; dairy products (mainly cheese and yogurt) in low-to-moderate amounts; fewer than four eggs *per* week; red meat in low frequency and amounts; fish and poultry in low-to-moderate amounts; wine in low-to-moderate amounts, generally with meals *(3–5)*.

PREVENTIVE ROLE OF MEDITERRANEAN DIET ON OBESITY AND DIABETES

Epidemiological evidence for the preventive role of Mediterranean diet on obesity showed inverse association of body mass index (BMI) and Mediterranean diet in a representative Mediterranean Spanish population and a reduced risk of being obese with higher adherence to the Mediterranean diet pattern, independently of whether olive oil was included in the Mediterranean diet or not *(6)*. Longitudinal analysis of Spanish men and women showed that subjects with high adherence to Mediterranean diet had lower crude increments of weight during 2 years of followup *(7)*. In a randomized intervention 54-month trial, Mediterranean diet improved endothelial function and significantly reduced waist circumference, plasma glucose, serum insulin and homeostasis model assessment (HOMA) score in metabolic syndrome patients, as epidemiological evidence for the preventive role of Mediterranean diet in obesity and type 2 diabetes *(8)*. The effectiveness of a Mediterranean lifestyle program (low-saturated fat diet, stress management training, exercise and group support, together with smoking cessation) in reducing cardiovascular risk factors in postmenopausal women with type 2 diabetes showed greater improvements in HbA1c, BMI and lipid profile in the intervention group as compared with control group *(9)*. A decrease in several cardiovascular risk factors such as glycemia, insulinemia or HOMA, among others, was observed after following a Mediterranean-type diet for 3 months *(10)*. Improvement in glucose metabolism was observed after administration of a Mediterranean-type diet *(11)*. The mechanisms inversely linking Mediterranean diet to excessive weight include the effect of Mediterranean diet on satiation (satisfying the appetite that develops during the course of eating and eventually results in cessation of eating) and satiety (the sensation that determines the inter-meal period of fasting). Dietary fibers induce prolonged mastication while fiber-rich foods generally contain a large volume of water, which also increases gastric distention. Gastrointestinal response to fiber food induces cholecystokinin production and olive oil promotes postprandial fat oxidation. These effects and low degree of energy density (available dietary energy *per* weight--energy content/weight of food or kJ/g) are favorable features of Mediterranean diet. The mechanisms inversely linking Mediterranean diet to type-2 diabetes include preventing obesity, antioxidant-rich foods, polyphenol--rich foods, magnesium rich foods, moderate alcohol consumption, carbohydrate and dietary fiber, and foods rich in unsaturated fat *(12)*. Several studies support the favorable effects of Mediterranean diet on plasma lipid profile: reduction of total and plasma LDL cholesterol levels, plasma triglyceride levels and apo-B and VLDL concentrations, and an increase in plasma HDL cholesterol levels. This effect is associated with increased plasmaantioxidant capacity, improved endothelial function, reduced insulin resistance, and reduced incidence of the metabolic syndrome. Mediterranean diet reduces the risk of coronary heart disease (CHD), which is not completely explained by its action on the lipid profile and is also attributable to non-lipid pathways *(3–5)*. The relationship between dietary glycemic index (GI), retinal microvasculature changes, and stroke-related mortality was assessed in the study which consisted of a population-based cohort. Validated food frequency questionnaires were used and retinal arteriolar and venular diameters were measured from photographs. Mortality data were derived using the National Death Index. Over 13 years, 3.5% of participants died from stroke. Increasing GI and decreasing low cereal fiber (CF) predicted greater risk of stroke death adjusting for multiple stroke risk factors. Subjects consuming food in the highest GI tertile and lowest CF tertile had a 5-fold risk of stroke death. Increasing GI and decreasing CF were also associated with retinal venular caliber widening. Adjustment for retinal venular caliber attenuated stroke death risk associated with high GI by 50% but did not affect the risk associated with low CF consumption. High-GI and low--CF diets predict greater stroke mortality and wider retinal venular caliber. The association between a high-GI diet and stroke death was partly explained by GI effects on retinal venular caliber, suggesting that a high-GI diet may produce deleterious anatomic changes in the microvasculature *(13)*.

Adherence to a Mediterranean Diet-Model of Healthy Lifestyle

A meta-analysis of adherence to Mediterranean diet and health status included twelve studies (N=1574299) and analyzed prospectively the association between adherence to Mediterranean diet, mortality and incidence of major cardiovascular diseases and chronic neurodegenerative diseases. Greater adherence to Mediterranean diet was associated with significant reduction in overall mortality (9%), cardiovascular disease (CVD) mortality (9%), incidence of or mortality from cancer (6%), and incidence of Parkinson's disease and Alzheimer's disease (AD) (13%). Adherence to Mediterranean diet was defined through scores that estimated conformity of the study population dietary pattern with the traditional Mediterra-

nean dietary pattern *(2)*. Several studies showed inverse association between adherence to Mediterranean diet and the risk of CHD. The Mediterranean Diet and Incidence and Mortality from Coronary Heart Disease and Stroke in Women study was performed in 4886 women with no history of CVD and diabetes (Nurses' Health Study). Alternate Mediterranean Diet Score (aMED) was computed from selfreported dietary data collected through administered food frequency questionnaires. The aMED is focused on higher consumption of plant foods, including plant protein, monounsaturated fat and fish, and lower consumption of animal products and saturated fat. The possible aMED score range was 0–9, with a higher score representing closer resemblance to Mediterranean diet. Results showed 2391 incident cases of CHD (1597 nonfatal and 794 fatal) and 1763 incident cases of stroke (959 ischemic, 329 hemorrhagic and 475 unclassified). Of all strokes, 1480 were nonfatal and 283 fatal. There were 1077 CVD deaths (fatal CHD and stroke combined) *(12)*.

Mediterranean Diet and the Risk of Alzheimer's Disease and Mild Cognitive Impairment

Higher adherence to a Mediterranean-type diet and higher level of physical activity have been independently associated with a reduced risk of AD. In a prospective cohort study (N=1880) including subjects without dementia with diet and physical activity information available, adherence to a Mediterranean-type diet (scale of 0–9: low, middle, or high) and physical activity (sum of weekly participation in various physical activities: light, moderate, or vigorous; no physical activity, some, or much) were evaluated in separate and in combination. A total of 282 incident AD cases occurred during a mean of 5.4 years of follow-up. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute AD risk of 12%). Both physical activity and diet were significantly associated with AD incidence when considered simultaneously in the same model. Belonging to the middle diet adherence tertile was associated with a 2%–14% risk reduction, while belonging to the highest diet adherence tertile was associated with a 32%–40% risk reduction. Similarly, compared with individuals with no physical activity, individuals reporting some physical activity had the risk of AD lower by 25%–38%, while individuals reporting much physical activity had the risk of AD lower by 33%–48%. Concerning the Mediterranean-type diet adherence, compared with low diet score, the hazard ratio (HR) for middle diet score was 0.98 and for high diet score 0.60. Concerning physical activity, compared with no physical activity, HR was 0.75 for some physical activity and 0.67 for much physical activity *(14)*. Higher adherence to Mediterranean diet may protect from AD and mild cognitive impairment. A community study in New York investigated the association between adherence to Mediterranean diet (scale 0–9: higher score, higher adherence), incidence of mild cognitive impairment and progression from mild cognitive impairment to AD. The study included 1393 cognitively normal subjects; 275 of them developed mild cognitive impairment during 4.5-year follow-up. Compared to subjects in the lowest Mediterranean diet adherence tertile, subjects in the middle Mediterranean diet adherence tertile had the risk of developing mild cognitive impairment lower by 17%, while those in the highest Mediterranean diet adherence tertile had the risk of developing mild cognitive impairment lower by 28%. There were 482 subjects with mild cognitive impairment, of which 106 developed AD during 4.3-year follow-up. Compared to subjects in the lowest Mediterranean diet adherence tertile, subjects in the middle Mediterranean diet adherence tertile had the risk of developing AD lower by 45%, while those in the highest Mediterranean diet adherence tertile had the risk of developing AD lower by 48%. Higher adherence to Mediterranean diet is associated with a trend of a reduced risk of developing mild cognitive impairment and of its conversion to AD *(15)*.

Fish Consumption Can Reduce the Risk of Cardiovascular Diseases and Stroke

The long-chain ω-3 polyunsaturated fatty acids (LCn3PUFAs), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in fish are the key nutrients responsible for the cardioprotective benefits and CVD prevention. The beneficial effects of fish consumption on the risk of CVD include the synergistic effects of nutrients in fish, and the integrative effects may reflect the interactions of nutrients. Fish is considered an excellent source of proteins with low saturated fat (taurine, arginine and glutamine, known to regulate cardiovascular function); some nutritious trace elements (selenium and calcium, which may directly or indirectly provide cardiovascular benefits, alone or in combination with LCn3PUFAs and vitamins (vitamins D and B). Interactions between LCn3PUFAs and other nutrients including nutritious trace elements and vitamins and amino acids are important in reducing the risk of CVD. The overall favorable effect is observed on lipid profiles, threshold for arrhythmias, platelet activity, inflammation and endothelial function, atherosclerosis and hypertension *(16)*. Consumption of whole fish would have greater benefits than fish oil supplements, calling for caution on recommending taking fish oil supplements instead of consuming whole fish. The American Heart Association recommends eating fish (particularly fatty fish) at least 2 times a week *(17)*. Fish consumption may be inversely associated with ischemic stroke but not with hemorrhagic stroke because of the potential antiplatelet aggregation property of LCn3PUFAs. A meta-analysis of 8 independent prospective cohort studies, which included 200 575 subjects and 3491 stroke events showed that individuals with higher fish intake had a lower total risk of stroke compared with those never consuming fish

or eating fish less than once a month. The reduction in the total risk of stroke was statistically significant for fish intake once *per* week; for individuals who ate fish 5 times or more *per* week, the risk of stroke was lower by 31%. The risk of ischemic stroke was significantly reduced by eating fish twice a month. The observation of the high incidence of hemorrhage in Eskimos, who consume large amounts of fish, has raised concerns about the possible adverse effects of high fish intake on the risk of hemorrhagic stroke. Further studies are needed to investigate fish or LCn3PUFA intake in relation to the risk of hemorrhagic stroke. The types of fish appear to be less important as long as one takes certain amounts of LCn3PUFAs. Different types of fish may exert different effects if we consider fish as a nutrient package. The type of fish is important with respect to investigating contaminants in fish.

Dietary Intake of Fish and Cooking Methods

The benefits from different cooking methods have not yet been studied thoroughly. It has been suggested that broiled and baked fish, but not fried fish and fish sandwiches, are associated with a lower incidence of atrial fibrillation and ischemic heart disease. Studies suggest that vascular benefits of fish consumption may be altered by preparation methods. Frying may modify the lipid profile through a decrease in the ω-3/ω-6 fatty acid ratio *(18)*. In the Cardiovascular Health Study, 3660 participants aged over 65 underwent an MRI scan to evaluate fish consumption and risk of subclinical brain abnormalities on MRI in older adults. In the elderly, modest consumption of tuna/other fish, but not fried fish, was associated with a lower prevalence of subclinical infarcts and white matter abnormalities on MRI examination. Tuna or other fish consumption was also associated with a trend toward a lower incidence of subclinical infarcts and with better white matter grade. No significant associations were found between fried fish consumption and any subclinical brain abnormalities. Dietary intake of fish with higher eicosapentaenoic acid and docosahexaenoic acid content, and not fried fish intake, may have clinically important health benefits. After adjustment for multiple risk factors, the risk of having one or more prevalent subclinical infarcts was lower among those consuming tuna or other fish ≥3 times *per* week compared to <1 *per* month. The risk reduction in those consuming tuna/other fish ≥3 times *per* week was 0.56 compared to <1 *per* month. Each serving/week of tuna/other fish was associated with a trend toward 11% lower risk reduction of any incident subclinical infarct and 12% lower risk reduction of each additional multiple infarct *(19)*.

According to the Genetics of Coronary Artery Disease in Alaska Natives Study, consumption of ω-3 fatty acids is not associated with a reduction in carotid atherosclerosis. The study included a populationbased sample that underwent ultrasound assessment of carotid atherosclerosis. Diet was assessed by a food frequency questionnaire. The intima-media thickness (IMT) of the distal wall of distal common carotid arteries and plaque score (number of segments containing plaque) were assessed. The mean consumption of total ω-3 fatty acids was 4.76 g/day in those without and 5.07 g/day in those with plaque. The presence and extent of plaque were unrelated to the intake of C20–22 ω-3 fatty acids or total ω-3 fatty acids. The odds of plaque rose significantly with quartiles of the palmitic and stearic acid intake. The extent of plaque (or plaque score) was also associated with a higher percentage intake of palmitic acid. IMT was negatively associated with grams of C20–22 ω-3 fatty acids, total ω-3, palmitate and stearate consumed. Dietary intake of ω-3 fatty acids in a moderate-to-high range does not appear to be associated with reduced plaque, but is negatively associated with IMT. The presence and extent of carotid atherosclerosis among Eskimos is higher with increasing consumption of saturated fatty acids. There were no significant differences in the prevalence of atherosclerotic plaque or mean plaque score with increasing quartiles of dietary intake of either total ω-3 fatty acids or C20–22 ω-3 fatty acids.

When analyzed as percentage of total fat intake, C20–22 consumption and total ω-3 fatty acid consumption were not related to average IMT. When the analyses were adjusted for age and sex, positive associations were observed between the percentage of fat intake from palmitic acid or stearic acid and the presence of plaque and plaque score. When analyzed as daily intake in grams, higher quartiles of intake of either palmitate or stearate were associated with significantly higher average IMT, when adjusted for age and sex *(20)*.

Tea Consumption and the Risk of Stroke

A meta-analysis of green and black tea consumption and the risk of stroke included data from 9 studies involving 4378 strokes in 194 965 individuals. The main outcome assessed was the occurrence of fatal or nonfatal stroke. The summary effect associated with consumption of ≥3 cups of tea (green or black) *per* day was calculated. Regardless of their country of origin, individuals consuming ≥3 cups of tea *per* day had by 21% lower risk of stroke than those consuming less then 1 cup *per* day (absolute risk reduction 0.79; CI 0.73– 0.85). The results are consistent across green and black tea. The types of catechins differ between green and black tea; their total amounts are comparable because both black and green tea are derived from the same source: the catechins produced within the *Camelia sinensis* plant and both have demonstrated effects on vascular function. Both types of tea have been shown to reduce blood pressure in stroke prone hypertensive rats at doses equivalent to 1 L *per* day in humans. Population- based analyses do not support a generalized negative association between tea consumption and blood pressure. Catechin ingestion blocked the increase in serum nitric oxide concentration in rats after reperfusion and tea had evident effect on endothelial function. Theanine is readily bioavailable from both green and black tea, crosses the blood-brain barrier, and has effects on brain function; it contains the

glutamate molecule and it might reduce the glutamate--related endothelial damage. Studies of middle cerebral artery occlusion in mice demonstrated the neuroprotective effect of Y-glutamylethylamide (theanine) at dosages of 0.5 and 1.0 mg/kg reducing the size of cerebral infarct. Regular tea consumption, instead of preventing overt stroke, may reduce the post-ischemic damage to a level that results in subclinical ischemia or hidden strokes. This would result in the diagnosis of stroke only in individuals with more extensive post-ischemic damage or greater stroke volume *(21)*. Three-City Study showed tea consumption to be inversely associated with carotid plaques in women. Results were tested for replication in younger population sample, in the EV A Study. Atherosclerotic plaques in extracranial carotid arteries and common carotid artery (CCA) IMT were measured. In the Three-City Study, increasing daily tea consumption was associated with a lower prevalence of carotid plaques in women: 44.0% in women drinking no tea, 42.5% in those drinking 1 to 2 cups *per* day, and 33.7% in women drinking more then 3 cups *per* day. This association was independent of age, center, major vascular risk factors, educational level, and dietary habits. There was no association of tea consumption with carotid plaques in men, or with CCA-IMT in both sexes. In the EV A study, the carotid plaque frequency was 18.8% in women drinking no tea, 18.5% in those taking 1 to 2 cups *per* day, 8.9% in those taking 3 cups *per* day. Carotid plaques were less frequent with increasing tea consumption in women *(22)*. Coffee and tea consumption could potentially reduce the risk of stroke because these beverages have antioxidant properties, and coffee may improve insulin sensitivity. Data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study included 26556 male Finnish smokers aged 50–69 years, without a history of stroke. Coffee and tea consumption was assessed at baseline. After adjustment for age and cardiovascular risk factors, consumption both of coffee and tea was statistically significantly inversely associated with the risk of cerebral infarction but not of intracerebral or subarachnoid hemorrhage. The multivariate risk reduction of cerebral infarction for men in the highest category of coffee consumption (≥8 cups *per* day) was 0.77 compared with those in the lowest category (<2 cups *per* day). The corresponding risk reduction comparing men in the highest category of tea consumption (≥2 cups *per* day) with those in the lowest category (non-drinkers) was 0.79. These results suggest that high consumption of coffee and tea may reduce the risk of cerebral infarction among men, independently of the known cardiovascular risk factors. The risk reduction of cerebral infarction for men in the highest compared with the lowest category of consumption was 0.77 for coffee and 0.79 for tea. Additional adjustment for consumption of fruits, vegetables, fish, and total fat did not appreciably alter the results for coffee or tea. Regression analysis demonstrated a dose-response relationship between coffee consumption and the risk of cerebral infarction *(23)*.

Whole-Grain Intake and the Importance of Glycemic Index in Cholesterol Management

In the Insulin Resistance Atherosclerosis Study, whole--grain intake and carotid artery atherosclerosis were evaluated in a multiethnic cohort. Association of whole--grain intake with carotid IMT and progression was evaluated by color Doppler flow imaging (CDFI). Baseline whole-grain intake estimate was based on the intake of dark breads, cooked cereals and high-fiber cereals as assessed with a validated food-frequency questionnaire; median whole-grain intake was 0.79 servings *per* day. Whole-grain intake was inversely associated with CCA IMT and IMT progression. This association was less significant for ICA IMT and not significant for ICA IMT progression. The relation between whole-grain intake and CCA IMT remained significant after adjustment for mediating pathways (lipids, adiposity and insulin resistance), nutrient constituents, and the principal components-derived healthy dietary pattern. Wholegrain intake was inversely associated with CCA IMT and this relation was not attributable to individual risk intermediates, single nutrient constituents, or larger dietary patterns *(24)*.

Vitamin C is Associated with a Lower Risk of Stroke

A 3-year intervention study showed the vitamin C consumption to be associated with less progression in carotid IMT in elderly men. Carotid artery IMT and diet were assessed in elderly men. Men were randomly assigned to 1 of 4 groups: dietary intervention, ω-3 supplementation, both, or neither. Results previously showed that omega-3 supplementation did not influence the IMT, thus the dietary intervention and no dietary intervention groups were pooled. The dietary intervention group had less progression in carotid IMT compared with controls. This group increased their daily vitamin C intake and intake of fruit, berries and vegetables. Increased intake of vitamin C and of fruit and berries was inversely associated with IMT progression. Multivariate linear regression analysis showed that increased intakes of vitamin C and of fruit and berries were associated with less IMT progression in the intervention group and in the total study population, after adjustment for consumption of dietary cholesterol, cheese, saturated fat and group assignment. Vitamin C containing foods may protect against the progression of carotid atherosclerosis in elderly men *(25)*. Fruits and vegetables, and foods rich in flavonoids and antioxidants have been associated with a lower risk of stroke, CHD, and markers of inflammation and oxidative stress in adults. Markers of inflammation and oxidative stress are predictors of the CHD risk; however, it is unknown whether these markers are related to dietary flavonoid and antioxidant intake in youth. Correlation analyses evaluated the relation of the intakes of fruit and vegetables, antioxidants, folate and flavonoids with markers of inflammation (C-reactive protein, interleukin-6, tumor necrosis factor-α and 15-keto-dihydro-PGF2α metabolite) and oxidative stress (urinary 8-iso prostaglandin

F2α and F2-isoprostane). The association of nutrient intake and markers of inflammation and oxidative stress was inversely related to some markers of inflammation, including CRP and IL -6, and oxidative stress (F2-isoprostane). The beneficial effects of fruit and vegetable intake on markers of inflammation and oxidative stress are already present by early adolescence, thus the results of this study support Dietary Guidelines for Americans to consume 5 or more servings *per* day of fruits and vegetables for cardiovascular health *(26)*.

The Importance of Chocolate in Brain Health

Chocolate has always been considered distinctive among foods. It has always held a particular place in human society, from its historical use as a divine essence up to its status today as the food of pleasure. Chocolate is not classified as part of any of the four fundamental plant groups of food (whole grains, vegetables, fruit, and legumes). It is rather defined as „a paste, powder, syrup or bar, made from cacao seeds that have been roasted and ground". It contains nutrients and provides nourishment, thus fitting the definition of a food. It contains approximately 50% of fat and close to 50% of carbohydrate; this combination of nutrients results in a powerful effect whereby all brain chemicals (serotonin, dopamine, and opiate peptides) are positioned at optimal levels for positive mood and euphoric feelings. Chocolate also contains more than 400 distinct flavor compounds (more than twice as many as any other food) *(27)*.

Chocolate and Heart

In various controlled studies, consumers of dark chocolate showed benefits such as lowered blood pressure, reduced oxidation of low-density lipoproteins and reduced platelet aggregation. These findings are attributed to the presence in cocoa of a certain group of flavonoids including epicatechin, catechin, and procyanidins. These substances have pronounced antioxidative properties to which the beneficial effects are being ascribed. Stimulation of nitric oxide production is another possible route for their effects, and they have also been suggested to modulate certain cell signaling pathways and gene expression, and to influence cell membrane properties and receptor function. The positive effects seem to be limited to dark chocolate, the milk in milk chocolate apparently interfering with flavonoid absorption in the gut *(28)*.

Environmental Vascular Risk Factors: New Perspectives for Stroke Prevention

In addition to traditional and non-traditional vascular risk factors, a number of environmental risk factors for stroke have been identified in the last decade, i.e. lower education and poor socioeconomic status as surrogates for exposure to traditional high-risk behaviors such as smoking, poor nutrition, lack of prenatal control, absence of preventive medical and dental care, and noncompliance with the treatment of conditions such as hypertension; depression, stress and affective disorders; obstructive sleep apnea; passive smoking and environmental pollution; infections, in particular periodontal diseases that increase C-reactive protein (CRP); raised BMI (obesity); lack of exercise; and diet *(29, 30)*. Protective diets include Mediterranean diet, as well as probiotic bacteria in yogurt and dairy products. Attention should be paid to the patient's environment looking for modifiable factors. The effects of clean environmental air and water, adequate diet and appropriate nutrition, healthy teeth, exercise, and refreshing sleep in the prevention of stroke and CVD appear to be quite compelling. Although some of these modify able risk factors lack evidence-based information, judicious clinical sense should be used to counteract the potentially damaging effects of adverse environmental vascular risk factors *(31)*. Dietary fat intake is associated with the risk of CHD and ischemic stroke. As part of the prospective Northern Manhattan Study, 3183 stroke free community residents underwent evaluation of their medical history and had their diet assessed by a food-frequency survey. During the study, 142 ischemic strokes occurred and after adjusting for potential confounders, the risk of ischemic stroke was higher in the upper quintile of total fat intake compared to the lowest quintile. Total fat intake >65 g was associated with an increased risk of ischemic stroke. The results suggest that increased daily total fat intake, especially above 65 g, significantly increases the risk of ischemic stroke. The ischemic stroke risk for those in the highest quintile of fat intake was higher than for those in the lowest quintile, both in unadjusted analyses and after adjusting for age, race/ethnicity, sex, education, hypertension, diabetes, coronary artery disease, moderate alcohol consumption, current smoking, previous smoking, any physical activity and BMI. Similarly, when fat as a percentage of total daily calories was examined, those who obtained 45% or more of their calories from fat showed a trend toward an increased risk of ischemic stroke *(32)*. Fast food options have become a quickly growing and universal phenomenon offering a quick and inexpensive meal high in fat and salt, and rarely providing fruit, vegetables or whole grains. Fast food restaurants tend to cluster in neighborhoods that are more economically disadvantaged and in areas with high proportions of minority residents. Neighborhood disadvantage has been linked to stroke risk. Accessibility to fast food restaurants may be one pathway by which neighborhood disadvantage contributes to atherosclerosis. Neighborhoods that have high fast food restaurant densities have less options for healthy eating. If fast food restaurant density is associated with stroke risk, then appropriate public health interventions in specific neighborhoods can be suggested. Other risk factors that go beyond traditional biologic and social risk factors may potentially contribute risk for common, severe diseases such as stroke. The association of the density of fast food restaurants with ischemic stroke in neighborhoods was evaluated as part of a population based study in South Texas. There were 1247 completed ischemic strokes during 3 years and 262 fast food restaurants located in the area. The association of fast food restaurants with stroke was significant. The association suggested

that the risk of stroke in the neighborhood increased by 1% for every fast food restaurant. There was a significant association between fast food restaurants and stroke risk in neighborhoods in this community based study *(33)*. The combined effect of health behaviors and risk of first-ever stroke was assessed in 20 040 men and women during 11-year follow-up in Norfolk cohort of the European Prospective Investigation of Cancer. The potential combined impact of 4 health behaviors on the incidence of stroke was followed up over 14 years in men and women aged 40–79 with no known stroke or myocardial infarction, living in the general community. Participants scored one point for each health behavior: current non-smoking, physically not inactive, moderate alcohol intake (1–14units a week), and plasma concentration of vitamin C ≥50 μmol/L, indicating fruit and vegetable intake of at least five servings a day, for a total score ranging from 0 to 4. Four health behaviors combined predict more than a two-fold difference in the incidence of stroke in men and women. There were 599 incident strokes during a 11.5-year follow-up period. After adjustment for age, sex, BMI, systolic blood pressure, cholesterol concentration, history of diabetes and aspirin use, and social class, compared with people with the four health behaviors, the relative risk of stroke in men and women was 1.15 (95% CI 0.89–1.49) for three health behaviors, 1.58 for two, 2.18 for one, and 2.31 for none ($P<0.001$ for trend). The relations were consistent in subgroups stratified by sex, age, BMI and social class, and after exclusion of deaths within two years *(34)*. The preventive role of Mediterranean diet on the occurrence of cardiovascular events and stroke has been well established in randomized clinical trials. Some authors even suggest taking certain foods as treatment for various neurological and psychological disorders such as dementia, headache, depression, neurodegenerative disorders and schizophrenia, as well as for other health problems such as carcinoma. Different nutrients found in different foods have a strong impact on our memory, concentration, thinking processes and emotional state, but the most wanted on the brain-smart grocery list include salmon, virgin olive oil, romaine lettuce, dark chocolate (at least 60% of cocoa), hazelnuts and raspberries. It is scientifically proven that the food we consume greatly affects our body and the health of our brain, thus Mediterranean diet is the best way to feed your neurons *(35)*.

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