# CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

## Prevention of Stroke Evidence Tables

## *Lifestyle & Risk Factor Management*

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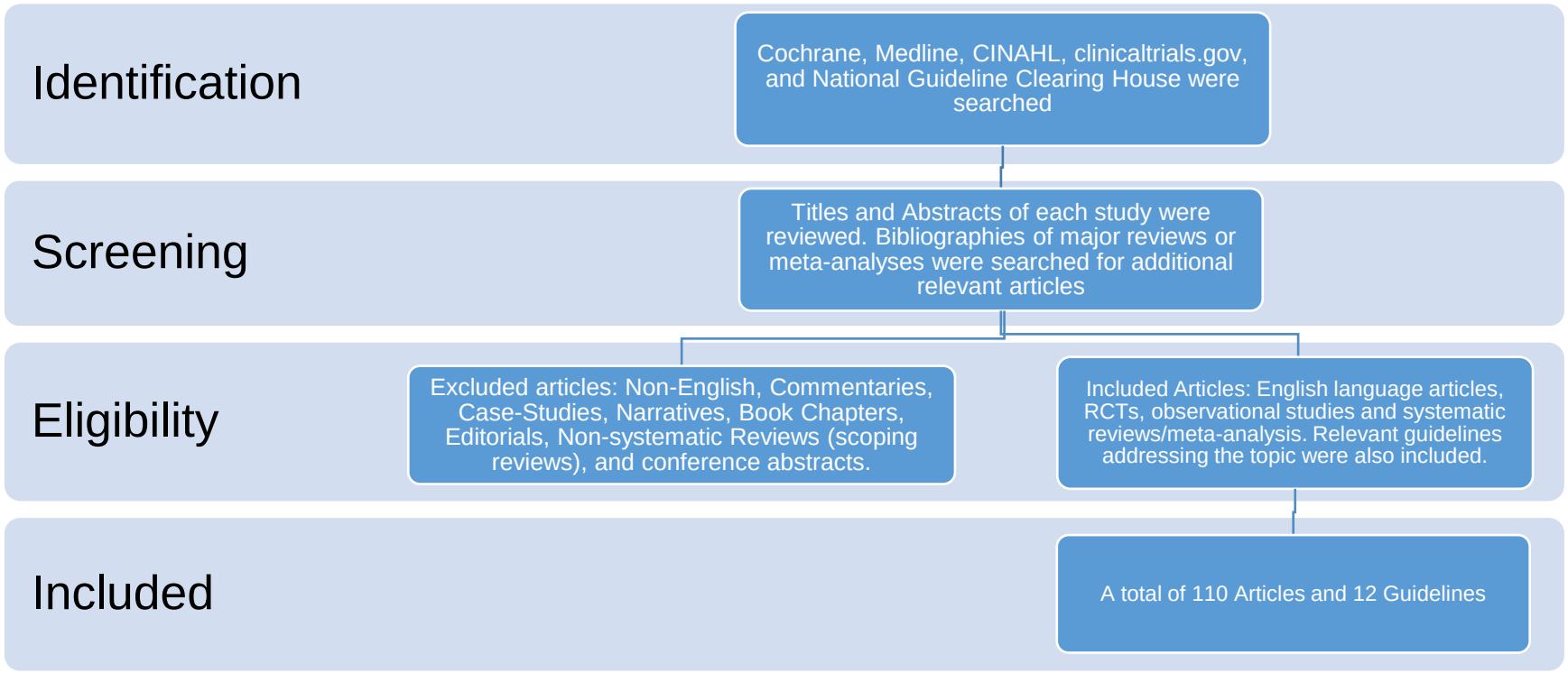
# Search Strategy




Cochrane, Medline, CINAHL, clinicaltrials.gov, and National Guideline Clearing House were search using the terms (“Stroke” and “lifestyle” or “diet” or “alcohol” or “sodium” or “body mass index” or “weight” or “diet” or “waist circumference” or “exercise” or “contraceptive” or “hormone replacement therapy”). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review.

# Published Guidelines

| Guideline | Recommendations |
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| **Heart and Stroke Foundation of Canada Position Statement**<br>**Saturated fat heart disease and stroke**<br>**(selected)** | 1. Eat a healthy balanced diet.<br>• Consume a variety of natural/whole and minimally processed foods at every meal.<br>• Eat more vegetables and fruit. Fill half your plate with vegetables and fruit at every meal. Buy fresh or frozen unsweetened fruit, or fruit canned in water without added/free sugars or artificial/non-caloric sweeteners. Buy fresh or frozen vegetables without added sauce, or canned vegetables with no added salt.<br>• Choose whole grains.<br>• Include a variety of proteins from various sources. These protein sources can include beans, lentils, legumes, nuts, lower fat dairy or dairy alternatives (without added/free sugars or artificial/non-caloric sweeteners), lean meats, poultry and fish.<br>• Eat fewer highly processed foods which include highly refined foods, confectionaries, sugary drinks, processed meats, and snack foods. • Plan healthy snacks. Include foods from at least 2 food groups with 1-2 servings of vegetables or fruit at every snack.<br>• Drink water to satisfy thirst. Avoid consumption of sugary drinks including soft drinks, sports drinks, fruit drinks, 100 per cent fruit juices, and ready-to-drink sweetened coffees and teas.<br>• Learn what a recommended serving size looks like and choose healthy portions for meals and snacks. |
| **Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. for Hypertension Canada, Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults, *Canadian Journal of Cardiology* 2017;33(5):557-576.** | **Primary Prevention (general)**<br><br>A. Physical exercise: For non-hypertensive individuals (to reduce the possibility of becoming hypertensive) or for hypertensive patients (to reduce their BP), prescribe the accumulation of 30-60 minutes of moderate intensity dynamic exercise (e.g., walking, jogging, cycling, or swimming) 4-7 days per week in addition to the routine activities of daily living (Grade D). Higher intensities of exercise are not more effective (Grade D). For non-hypertensive or stage 1 hypertensive individuals, the use of resistance or weight training exercise (such as free weight lifting, fixed weight lifting, or handgrip exercise) does not adversely influence BP (Grade D).<br><br>B. Weight reduction: 1. Height, weight, and waist circumference should be measured and body mass index calculated for all adults (Grade D). 2. Maintenance of a healthy body weight (body mass index 18.5 to 24.9 kg/m2, and waist circumference <102 cm for men and <88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension (Grade C) and for hypertensive patients to reduce BP (Grade B). All overweight hypertensive individuals should be advised to<br>lose weight (Grade B). 3. Weight loss strategies should employ a multidisciplinary approach that includes dietary education, increased physical activity, and behavioral intervention (Grade B).<br><br>C. Alcohol consumption: To prevent hypertension and reduce BP in hypertensive adults, individuals should limit alcohol consumption to ≤ 2 drinks per day, and consumption should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women (Grade B). (Note: One standard drink is considered to be equivalent of 13.6 g or 17.2 mL of ethanol or approximately 44 mL [1.5 oz] of 80 proof [40%] spirits, 355 mL [12 oz] of 5% beer, or 148 mL [5 oz] of 12% wine.<br><br>D. Diet: It is recommended that hypertensive patients and normotensive individuals at increased risk of developing hypertension consume a diet that emphasizes fruits, vegetables, low-fat dairy products, whole grain foods rich in dietary fibre, and protein from plant sources that is reduced in saturated fat and cholesterol (Dietary Approaches to Stop Hypertension [DASH] diet. (Grade B).<br><br>E. Sodium intake: To prevent hypertension and reduce BP in hypertensive adults, consider reducing sodium intake |

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| | towards 2000 mg (5 g of salt or 87 mmol of sodium) per day (Grade A).<br><br>F. Calcium and magnesium intake: Supplementation of calcium and magnesium is not recommended for the prevention or treatment of hypertension (Grade B).<br><br>G. Potassium intake: In patients not at risk of hyperkalemia, increase dietary potassium intake to reduce BP (Grade A).<br><br>H. Stress management: In hypertensive patients in whom stress may be contributing to high BP, stress management should be considered as an intervention (Grade D). Individualized cognitive-behavioural interventions are more likely to be effective when relaxation techniques are used (Grade B). |
| **Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland** | **Diet**<br>A- People with stroke or TIA should be advised to eat an optimum diet that includes:<br>− five or more portions of fruit and vegetables per day from a variety of sources;<br>− two portions of oily fish per week (salmon, trout, herring, pilchards, sardines, fresh tuna).<br>B- People with stroke or TIA should be advised to reduce and replace saturated fats in their diet with polyunsaturated or monounsaturated fats by:<br>− using low-fat dairy products;<br>− replacing butter, ghee and lard with products based on vegetable and plant oils;<br>− limiting red meat intake, especially fatty cuts and processed meat.<br>C- People with stroke or TIA who are overweight or obese should be offered advice and support to aid weight loss including adopting a healthy diet, limiting alcohol intake to 2 units a day or less and taking regular exercise. Targeting weight reduction in isolation is not recommended.<br><br>D- People with stroke or TIA should be advised to reduce their salt intake by:<br>− not adding salt to food at the table;<br>− using little or no salt in cooking;<br>− avoiding high-salt foods, e.g. processed meat such as ham and salami, cheese, stock cubes, pre-prepared soups and savoury snacks such as crisps and salted nuts.<br><br>E- People with stroke or TIA who drink alcohol should be advised to limit their intake to 14 units a week, spread over at least three days.<br><br>F- Unless advised to do so for other medical conditions, people with stroke or TIA should not routinely supplement their diet with:<br>− B vitamins or folate;<br>− vitamins A, C, E or selenium;<br>− calcium with or without vitamin D.<br><br>**Physical activity**<br>A- People with stroke or TIA should participate in physical activity for fitness unless there are contraindications. Exercise |

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| | prescription should be individualised, and reflect treatment goals and activity recommendations.<br><br>B- People with stroke or TIA should aim to be active every day and minimise the amount of time spent sitting for long periods.<br><br>C- People with stroke or TIA should aim to achieve 150 minutes or more of moderate intensity physical activity per week in bouts of 10 minutes or more (e.g. 30 minutes on at least 5 days per week). They should also engage in muscle strengthening activities at least twice per week.<br><br>D- People with stroke or TIA who are at risk of falls should engage in additional physical activity which incorporates balance and co-ordination at least twice per week.<br><br>E- Physical activity programmes for people with stroke or TIA may be delivered by therapists, fitness instructors or other appropriately trained people, supported by interagency working where possible; regular monitoring and progression should occur to promote physical fitness.<br><br>F- Physical activity programmes for people with stroke or TIA should be tailored to the individual after appropriate assessment, starting with low-intensity physical activity and gradually increasing to moderate levels.<br><br>**Oral contraception**<br>Pre-menopausal women with stroke and TIA should not be offered the combined oral contraceptive pill. Alternative hormonal (progestogen-only) and non-hormonal contraceptive methods should be considered instead.<br><br>**Hormone replacement therapy**<br>A-Post-menopausal women with ischaemic stroke or TIA who wish to start or continue hormone replacement therapy should receive advice based on the overall balance of risk and benefit, taking account of the woman's preferences.<br><br>B-Post-menopausal women with ischaemic stroke or TIA should not be offered hormone replacement therapy for secondary vascular prevention.<br><br>**Smoking**<br>People with stroke or TIA who smoke should be advised to stop immediately. Smoking cessation should be promoted in an individualised prevention plan using interventions which may include pharmacotherapy, psychosocial support and referral to NHS Stop Smoking Services. |
| **Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA** | **Diet**<br>• It is reasonable to conduct a nutritional assessment for patients with a history of ischemic stroke or TIA, looking for signs of overnutrition or undernutrition (Class IIa; Level of Evidence C). New recommendation<br>• Patients with a history of ischemic stroke or TIA and signs of undernutrition should be referred for individualized nutritional counseling (Class I; Level of Evidence B). New recommendation |

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| **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.**<br><br>***Stroke 2014*;45:2160-2236.** | • Routine supplementation with a single vitamin or combination of vitamins is not recommended (Class III; Level of Evidence A). New recommendation<br>• It is reasonable to recommend that patients with a history of stroke or TIA reduce their sodium intake to less than ≈2.4 g/d. Further reduction to <1.5 g/d is also reasonable and is associated with even greater BP reduction (Class IIa; Level of Evidence C). New recommendation<br>• It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats (Class IIa; Level of Evidence C).<br>**Cigarette smoking**<br>• Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit (Class I; Level of Evidence C).<br>• It is reasonable to avoid environmental (passive) tobacco smoke (Class IIa; Level of Evidence B).<br>• Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers to quit (Class I; Level of Evidence A).<br>**Alcohol consumption**<br>• Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol (Class I; Level of Evidence C).<br>• Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking (Class IIb; Level of Evidence B).<br>**Physical activity**<br>• For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, 1 to 3 times a week (eg, walking briskly, using an exercise bicycle) may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrent stroke (Class IIb; Level of Evidence C).<br>• For those individuals with a disability following ischemic stroke, supervision by a healthcare professional, such as a physical therapist or cardiac rehabilitation professional, at least on initiation of an exercise regimen, may be considered (Class IIb; Level of Evidence C).<br>• For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviorally oriented program is probably recommended (Class IIa; Level of Evidence C). New Recommendation.<br>**Overweight/obesity**<br>• All patients with TIA or stroke should be screened for obesity with measurement of BMI (Class I; Level of Evidence C). New recommendation<br>Given the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain (Class IIb; Level of Evidence C).<br>Homocysteinemia<br>Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated (Class III; Level of Evidence C). New recommendation<br>In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, |

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| | supplementation with folate, vitamin B6, and vitamin B12 safely reduces levels of homocysteine but has not been shown to prevent stroke (Class III; Level of Evidence B).<br><br>**Smoking**<br>1. Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit (Class I; Level of Evidence C).<br><br>2. It is reasonable to advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke (Class IIa; Level of Evidence B).<br><br>3. Counseling, nicotine products, and oral smoking cessation medications are effective in helping smokers to quit (Class I; Level of Evidence A). |
| **Eckel RH, Jakicic JM, Ard JD et al.**<br><br>**2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.**<br><br>***J Am Coll Cardiol* 2014;63(25 Pt B):2960-2984.** | **Diet**<br>Advise adults who would benefit from LDL–C lowering to:<br>Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red **meats (Level A recommendation),** a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus)**,** b. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.<br><br>Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat (Level A recommendation).<br><br>Reduce percent of calories from saturated fat (Level A recommendation).<br><br>Reduce percent of calories from *trans* fa*t (Level A recommendation)*<br><br>Advise adults who would benefit from BP lowering to:<br>Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red **meats (Level A recommendation),** a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical condition**s (including diabetes mellitus), b** Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or AHA diet.<br><br>Reduce sodium intake (Level A recommendation)<br>a. Consume no more than 2,400 mg of sodium/day<br>b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with even greater reduction in BP<br>c. Reduce intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not yet achieved<br>Combine the DASH dietary pattern with lower sodium intake. |

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| | **Physical Activity**<br>Lipids<br>In general, advise adults to engage in aerobic physical activity to reduce LDL–C and non-HDL–C: 3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity (Level B recommendation).<br><br>Blood pressure<br>In general, advise adults to engage in aerobic physical activity to lower BP: 3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate to-vigorous intensity physical activity (Level B recommendation). |
| **Billinger SA, Arena R, Bernhardt J et al.**<br><br>**Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association.**<br><br>***Stroke* 2014;45(8):2532-2553.** | The recommendation is that physical activity and exercise prescription should be incorporated into the management of stroke survivors. The promotion of physical activity in stroke survivors should emphasize low- to moderate-intensity aerobic activity, muscle-strengthening activity, reduction of sedentary behavior, and risk management for secondary prevention of stroke. |
| **Institute for Clinical Systems Improvement (ICSI). Healthy lifestyles. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 May. 68 p.** | •Four lifestyle behaviors—adequate physical activity, a diet that emphasizes fruits and vegetables, abstinence from tobacco and avoidance of tobacco smoke, and avoidance of hazardous and harmful drinking—are associated with a decade or more of increased life expectancy. Individuals who adopt this lifestyle, at any age, have significantly lower total mortality rates. A fifth factor, practice positive thinking, has been shown to increase reports of happiness and decrease symptoms of depression. (Annotation #6a-e; Aim #2)<br>•Medical groups cannot be given the sole responsibility for supporting healthy lifestyle. There is a growing recognition and understanding of the role that community networks, physical and social environments, and public policy all play in fostering healthy lifestyles. (Annotation #1; Aim #3)<br>•A broad approach is necessary to achieve and support healthy lifestyles in individuals. It requires individual commitment, health care system redesign, as well as community, employer and payer support. (Annotation #2; Aim #3)<br>•Health assessments are most effective when combined with feedback and access to interventions that support healthy lifestyles. (Annotation #3; Aim #1)<br>•Collaborative decision-making and brief, combined interventions are effective in helping motivate and engage patients in maintaining or adopting healthy lifestyles. (Annotation #5) |
| **Secondary prevention. In: Clinical guidelines for stroke management 2010. Melbourne (Australia): National Stroke Foundation; 2010** | Every stroke patient should be assessed and informed of their risk factors for a further stroke and possible strategies to modify identified risk factors. The risk factors and interventions include:<br><br>•Stopping smoking: nicotine replacement therapy, bupropion or nortriptyline therapy, nicotine receptor partial agonist |

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| **Sep. p. 68-76.** | therapy and/or behavioural therapy (Grade A [Hughes, Stead, & Lancaster, 2007; Cahill, Stead, & Lancaster, 2007; Stead & Lancaster, 2005; Sinclair, Bond, & Stead, 2004; Rice & Stead, 2004; Lancaster & Stead, 2005])<br>•Improving diet: a diet low in fat (especially saturated fat) and sodium but high in fruit and vegetables (Grade A [He & MacGregor, 2004; He, Nowson, & MacGregor, 2006; Dauchet, Amouyel, & Dallongeville, 2005; Sacks et al., 2001; Appel et al., 1997; Barzi et al., 2003; de Lorgeril et al., 1999])<br>•Increasing regular exercise (Grade C [Lee, Folsom, & Blair, 2003; Wendel-Vos et al., 2004])<br>•Avoiding excessive alcohol (i.e., no more than two standard drinks per day). (Grade C [Reynolds et al., 2003; National Health and Medical Research Council, 2009])<br>Interventions should be individualised and delivered using behavioural techniques such as educational or motivational counselling. (Grade A [Stead & Lancaster, 2005; Sinclair, Bond, & Stead, 2004; Lancaster & Stead, 2005; Rubak et al., 2005]) |
| **Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN 108); 2008. 103 p.** | **Diet**<br>• Diets low in total and saturated fats should be recommended to all for the reduction of cardiovascular risk. (Grade A)<br>• People with hypertension should be advised to reduce their salt intake as much as possible to lower blood pressure. (Grade A)<br>• Increasing fruit and vegetable consumption is recommended to reduce risk of stroke or TIA (Grade C)<br>• Vitamin supplementation is not recommended in patients following ischemic stroke. (Grade B)<br>**Weight Management**<br>• Patients and individuals at risk of cardiovascular disease, who are overweight, should be targeted with interventions designed to reduce weight, and to maintain this reduction. (Grade B)<br>**Smoking**<br>• All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks. (Grade B)<br>**Exercise**<br>• Lifelong participation in programmes of exercise after stroke should be encouraged. (Grade B) |
| **Stroke Foundation of New Zealand. New Zealand Clinical Guidelines for Stroke Management 2010** | Risk factors and interventions<br>Every person with stroke should be assessed and informed of their risk factors for a further stroke and possible strategies to modify identified risk factors. The risk factors and interventions include:<br>• Smoking cessation: nicotine replacement therapy, bupropion or nortriptyline therapy, nicotine receptor partial agonist therapy and/or behavioural therapy should be considered (Silagy et al, 2004; Hughes et al, 2007; Cahill et al, 2007, Stead & Lancaster, 2005; Sinclair et al, 2004; Rice & Stead, 2004; Lancaster & Stead, 2005; Stead et al, 2006) (Grade A)<br>• Improving diet: a diet that is low in fat (especially saturated fat) and sodium, but high in fruit and vegetables should be consumed (He et al, 2006; Dauchet et al, 2005; He & MacGregor, 2004; Hooper et al, 2004; Sacks et al, 2001; Appel et al, 1997; Barzi et al, 2003; de Lorgeril et al, 1999) (Grade A)<br>• Increasing regular exercise (Lee et al, 2003; Wendel-Vos et al, 2004) (Grade B)<br>• Avoidance of excessive alcohol (ie, no more than two standard drinks per day) (Reynolds et al, 2003; NHMRC, 2003; NHMRC, 2009). (Grade C)<br>Interventions should be individualised and delivered using behavioural techniques (such as educational or motivational |

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| | counselling) (Rubak et al, 2005; Lancaster & Stead, 2005; Stead & Lancaster, 2005; Stead et al, 2006; Sinclair et al, 2004). (Grade A)<br><br>Medication Adherence<br>Effective interventions to promote adherence with medication regimes are often complex and should include combinations of the following:<br>• Reminders, self-monitoring, reinforcement, counseling, family therapy, telephone follow-up, supportive care, or dose administration aids (Grade B)<br>Information and education while in hospital and/or in the community (Grade B) |
| **Irish Heart Foundation: Council for Stroke. National Clinical Guidelines and Recommendations for the Care of People with Stroke and transient Ischemic Attack. March 2010** | Persons at risk of stroke and those who have had a stroke should be assessed for and given information on risk factors, lifestyle management issues (exercise, smoking, diet, weight, alcohol, stress management) and should be counselled on possible strategies to modify their lifestyle and risk factors.<br><br>Risk Factors<br>Particular targeting of advice should be directed at those with pre-existing dietary risk factors including:<br>• Diabetes<br>• Hypertension<br>• Hyperlipidaemias<br>• Overweight and obesity.<br>**Diet**<br>• Dietary recommendations for primary prevention are as per the secondary prevention recommendations.<br>• In addition, oily fish 1-2 portions per week are recommended.<br>• Lifestyle management should include a healthy diet low in salt and saturated fat, high in fruit and vegetables and rich in fibre.<br>• Increasing fruit and vegetable consumption is recommended to reduce risk of stroke or TIA and we recommend consumption of a minimum of 5 portions of fruit & vegetables per day.<br>• Folic acid supplementation may help reduce homocysteine levels but have not been shown to influence risk of stroke.<br>• There is currently insufficient evidence to recommend vitamin therapy to prevent recurrent stroke.<br>**Smoking cessation**<br>• Tobacco smokers should be given specific advice and support to stop smoking. They should be given the opportunity to attend specialist stop smoking services if they wish to do so.<br><br>Interventions should be individualised and may be delivered using behavioural techniques (such as education or motivational counselling).<br>**Self-management and Support**<br>• Patients should be encouraged to take responsibility for their own health and be supported to identify, prioritise and manage their risk factors.<br>• People with stroke who do not have cognitive impairment should be made aware of the availability of generic |

| Guideline | Recommendations |
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| | self-management programmes before discharge from hospital and be supported to access such programmes once they have returned to the community.<br>• Stroke-specific programmes for self-management may be provided to people who require more specialised programs.<br>• A collaboratively developed self-management care plan may be used to harness and optimise self-management skills.<br>• Interventions should be individualised and may be delivered using behavioural techniques via a group or on a one-to-one basis.<br>• Motivational interviewing and counselling based on the individual situation of the patient and his or her readiness to adopt behaviour changes increases likelihood of these changes taking place and shared decision making can facilitate the maintenance of measures agreed upon.<br>• It is recommended that motivating and supporting people to change behaviour should be achieved through:<br>○ Helping them understand the short, medium and longer term consequences of their health-related behaviours for themselves and others<br>○ Feel positive about the benefits of health-enhancing behaviours and changing their behaviour<br>○ Plan their changes in terms of small, manageable steps over time<br>○ Recognise how their social contexts and relationships may affect their behaviour, and identify and plan for situations that might undermine the changes they are trying to make<br>○ Plan explicit 'if–then' coping strategies to prevent relapse<br>○ Make a personal commitment to adopt health-enhancing behaviours by setting (and recording) goals to undertake clearly defined behaviours, in particular contexts, over a specified time<br>○ Share their behaviour change goals with others.<br>**Activities of Daily Living and Exercise**<br>• People who are living in the community more than 6 months after their stroke should have access to interventions to improve fitness and mobility.<br>• All patients should be advised to take regular exercise as far as they are able: the aim should be to achieve moderate physical activity (sufficient to become slightly breathless) for 20-30 minutes each day.<br>• Exercise programmes should be tailored to the individual following appropriate assessment, starting with low intensity physical activity and gradually increasing to moderate levels.<br>• The combination of comorbidities, neurological deficits, and emotional barriers unique to each stroke survivor requires an individual approach to safe exercise programming.<br>• Subsets of stroke survivors (e.g. those with depression, fatigue syndrome, poor family support, or communication, cognitive or motor deficits) will require further evaluation and subsequent specialisation of their rehabilitation programme.<br>• To enhance exercise compliance, the issues of family support and social isolation need to be addressed and resolved.<br>• Physical activity and exercise training recommendations for stroke survivors should be viewed as one important component of a comprehensive stroke and cardiovascular risk reduction programme. |

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| **The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee**<br><br>**Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008**<br><br>***Cerebrovasc Dis 2008*;25:457–507** | **Smoking**<br>• It is recommended that cigarette smoking be discouraged (Class III, Level B)<br>**Alcohol**<br>• It is recommended that heavy use of alcohol be discouraged (Class III, Level B)<br>Physical Activity<br>• Regular physical activity is recommended (Class III, Level B)<br>**Diet**<br>• A diet low in salt and saturated fat, high in fruit and vegetables and rich in fibre is recommended (Class III, Level B)<br>Weight Management<br>• Subjects with an elevated body mass index are recommended to take a weight-reducing diet (Class III, Level B)<br>**Vitamin and Supplements**<br>• Antioxidant vitamin supplements are not recommended (Class I, Level A) |

# Evidence Tables

## Diet & Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| ***i) Studies primarily evaluating fruit and vegetable consumption*** | | | | | |
| **Du et al. 2016**<br>**China Kadoorie Biobank Study**<br><br>**China**<br><br>**Prospective study** | NA | 512,891 non-disabled adults, aged 35-74 years, who were recruited from the general population, from 10 regional study sites between 2004-08.<br><br>Persons with a history of CVD or antihypertensive treatment were excluded.<br><br>Mean age at admission was 50.5 years, 58.8% were women. Mean BMI was 23.5 | Baseline surveys were conducted to collect information on diet and lifestyle factors. A physical exam was also conducted to obtain data on blood pressure, random blood sugar, height and weight. A food frequency questionnaire was used to collect information on 12 major food groups, including the average daily number of servings of fruit consumed over the past 12 months. Response categories were daily, 4-6/week, 1-3/week, monthly and never/rarely. A portion of the participants were resurveyed in 2008 and 2013. | **Primary outcomes:**<br>Cardiovascular death, major coronary events ++nonfatal MI, hemorrhagic and ischemic stroke<br><br>Analysis was adjusted for education, ETOH consumption, smoking, physical activity, survey season, and consumption of other dietary components, and were stratified by age, sex and region. | During 3.2 million person-years of follow-up, there were 14,579 ischemic strokes and 3,523 hemorrhagic strokes<br><br>The incidence rates of ischemic and hemorrhagic stroke (no./1,000 person-years) among the fruit consumption categories were:<br>Never/rarely: 7.58/2.05<br>Monthly: 4.75/1.48<br>1-3 days/week: 3.88/1.00<br>4-6 days/week: 3.42/0.74<br>Daily: 5.17/0.47<br><br>Compared with rarely/never category, the consumption of any level of fruit consumption was associated with a significantly reduced risk of ischemic stroke. The reduction was dose-dependent, with daily consumption associated with the lowest risk (HR=0.75 vs. 0.79, 0.73 and 0.90 in descending order for the remaining categories.<br><br>Compared with rarely/never category, the consumption of any level of fruit consumption was associated with a significantly reduced risk of hemorrhagic stroke. The greatest reduction in risk was associated with the daily consumption category (HR=0.64). In descending order, the HRs associated with the remaining 3 consumption categories were 0.76, 0.81 and 0.86, respectively. |
| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of | Stroke burden (expressed as DALYs) | **Fruits**<br>Globally, 35.6% (95% uncertainty interval 26.5%-42.0%) of the stroke burden was attributed to diets low in fruit.<br><br>In high income countries, 24.3% (95% uncertainty |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including diets low in fruits and vegetables) in high-income countries and low-income and middle-income countries. Diets low in fruits were defined as consumption of <200 g/day. Diets low in vegetables were defined as consumption of <350 g/day. | | interval 16.0%-29.7%) of the stroke burden was attributed to diets low in fruits.<br><br>**In Canada, 20.4% (95% uncertainty interval 9.7%-31.5%) of the stroke burden was attributed to diets low in fruits**<br><br>Globally, during the study period, there was an increase of 22.9% (95% UI 18.8%-24.3%) in the burden of stroke related to diets low in fruits.<br><br>**Vegetables:**<br>Globally, 20.0% (95% uncertainty interval 17.0%-22.4%) of the stroke burden was attributed to diets low in vegetables.<br><br>In high income countries, 20.9% (95% uncertainty interval 18%-22.5%) of the stroke burden was attributed to diets low in vegetables.<br><br>**In Canada, 19.5% (95% uncertainty interval 14.4%-25.5%) of the stroke burden was attributed to diets low in vegetables**<br><br>Globally, during the study period, there was an increase of 23% (95% UI 22.7%, 23.3%) in the burden of stroke related to diets low in vegetables. |
| **Hu et al. 2014**<br><br>**China**<br><br>**Systematic review & meta-analysis** | NA | 20 prospective cohort studies including 760,629 participants. | The risk of stroke among the lowest vs. highest categories of fruit and vegetable intake in each study were pooled.<br><br>Food frequency questionnaires were used to estimate fruit/veg intake in all studies, except 3.<br><br>Most included studies adjusted for age, smoking, blood pressure, physical activity and BMI | Stroke | The mean duration of follow-up ranged from 4-37 years, during which time there were 16,981 stroke events.<br><br>The risk of stroke was significantly lower in the groups associated with the highest intake of fruits and vegetables<br>Total combined fruit and veg: RR=0.79, 95% CI 0.75-0.84<br>Fruit: RR=0.77, 95% CI 0.71-0.84<br>Vegetables: RR=0.86, 95% CI 0.79-0.93<br><br>For every increase of 200 g/day of vegetables, stroke risk was decreased by 11% (RR=0.89, 95% CI 0.81-0.98). |

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| | | | | | For every increase of 200 g/day of fruit, stroke risk was decreased by 32% (RR=0.68, 95% CI 0.56-0.82). |
| **Sharma et al. 2013**<br><br>**Canada**<br><br>**Prospective cohort study** | NA | 174,888 participants without a history of stroke (78,844 men, 96,044 women) aged 45 to 75 years across 5 ethnic groups<br><br>The average ages of women and men at study entry were 66 and 59 years, respectively.<br><br>10% of participants had a history of diabetes, 37% had a history of hypertension, 39% were current smokers and 19% had a BMI >30 | A one-time quantitative food frequency questionnaire was used to estimate daily number of servings of fruit and vegetable consumed.<br><br>An individual's daily consumption was then compared with the USDA's food pyramid. Based on caloric intake, the recommendations for vegetables range from 3-5 servings/day and 2-4 servings/day for fruit.<br><br>Compliance was categorized as adherent vs. non-adherent (<100% vs. ≥100%) of the daily servings of fruits and vegetables of the recommended number of servings based of age and caloric intake level. | Fatal stroke<br><br>Analyses were adjusted for: age, time in study, education, energy intake, smoking status, other dietary components, BMI, physical activity, alcohol intake, history of diabetes | At the end of follow-up (8 years), there were 860 fatal stroke,<br><br>The average number of daily vegetable servings for all men and those who died of stroke were 4.5±2.8 and 4.3±2.7. The average number of daily fruit servings for all men and those who died of stroke were 3.0±2.6 and 3.2±2.5<br><br>The average number of daily vegetable servings for all women and those who died of stroke were 4.6±2.9 and 4.2±2.6. The average number of daily fruit servings for all women and those who died of stroke were 3.5±2.9 and 3.4±2.6<br><br>The risk of stroke mortality was not associated with adherence to USDA dietary recommendations for fruits or vegetables<br><br>**Men (434 fatal strokes)**<br>Vegetables: adjusted RR (adherent vs. non-adherent) =0.99, 95% CI 0.81-1.22<br>Fruit: adjusted RR=1.13, 95% CI 0.92-1.37<br><br>**Women (426 fatal strokes)**<br>Vegetables: adjusted RR=0.84, 95% CI 0.68-1.04<br>Fruit: adjusted RR=0.97, 95% CI 0.75-1.19 |
| **He et al. 2006**<br><br>**UK**<br><br>**Systematic review & meta-analysis** | NA | 8 cohort studies including 257,551 participants.<br><br>Data from the Nurses' Health Study, the Health Professionals' Follow-up Study, NHANES I, Danish Diet, Cancer and Health Study, Life Span Study and ARIC studies, were included. | Fruit and vegetable consumption was standardized among studies and comprised 3 categories of daily intake: <3 servings, 3-5 servings and >5 servings, based on a serving size of 77 grams of vegetables and 80 g of fruit. | Risk of stroke<br><br>Most of the included studies, adjusted risk estimates for: age, sex, smoking, alcohol intake, education, BMI, physical activity, total energy intake, blood pressure, history of diabetes, cholesterol, consumption of fats and animal products | Over an average of 13 years of follow-up, there were 4,917 stroke events.<br><br>Increasing servings of fruits and vegetables/day was associated with a significantly decreased risk of stroke (compared with <3 servings)<br>3-5 servings/day: adjusted RR=0.89, 95% CI 0.83-0.97<br>>5 servings/day: adjusted RR=0.74, 95% CI 0.69-0.79.<br><br>In sub group analysis, the protective effect remained significant regardless of sex (male vs. |

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| | | | | | female), duration of follow-up (<10 vs. ≥10 years), and dietary assessment method (food frequency questionnaire vs. other method).<br><br>The protective effect was significant for ischemic stroke at both intake levels, but was only significant for the highest intake of fruit/veg for hemorrhagic stroke.<br>The protective effect was significant for fruit consumption at both intake levels, but was only significant for the highest intake for vegetable consumption. |
| ***ii) Studies evaluating fat consumption*** | | | | | |
| **Kiage et al. 2014**<br><br>**USA**<br><br>**Prospective cohort study** | NA | 17,107 participants, ≥45 years, without a previous history of stroke included in the REGARDS study.<br><br>Mean age was 65 years | Consumption of trans fat intake was assessed using the self-administered Block 1998 food-frequency questionnaire at baseline and categorized into quintiles.<br><br>The relationship between incident stroke and trans-fat consumption was examined. | Incident stroke, ischemic stroke<br><br>Models were adjusted for age, sex, smoking status, race, region, alcohol use, education, waist circumference, physical activity, diabetes, ischemic heart disease, hypertension, heart failure, kidney failure, medications, total energy intake, and intakes of saturated fat, monounsaturated fat, polyunsaturated fat, and protein | Median duration of follow-up was 6.8 years, during which time there were 479 incident strokes.<br><br>In the fully adjusted model, the overall risks of stroke and ischemic stroke were not significantly increased (HR=1.07, 95% CI 0.97-1.18 and HR=1.06, 95% CI 1.18).<br><br>There was a significant sex interaction (p=0.06), therefore results for men and women were reported separately.<br><br>Men: All stroke HR=1.14, 95% CI 1.02-1.28; ischemic stroke HR=1.13, 95% CI 1.00-1.28<br><br>Women: All stroke HR=0.93, 95% CI 0.79-1.11; ischemic stroke HR=0.93, 95% CI 0.77-1.12 |
| **De Oliveira Otto et al. 2012**<br><br>**USA**<br><br>**Prospective cohort study *Multi-Ethnic Study of Atherosclerosis (MESA)*** | NA | 5,209 persons aged 45-84 years, without clinical CVD, recruited from 6 US communities. Mean age was approx. 62 years | Baseline 120-item FFQs were conducted and used to estimate saturated fat levels from various foods (dairy, meat, butter, and plants). The relationship between saturated fat (SF) and the development of CVD was examined. | Cardiovascular disease<br><br>The model was adjusted for age, sex, race-ethnicity, energy intake, location (field centre), education, active and sedentary leisure activities, alcohol intake, smoking dietary supplements, cholesterol-lowering medications, fruit/vegetable | There were 316 new cases of CVD identified during 10-year follow-up (36,364 person-years).<br><br>For each 5 g/d increase in SF, the risk of CVD was significantly higher or lower depending on the food source<br>Total SF: HR=0.86, 95% CI 0.75-0.97, p=0.02<br>Dairy SF: HR=0.79, 95% CI 0.68-0.92, p<0.01<br>Meat SF: 1.26, 95% CI 1.02-1.54, p=0.03<br>Butter SF: 0.87, 95% CI 0.66-1.15, p=0.33<br>Plant SF: HR=1.00, 95% CI 0.50-2.01, p=0.99<br>Mixed sources: HR=1.01, 95% CI 0.77-1.32, |

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| | | | | intake, vit D and PUFA | p=0.96<br><br>The pattern of risk was similar for each 5% increment of SF as a percentage of total energy intake.<br><br>The substitution of 2% of energy from meat with energy from dairy products was associated with a significantly decreased risk of CVD (HR=0.75, 95% CI 0.63-0.91), while substitutions of butter and plant sources of SF were not.<br><br>Across quintiles, there was an inverse association between dairy SF and CVD (Q5 vs. Q1; HR=0.56, 95% CI 0.38-0.82, p=0.01). There were no significant associations between any of the other sources of SF and CVD. |
| **Siri-Tarino et al. 2010**<br><br>**US**<br><br>**Systematic review & meta-analysis** | NA | 21 prospective cohort studies, including the results from 347,747 subjects. Stroke was the outcome in 8 of the included studies (n=179,436).<br><br>In the stroke studies, participants ranged from 35-45 to 59-89 years at baseline. Studies included men only (n=4), women only (n=1) and both sexes (n=3) | Dietary fat intake was assessed using a food frequency questionnaire (n=4), 24-hour recall (n=3) and 1-day diet record (n=1). Diet was assessed only at baseline in 6 studies and 3 and 4 times at 2-4 year intervals in 2 studies. | Stroke events: total stroke (n=2), ischemic stroke (n=3), hemorrhagic stroke (n=2), fatal stroke (n=1)<br><br>Variables adjusted for included: age, sex (where applicable), energy intake, other dietary components, smoking status, alcohol intake, BMI, physical activity, hypertension or blood pressure, menopausal status (where applicable), other stroke risk factors, family history of stroke | The average duration of follow-up ranged from 8-23 years.<br><br>There were 2,362 total stroke events.<br><br>Fat intake: in studies that compared 1$^{st}$ and 5$^{th}$ quintile, (n=2) mean fat intakes were 20g vs.36g/day and 17g vs. 31 g/day. In studies that compared 1$^{st}$ and 4$^{th}$ quartile, (n=1) mean fat intake was 5.2g vs.17.1g/day. Fat comprised an average of 12.7% and 15% of total calories. Fat intakes for men and women were calculated separately in one study. Mean fat intake was 12.3% of total calories for men (1$^{st}$ quartile) compared with 22.3% in the 4$^{th}$ quartile. Results for women were similar. Fat intake was not reported in 2 studies.<br><br>There was a significant reduction in the risk of hemorrhagic stroke in 2 studies, but there was a non-significant reduction for all other stroke events.<br><br>Adjusted RR=0.81, 95% CI 0.62-1.05, p=0.11 |
| **Micha et al. 2010**<br><br>**USA** | NA | 20 studies (17 prospective cohort and 3 case-control) including 1,218,380 subjects who | Examination of red and processed meats.<br><br>Most studies used | Coronary heart disease (CHD), diabetes, stroke<br><br>Most studies adjusted for | Follow-up periods ranged from 3-18 years (4,381 to 856,539 person years). There were 2,280 stroke events |

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| **Systematic review & meta-analysis** | | ranged in age from 15-55 years to 46-103 years at baseline. | validated food-frequency questionnaires. | sociodemographic and disease risk factors | Mean (±sd) daily intakes (servings) from lowest to highest category of intake were:<br>Red meat: 1.1±1.1 vs. 8.3±2.7<br>Processed meat: 0.4±0.8 vs. 5.7±3.9<br>Total: 1.8±1.7 vs. 10.5±4.2<br><br>The risk of stroke was evaluated as an outcome in 3 studies. There was no association between meat consumption and incident stroke.<br>Red meat (100 g/day): RR=1.17, 95% CI 0.40 to 3.43 Results from 2 studies included.<br>Processed meat (50 g/day): RR=1.14, 95% CI 0.94-1.39. Results from 2 studies included.<br>Total meat (100 g/day); RR=1.24, 95% CI 1.08-1.43. Results from 2 studies included. |
| **He et al. 2003**<br><br>**USA**<br><br>**Prospective cohort study** | NA | 43,732 men aged 40-75 years included in the Health Professionals' follow-up study who were free of cardiovascular disease and diabetes at baseline | Dietary intake was assessed on 3 occasions using a semi quantitative food frequency questionnaire. There were 9 response categories ranging from <1/month to ≥6x/day.<br><br>All dietary fat sources were collected. | Fatal and non-fatal stroke<br><br>Analysis were adjusted for: i) age and smoking and ii) multivariable (BMI, physical activity, history of hypertension, smoking status, aspirin use, alcohol intake, dietary intake and hypercholesterolemia) | During the 14-year follow-up period, there were 725 stroke events (ischemic n=455, hemorrhagic n=125, unknown etiology n=145).<br><br>There were no associations between amount of total fat, source of fat (animal or vegetable), type of fat (saturated, unsaturated, monounsaturated, polyunsaturated, trans fat or cholesterol) or selected foods (red meat, high-fat dairy products, nuts or eggs) and incidence of ischemic or hemorrhagic stroke.<br><br>For example, comparing lowest to highest quintile of fat intake in fully adjusted analyses:<br><br>Total fat: RR (ischemic stroke) =0.91, 95% CI 0.65-1.28, p for trend=0.77. |
| ***iii) Studies evaluating dairy consumption*** | | | | | |
| **Qin et al. 2015**<br><br>**China**<br><br>**Systematic review & meta-analysis** | NA | 22 prospective studies with cohort sizes ranging from 1,529 to 223,170 including participants ≥18 years.<br><br>Studies included both sexes (n=15), only men (n=3) and women only | The association between risk of cardiovascular diseases and dairy consumption (with sub group analyses for high fat, low fat yogurt, cheese and butter) was explored, by comparing the highest dairy consumer groups | Cardiovascular diseases (total), stroke, coronary heart disease | Duration of follow-up varied from 8-26 years<br><br>Consumption of dairy products was associated with a significant reduction in the risk of total CVD (RR=0.88, 95% CI 0.81-0.96. Data from 9 studies), and stroke (RR=0.87, 95% CI 0.77-0.99. Data from 12 studies), but not CHD (RR=0.94, 95% CI 0.82-1.07. Data from 12 studies). |

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| | | (n=4) | with the lowest (tertiles, quintiles).<br><br>Dietary exposure was assessed using validated food frequency questionnaires (n=20 studies), a non-validated FFQ (n=1) and a 3day diet record (n=1) and most studies adjusted for potential confounders (age, gender, BMI, smoking, alcohol consumption, physical activity, energy and certain food intakes, and diseases related to CVD | | In sub group analysis of dairy types, only low-fat dairy significantly reduced the risk of stroke (RR=0.91, 95% CI 0.88-0.99). |
| **Hu et al. 2014**<br><br>**China**<br><br>**Systematic review & meta-analysis** | NA | 15 prospective population-based studies (n=764,635) including men and women aged ≥30 years. | The association between risk of stroke and dairy consumption (total dairy, milk, and cheese, butter and cream) was explored, using a restricted cubic spline model with 3 knots (25 $^{th}$, 50$^{th}$ and 75$^{th}$ percentiles). Dairy intake was estimated using a weighted 3-day diet record (n=1), a 7-day household inventory method (n=1) and self-administered food frequency questionnaires (n=13). | Risk of stroke, stroke mortality<br><br>Most studies adjusted for known stroke risk factors, BMI, energy and alcohol intake. | Mean duration of follow-up was >10 years.<br><br>There was a total of 28,138 stroke events.<br><br>Compared with the lowest dairy intake group, the highest group was associated with significantly reduced for risk of stroke (RR=0.80, 95% CI 0.76-0.84). Results from 11 studies included.<br><br>Compared with the lowest dairy intake group, the highest group was associated with significantly reduced for risk of stroke mortality (RR=0.88, 95% CI 0.82-0.94).<br><br>Compared with the lowest milk intake group, the highest group was not associated with a significantly reduced for risk of stroke (RR=0.91, 95% CI 0.82-1.01). Results from 10 studies were included. In sub group analysis, fermented milk was associated with a reduced risk of stroke (RR=0.80, 95% CI 0.71-0.89. Results from 3 studies included. A non-linear dose-response relationship was observed between milk consumption and stroke risk whereby 200 mL/day was most protective |

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| | | | | | (RR=0.82, 95% CI 0.79-0.86)<br><br>Compared with the lowest cheese consumption group, the highest group was associated with significantly reduced for risk of stroke (RR=0.94, 95% CI 0.89-0.99). Results from 6 studies included.<br><br>Butter and cream consumption was not associated with a significantly reduced risk of stroke. |
| **De Oliveira Otto et al. 2013**<br><br>**USA**<br><br>**Prospective cohort study *Multi-Ethnic Study of Atherosclerosis (MESA)*** | NA | 2,837 persons aged 45-84 years, without clinical CVD, recruited from 6 US communities. Mean age was 61.5 years, 53% were women. | Plasma phospholipid fatty acids (14:0,15:0 and trans-16:1n7) were measured at baseline. Baseline 120-item FFQs were conducted and used to estimate saturated fat levels from various foods (dairy, meat, butter, and plants). The relationship between phospholipid fatty acids and saturated fat (SF) and the development of CVD was examined. | Incident CVD<br><br>Models were adjusted for age, sex, race/ethnicity, field center (6 sites), education, cigarette smoking, alcohol intake, physical activity, whole-fat dairy, processed and unprocessed meat, total energy intake, fiber and fruits and vegetables | There were 146 incident cases of CVD during 10-year follow-up (19,778 person years).<br><br>Plasma phospholipid fatty acid 15:0 was most strongly correlated with the consumption of high-fat dairy.<br><br>For each 1 standard deviation unit in 15:0 FA concentration, the risk of CVD was decreased significantly (HR=0.81, 95% CI 0.68-0.98).<br><br>For each 1 standard deviation unit in 14:0 and trans-16:1n7 FA concentration, the risk of CVD was not decreased significantly (HR=1.02, 95% CI 0.87-1.20 and HR=0.97, 95% CI 0.82-1.13).<br><br>Across quintiles, there was an inverse association between FA 15:0 and CVD risk (Q5 vs. Q1; HR=0.41,95% CI 0.22-0.78, p for trend=0.01). |
| **Larsson et al. 2012**<br><br>**Sweden**<br><br>**Prospective cohort study** | NA | 74,961 Swedish men and women, aged 45-83 years without a history of stroke, coronary heart disease or cancer at study baseline. | Participants completed a 350-item diet and lifestyle questionnaire. A 96-item food frequency questionnaire, with 8 response categories was used to estimated dairy consumption (milk, yogurt, cottage cheese, ice cream, crème fraiche) | Incident stroke<br><br>Analysis were adjusted for: i) age and sex and ii) multivariable (age, sex, smoking status, education, BMI, physical activity, history of hypertension, aspirin use, diabetes, family history, alcohol intake and other dietary components) | Mean duration of follow-up was 10.2 years.<br><br>There were 4,089 new stroke incidents.<br><br>Median total daily servings of dairy products for persons in the 1st and 5th quintiles were 2.3 and 9.3, respectively.<br><br>Comparing the highest quintile with the lowest (reference):<br><br>There was no association between consumption of dairy products and risk of stroke<br>Total dairy: RR=0.91, 95% CI 0.80-1.03.<br>Full-fat dairy: RR=0.94, 95% CI 0.83-1.07 |

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| | | | | | Cheese: RR=0.91, 95% CI 0.81-1.01<br>Consumption of low-fat dairy products was associated with a decreased risk of all stroke (RR=0.88, 95% CI 0.80-0.97) and ischemic stroke (RR=0.87, 95% CI 0.78-0.98) |
| **Soedamah-Muthu et al. 2011**<br><br>**The Netherlands**<br><br>**Systematic review & meta-analysis** | NA | 17 studies including the results from 611,430 subjects. Mean age at baseline was 56±13 years. Studies included women only (n=3), men only (n=4) and both sexes (n=10) | Dairy consumption, including milk, cheese and yoghurt was estimated using validated food-frequency questionnaires and diet histories (n=11) and non-validated FFQs and questionnaires (n=6). Dairy servings were converted from servings to g/day using standard conversions | Cardiovascular disease, coronary heart disease, stroke, all-cause mortality<br><br>Most studies adjusted for age, sex, smoking status, alcohol intake, BMI, traditional stroke risk factors and physical activity | The mean duration of follow-up was 14.0±6.0 years.<br><br>Overall, mean milk intake/day was 266±210 mL<br><br>There was no association between intake of milk (200 mL/day) and all-cause mortality. RR=0.99, 95% CI 0.95-1.03. Results from 8 studies included.<br><br>Stroke was an outcome in 6 studies (n=375,381). 15,554 fatal and non-fatal strokes occurred. Mean milk intake in stroke studies was 219 mL/day<br>There was no association between intake of milk (200 mL/day) and stroke risk. RR=0.87, 95% CI 0.72-1.05. |
| ***iv) Studies evaluating whole grains/fiber*** | | | | | |
| **Larsson & Wolk 2014**<br><br>**Sweden**<br><br>**Prospective study** | NA | 69,677 participants from 2 large population-based studies (Swedish Mammography Cohort and Cohort of Swedish Men), aged ≥18 years, free of CVD, cancer and diabetes at baseline. | A 96-item food frequency questionnaire (FFQ) with 8 response categories was used to estimate dietary fiber intake (fruits, vegetables and cereal grains) at baseline. Associations with incident stroke and dietary fiber (quintiles) were examined, adjusting for potential confounders (sex, age, education, family history of MI before age 60, smoking, physical activity, BMI, diabetes, HTN, aspirin use, total energy and alcohol use) | Total stroke, ischemic stroke and ICH | Mean duration of follow-up was 10.3 years.<br><br>There were 3680 incident strokes.<br><br>Mean fiber intake/day was 25.6 g (women) and 23.4 g (men).<br><br>The risk of all stroke was significantly lower among persons in the highest total fiber intake group (Q5), compared with Q1: RR=0.90, 95% CI 0.81-0.99). p for trend=0.03.<br><br>The risk of all stroke was not significantly lower among persons in the highest cereal fiber group (Q5), compared with Q1: RR=0.94, 95% CI 0.84-1.04). p for trend=0.42<br><br>The risk of all stroke was significantly lower among persons in the highest fruit fiber group (Q5), compared with Q1: RR=0.85, 95% CI 0.77-0.95). p |

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| | | | | | for trend=0.007<br><br>The risk of all stroke was significantly lower among persons in the highest vegetable fiber group (Q5), compared with Q1: RR=0.90, 95% CI 0.82-1.00). p for trend=0.12.<br><br>Only vegetable fiber was associated with a significantly reduced risk of cerebral infarction (Q5 vs. Q1 (RR=0.77-0.98) p for trend=0.06.<br><br>Increasing fiber intake (total, cerebral fruit or vegetable) was not associated with significant reduction in the risk of ICH. |
| **Mellen et al. 2008**<br><br>**USA**<br><br>**Systematic review & meta-analysis** | NA | 7 studies (288,376 subjects). Age at baseline ranged from 38-50 years (youngest) to 63-84 years (oldest). Studies included women only (n=2), men only (n=2) and both sexes (n=3). | Whole grain intake was measured using food frequency questionnaires (servings/day or week grams/day) (n=6) and a 3-day day food intake record (n=1) | Incident coronary heart disease, CHD death, incident stroke, stroke death, cardiovascular death.<br><br>Most common covariates adjusted for in analyses were age, sex, smoking blood pressure, BMI, physical activity and total energy intake | Follow-up ranged from 6-14 years.<br><br>Median intake of grains (servings/day) for persons in the lowest and highest quantiles were 0.2 vs. 2.5.<br><br>There was no association between incidence of stroke and whole grain intake. RR=0.83, 95% CI 0.68-1.02. Results from 4 studies included.<br>CVD events were significantly lower for persons consuming higher amounts of whole grains. RR=0.79, 95% CI 0.73-0.85. |
| ***v) Studies evaluating dietary patterns*** | | | | | |
| **O'Donnell et al. 2016**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 2**<br><br>**Case-control study** | NA | Participants were recruited from 32 countries from 2007-2015.<br><br>Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women. | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>A modified version of the Alternative Healthy Eating Index (mAHEI) was used | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) | Dietary risk factor scores were presented as tertiles, with T1 representing the highest risk.<br><br>**T2 vs. T1**<br>All stroke: OR=0.77, 99% CI 0.69-0.86,<br>Ischemic stroke: OR=0.75, 99% CI 0.66-0.85<br>ICH: OR=0.80, 99% CI 0.68-0.94<br><br>**T3 vs. T1**<br>All stroke: OR=0.60, 99% CI 0.53-0.67; PAR 23.2%, 99% CI 18.2-28.9%<br>Ischemic stroke: OR=0.59, 99% CI 0.52-0.68; PAR 22.4%, 99% CI 17.0-29.0<br>ICH: OR=0.61, 99% CI 0.50-0.74; PAR 24.5%, 99% CI 16.5-34.8% |

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| | | 13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | to measure diet quality. Higher mAHEI scores reflect better diet quality (higher intakes of fruits/vegetables, whole grains, polyunsaturated fatty acids, nuts, and long chain omega-3 fats and low intakes of red/processed meats, refined grains, and sugar sweetened drinks). The score was based on dietary patterns identified using a 19-item qualitative food group frequency questionnaire. | | The results were similar for men and women in sub group analysis (T1+T2 vs. T3 PAR: men 23.5%, 99% CI 17.4-31.0% and women PAR 22.9%, 99% CI 15.3-32.7%) |
| **O'Donnell et al. 2010**<br><br>**Canada (International)**<br><br>**INTERSTROKE**<br><br>**Phase 1**<br><br>**Case-control study** | NA | Participants were recruited from 22 countries from 2007-2010.<br><br>Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% of cases were women.<br><br>3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>A diet risk score was used to estimate the progression from healthy to unhealthy diet. The score was based on dietary patterns identified using a 19-item qualitative food group frequency questionnaire. | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)<br><br>Results were adjusted for age, sex, and region | Dietary risk factor scores were presented as tertiles, with T1 representing the lowest risk.<br><br>**T2 vs. T1**<br>All stroke: adjusted OR=1.35, 99% CI 1.12-1.61, PAR 18.8%, 99% CI 11.2-29.7%<br>Ischemic stroke: adj OR=1.29, 99% CI 1.06-1.57<br>ICH: adj OR=1.53, 99% CI 1.13-2.08<br><br>**T3 vs. T1**<br>All stroke: adj OR=1.35, 99% CI 1.11-1.64<br>Ischemic stroke: adj OR=1.34, 99% CI 1.09-1.65<br>ICH: adj OR=1.41, 99% CI 1.01-1.97<br><br>Increased consumption of fruits was associated with a decreased risk of stroke: adj OR (T3 vs. T1) =0.61, 99% CI 0.66-0.91.<br><br>Increased consumption of vegetables was not associated with a decreased risk of stroke: adj OR (T3 vs. T1) =0.91, 99% CI 0.75-1.00. |
| **Larsson et al. 2016**<br>**Sweden** | NA | 74,404 men and women, aged 45-83 years from 2 population-based cohort studies (Cohorts of | Dietary intake during the previous years was assessed using a 96-item FFQ. Adherence to the | Stroke incidence | Mean duration of follow-up was 11.9 years.<br><br>There were 3,896 ischemic strokes, 560 ICHs and 176 SAHs during 882,727 person-years follow-up. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Prospective study** | | Swedish men and Swedish Mammography), with no prior history of stroke. Mean age was 60 years, 54% men | DASH diet was evaluated using an adaptation of the Fung score (7 minimal adherence to 35 maximum adherence) and scores arranged by quartiles. | | The risk of stroke was adjusted for age, sex, education, family history of MI before 60 years, smoking status, aspirin use, exercise BMI, HTN, high chol, diabetes, atrial fibrillation and total energy and alcohol.<br><br>**Ischemic stroke**<br>Men<br>DASH score of 7-18 was reference category<br>19-21: RR=0.93, 95% CI 0.83-1.04<br>21-23: RR=0.92, 95% CI 0.82-1.03<br>24-35: RR=0.89, 95% CI 0.78-1.01<br>p for trend 0.06<br><br>Women<br>DASH score of 7-18 was reference category<br>19-21: RR=0.86, 95% CI 0.75-1.00<br>21-23: RR=0.87, 95% CI 0.75-1.01<br>24-35: RR=0.80, 95% CI 0.69-0.92<br>p for trend 0.0005<br><br>The risks of ICH and SAH were not decreased among men or women with higher adherence to a DASH diet. |
| **Tsivgoulis et al. 2015**<br><br>**Greece**<br><br>**Prospective cohort study** | NA | 20,197 participants, aged ≥45 years, without previous history of stroke, enrolled in the REGARDS study.<br><br>Mean age was 65 years, 44% were male. | A self-administered 98-item food frequency questionnaire (FFQ) was obtained at baseline. Adherence to the Mediterranean diet was based on the MeD score, with scores of 0-3 (low), med (4-5) and high (6-9).<br><br>The association between incident stroke and Mediterranean diet adherence was examined | Incident ischemic and hemorrhagic stroke | Mean duration of follow-up was 6.5 years. There were 565 strokes (2.8%)<br><br>The mean MeD score was 4.4<br><br>The risk of stroke was significantly reduced among participants with high MeD scores (vs. low MeD) in the fully adjusted model (age, race, region, sex, income, education, smoking, energy intake, sedentary behaviour, medication, BMI, waist circumference, DM, HTN and blood pressure); HR=0.79, 95% CI 0.65-0.96, p=0.00164.<br><br>Each 1-point increase in MeD score was associated with a 5% reduction (95% CI 0-11%) in the risk of ischemic stroke.<br><br>The risk of hemorrhagic stroke was not reduced |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | significantly in participants with high MeD scores. |
| **Martınez-Gonzalez et al. 2014**<br><br>**Spain**<br><br>**Systematic review & meta-analysis** | NA | 9 studies (3 case-control studies, 5 cohort studies and 1 RCT-PREDIMED) including participants with no previous history of CVD at baseline | The association between the consumption of olive oil and cardiovascular disease was explored.<br><br>In all included studies, olive oil consumption was assessed using validated food frequency questionnaires. Repeated FFQs were repeated (yearly) in one study | Coronary heart disease (CHD), stroke and CHD/stroke combined | In cohort studies, there were 543 cases of stroke reported during follow-up periods that ranged from 4.8-10.4 years.<br><br>For each 25 g/day increase in olive oil consumption there was a significant reduction in the risk of stroke (RR=0.76, 95% CI 0.67-0.86, p<0.001). The results from 3 studies were included.<br><br>For each 25 g/day increase in olive oil consumption there was a significant reduction in the risk of CHD and stroke combined (RR=0.82, 95% CI 0.70-0.96, p<0.001). The results from 9 studies were included. |
| **Psaltopoulou et al. 2013**<br><br>**Greece**<br><br>**Systematic review & meta-analysis** | NA | 22 studies examining the relationship between adherence to a Mediterranean diet and risk of stroke, cognitive impairment, Alzheimer's disease and depression.<br><br>In the 11 studies that assessed stroke as outcome (9 cohort studies, n=162,092 and 2 case-control studies, n=297 cases, 296 controls) both males and females were recruited in 10 studies and the 11th was restricted to females. The age ranges were 23-66 (youngest) to 55-92 years (oldest. The minimum age of participants was 65 years in 3 studies and 60 years in 1 study. | Since different methods were used to assess adherence to the Mediterranean diet across studies, the method developed by Trichopoulou et al, (0-9) was used to standardize scores to represent low, medium and high adherence. | Stroke | Length of follow-up in the cohort studies ranged from 4.1 to 20 years.<br><br>**High adherence** to a Mediterranean diet was associated with reduced risk of total stroke and ischemic stroke.<br><br>Overall: RR=0.71, 95% CI 0.57-0.89. Results from 11 trials included<br>Ischemic stroke: RR=0.52, 95% CI 0.28-0.96. Results from 5 studies included.<br>Hemorrhagic stroke: RR=0.97, 95% CI 0.57-1.67. Results from 2 studies included.<br>Non-fatal stroke: RR=0.48, 95% CI 0.14-1.71. Results from 2 studies included.<br>Fatal stroke: RR=0.69, 95% CI 0.44-1.08. Results from 1 study included.<br><br>**Moderate adherence** to a Mediterranean diet was not associated with reduced risk of total stroke.<br>Overall: RR=0.90, 95% CI 0.81-1.00. Results from 11 trials included.<br>Ischemic stroke: RR=0.91, 95% CI 0.74-1.13). Results from 6 studies included.<br>Hemorrhagic stroke: RR= 0.91, 95% CI 0.72-1.16. Results from 3 studies included.<br>Non-fatal stroke: RR=0.84, 95% CI 0.64-1.09. Results from 3 studies included.<br>Fatal stroke: RR=1.12, 95% .0.86-1.46. Results |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | from 2 study included. |
| **Salehi-Abargouei et al. 2013**<br><br>**Iran**<br><br>**Systematic review & meta-analysis** | NA | 6 studies that examined the relationship between the Dietary Approaches to Stop Hypertension (DASH)-style diet and cardiovascular disease were included. 4 studies included females only, 1 included only males and 1 included both sexes. Age range at baseline was 30. | All studies, except one identified 8 DASH components (fruits. Vegetable, nuts and legumes, whole grains, low-fat dairy, sodium, red and processes meats and sweetened beverages) and expressed the results as quintiles.<br><br>No information provided on method used to collect dietary intake data or how diet was scored/ranked. | Heart failure, cardiovascular deaths, coronary heart disease, stroke, stroke death.<br><br>Most common covariates adjusted for in analyses were age, sex, smoking blood pressure, BMI, physical activity and total energy intake, menopausal status | Follow-up ranged from 7-24 years.<br><br>DASH diet was protective for all outcomes.<br><br>When highest concordance groups were compared with lowest: RR (stroke)=0.81, 95% CI 0.72-0.92, p<0.001. Results from 3 studies included<br><br>High adherence to a DASH diet was protective for the development of CVD. RR=0.80, 95% CI 0.74-0.86. Results from 6 studies included |
| **Estruch et al. 2013**<br><br>**Spain**<br><br>**RCT**<br>***Prevención con Dieta Mediterránea Trial (PREDIMED)*** | CA: ☑<br><br>Blinding:<br>Patient ☒<br>Assessor ☑<br><br>ITT: ☑ | 7,447 men (aged 55 to 80 years) and women (aged 60 to 80 years) with no cardiovascular disease with either type 2 diabetes mellitus or at least three major risk factors: smoking, hypertension, elevated LDL cholesterol levels, low HDL cholesterol levels, overweight or obesity, or a family history of premature coronary heart disease.<br><br>Mean age: 67 years, 57% women. | Participants were randomized (1:1:1) to a Mediterranean diet supplemented with extra-virgin olive oil (EVOO), a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat).<br><br>A 137-item food frequency questionnaire and a 14-item questionnaire were used to assess adherence to a Mediterranean diet at baseline and yearly. | **Primary outcome:**<br>Major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes)<br><br>**Secondary outcomes:**<br>changes in blood pressure, body weight, adiposity measures, blood sugar, lipids | The median duration of follow-up was 4.8 years.<br><br>The mean scores for adherence to the Med diet (0=no adherence, 14=maximum adherence) across groups were 8.7 (2 study diet groups) and 8.4 for the control group.<br><br>Participants in the two Mediterranean-diet groups significantly increased their weekly servings of fish (by 0.3 servings), legumes (by 0.4 servings), olive oil and nuts compared with the control group.<br><br>The crude event rates/1,000 person yrs for the primary outcome were significantly lower for the 2 Med diets: EVOO: 8.1, nuts: 8.0, control 11.2<br><br>Compared with the control diet, the risk of the primary outcome was significantly reduced.<br>EVOO: HR=0.70, 95% CI 0.54–0.92, p<0.01<br>Nuts: HR=0.70, 95% CI 0.54–0.96, p=0.03<br><br>The crude event rates/1,000 person yrs for stroke were significantly lower for the 2 Med diets: EVOO: 4.1, nuts: 3.1, control 5.9<br><br>Compared with the control diet, the risk of stroke was significantly reduced. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | EVOO: HR=0.67, 95% CI 0.46–0.98, p=0.04<br>Nuts: HR=0.54, 95% CI 0.35–0.84, p=0.006<br><br>There were no significant reductions associated with the Med diet for MI, death from cardiovascular causes, or death from any cause.<br><br>No interactions were observed in subgroups analyses: sex, diabetes, age (<70 vs. ≥70 yrs), hypertension, dyslipidemia, smoking, family history of CHF) |
| **Misirli et al. 2012**<br><br>**Greece**<br><br>**Prospective cohort study** | NA | 23,601 adults who were participants in the Greek cohort of the EPIC study, free of cancer and CVD at baseline | Dietary intake was assessed using a validated semi quantitative FFQ including 150 items.<br><br>Adherence to the Mediterranean diet was assessed using the 10-point scale developed by Trichopoulou et al. (0-9) with higher scores indicating better adherence. Scores of 0-3 (low), med (4-5) and high (6-9).<br><br>Associations between adherence to a Mediterranean diet and CVD were examined with adjustment for sex, age, education, smoking status, BMI, physical activity, hypertension, diabetes, and total energy intake | CVD, mortality-associated CVD, all stroke, ischemic and hemorrhagic stroke | The median duration of follow-up was 10.6 years.<br><br>There was a total of 395 CV events and 196 deaths.<br><br>Compared with the reference category (diet scores 0-3), scores of 4-5 and 6-9 were associated with significantly reduced risk of CVD (HR=0.80, 95% CI 0.64-1.00 and HR=0.72, 95% CI 0.54-0.97, respectively). Each 2-point increase in diet scores was associated with a significant decrease in incident CVD (HR=0.85, 95% CI 0.74-0.96). There were no associated reductions in the risk of CV-associated mortality.<br><br>Compared with the reference category (diet scores 0-3), scores of 4-5 and 6-9 were not associated with significantly reduced risk of stroke<br><br>Ischemic stroke (n=95) HR=0.77, 95% CI 0.50-1.21 and 0.54, 95% CI 0.29-1.01<br><br>Hemorrhagic stroke (n=59) HR=1.25, 95% CI 0.69-2.26 and HR=0.86, 95% CI 0.40-1.87.<br><br>Dietary components that were associated with reduction in the risk of incident CVD were vegetables, legumes and monounsaturated oils |
| **Agnoli et al. 2011**<br><br>**Italy** | NA | 40,681 men and women aged 35-74 years with no history of stroke, MI, | Dietary intake data was collected using a semi-quantitative FFQ. | The Hazard Ratio (HR) associated with all stroke, hemorrhagic and ischemic | There were 178 strokes during the follow-up of 7.9 years. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Cohort Study** | | hyperlipidemia, diabetes, and those following a special diet for hypertension. | This information was used to develop a score to assess adherence to 4 different dietary eating patterns, Healthy Eating Index (HEI-2005), Dietary Approaches to Stop Hypertension (DASH), Greek Mediterranean Index and the Italian Mediterranean Index. | stroke. Dietary scores of the 4 diet types were expressed as tertiles (T1, T2, T3).<br><br>Analysis was adjusted for sex, smoking status, education, non-alcoholic energy intake, and BMI. | The risk of all stroke was significantly reduced for the Italian Mediterranean Diet pattern (T1 vs. T2 HR=0.68, 95% CI 0.48-0.94 & T1 vs. T3 HR=0.47, 95% CI 0.30-0.75, p=0.001).<br><br>The risk of ischemic stroke was significantly reduced for the HEI-2005, DASH and Italian Mediterranean diet, while no diet pattern was protective for hemorrhagic stroke. |
| **Fung et al. 2004**<br><br>**USA**<br><br>**Prospective Cohort study** | NA | 71,768 women enrolled in the Nurses' Health Study aged 38-63 years, without CVD or diabetes. | Dietary intake data was collected every 2-4 years from 1984-1998 using a 116-item food-frequency questionnaire. The FFQ had 9 response categories, which were the assembled into 36-42 food groups. Dietary patterns were identified using factor analysis<br><br>Two dietary eating patterns were compared, the "prudent diet", characterized by higher intakes of fruits, vegetables, legumes, fish, and whole grains, and the "Western" pattern, characterized by higher intakes of red and processed meats, refined grains, and sweets and desserts. | Incidence of stroke (total, ischemic, hemorrhagic).<br><br>Analysis were adjusted for; i) age and energy adjusted and ii) fully adjusted-age, smoking status, BMI, menopausal status, aspirin use, energy intake, alcohol intake, physical activity | Over the 14 years of follow-up, there were 791 incident strokes (476 ischemic and 189 hemorrhagic).<br><br>Comparing the 5$^{th}$ with the 1$^{st}$ quintile, the **prudent diet** was associated with a trend towards lower risk of stroke in the fully adjusted analyses.<br><br>All stroke: RR=0.78, 95% CI 0.61-1.01, p for trend=0.13.<br><br>Ischemic stroke: RR=0.74, 95% CI 0.54-1.02, p for trend=0.13.<br><br>Hemorrhagic stroke: RR=1.01, 95% CI 0.47-1.30, p for trend=0.51.<br><br>Comparing the 5$^{th}$ with the 1$^{st}$ quintile, the Western diet was associated with an increased risk of stroke in the fully adjusted analyses.<br><br>All stroke: RR=1.58, 95% CI 1.15-2.15, p for trend=0.0002.<br><br>Ischemic stroke: RR=1.56, 95% CI 1.05-2.33, p for trend=0.02.<br><br>Hemorrhagic stroke: RR=1.63, 95% CI 0.86-3.090, p for trend=0.098. |
| ***vi) Studies evaluating fish consumption*** | | | | | |
| **Xun et al. 2012** | NA | 16 prospective studies | Studies were included if | Stroke incidence | Mean duration of follow-up ranged from 8.5-28 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **USA**<br><br>**Systematic review & meta-analysis** | | including 402,127 adult participants. 8 studies included men and women, 5 included only men and 3 included only women. | fish consumption and stroke risk was assessed, with the lowest category of fish consumption serving as the reference group.<br><br>Frequency of intake was obtained using self-administered questionnaires or by interview in the majority of studies. | All studies adjusted for age, sex, smoking, blood pressure and most studies also controlled for alcohol consumption, lipids, BMI or obesity diabetes, physical activity and other dietary factors. Some studies adjusted for other factors such as aspirin use and education | years (mean 12.8).<br><br>There were 10,568 stroke events.<br><br>The risk of stroke was inversely associated with fish consumption. Compared with those that consumed fish never or <1 a month:<br>1-3x/month: HR= 0.97, 95% CI 0.87-1.08<br>1/week: HR= 0.86, 95% CI 0.80-0.93<br>2-4x/week: HR= 0.91, 95% CI 0.85-0.98<br>≥5/week: HR= 0.87, 95% CI 0.79-0.96<br><br>The pattern of results was similar for ischemic stroke. There was no reduced risk associated with hemorrhagic stroke.<br><br>Compared with fish consumption of less than once a month, the risk of stroke was significantly reduced for consumption of 2-4x/week (HR=0.91, 95% CI 0.85-0.98). |
| **Larson & Orsini 2011**<br><br>**Sweden**<br><br>**Systematic review & meta-analysis** | NA | 15 prospective studies including 383,838 adult participants. 8 studies included men and women, 4 included only men and 3 included only women. | Studies were included if at least 3 categories of fish consumption were used. | Stroke incidence or mortality<br><br>All studies adjusted for age, smoking, and history of hypertension or measured blood pressure, while most studies also controlled for alcohol consumption, BMI or obesity diabetes, physical activity and other dietary factors | Mean duration of follow-up ranged from 4-28 years.<br><br>There were, 9360 stroke events.<br><br>The risk of stroke was significantly decreased for a 3-serving/week increase in fish consumption (RR=0.94, 95% CI 0.89-0.99).<br><br>Compared with the lowest consumption group, the risk of stroke was significantly decreased in the highest fish intake group (RR=0.88, 95% CI 0.81-0.96). |

CA: concealed allocation; ITT: intention-to-treat

## Vitamin B Supplementation to Reduce Risk of Recurrent Stroke

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Hankey et al. 2010**<br><br>**International** | CA: ☑<br><br>Blinding: Patient ☑ | 8,164 patients with recent stroke or TIA (within previous 7 months) recruited from 20 | Patients were randomized 1:1 to receive B vitamins (2 mg folic acid, 25 mg vitamin | **Primary outcome:** Composite of non-fatal stroke, non-fatal MI, or death from any vascular causes | Median duration of follow-up was 3.4 years. (14,182 person-years).<br><br>There was a borderline reduction in the risk of the |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **RCT**<br>***VITAmins TO Prevent Stroke (VITATOPS)*** | Assessor ☑<br><br>ITT: ☑ | countries from 1998-2008. Mean age was 62.6 years, 64% were men, 71% ischemic stroke, 17% TIA, 10% ICH or SAH | $B_6$, and 0.5 mg vitamin $B_{12}$) or placebo for the duration of the trial | **Secondary outcome:**<br>Stroke (non-fatal or fatal), MI non-fatal or fatal), death from any vascular cause, death from any cause, revascularisation procedures, the composite of non-fatal stroke, non-fatal MI, and death from any vascular cause, and revascularisation procedures of the coronary, cerebral, or peripheral circulation | composite outcome in the vitamin B group (15% vs. 17%, RR=0.91, 95% CI 0.82-1.00, p=0.05, absolute risk reduction of 1.56%, 95% CI -0.01-3.16). There were no significant interactions based on subgroup analyses (age, sex, ethnicity, clinical stroke syndrome, stroke pathology, stroke cause, stroke severity, baseline blood creatinine, total homocysteine, and vitamin B12 status).<br><br>The risk of stroke or stroke/MI or death was not reduced significantly with vitamin B supplementation (9% vs. 10%, RR=0.92, 95% CI 0.81-1.06, p=0.25 and 21% vs. 22%, RR=0.96, 95%CI 0.88-1.04, p=0.26).<br><br>The risk of fatal or nonfatal stroke was not reduced significantly with vitamin supplementation (9% vs. 10%, RR=0.92, 95% CI 0.81-1.06, p=0.25)<br><br>At the end of follow-up, the mean total homocysteine concentration was significantly lower in the supplement group 10.5 vs. 14.3 µmol/L, p<0.0001. |
| **Toole et al. 2004**<br><br>**USA**<br><br>**RCT**<br>***Vitamin Intervention for Stroke Prevention (VISP)*** | CA: ☑<br><br>Blinding:<br>Patient ☑<br>Assessor ☑<br><br>ITT: ☑ | 3,680 patients, recruited from 1997-2002, ≥35 years with non-disabling ischemic stroke (mRS ≤3), occurring ≤120 days previously, with a total homocysteine level ≥25$^{th}$ percentile. Mean age was 66.3 years, 62.5% men. Mean baseline total homocysteine level at randomization was 13.4 µg | Patients were randomized 1:1 to receive high-dose B vitamins (25 mg $B_6$, 0.4 mg $B_{12}$, and 2.5 mg folic acid) or low-dose B vitamins (200 µg $B_6$, 6 µg $B_{12}$, and 20 µg folic acid), for the duration of the trial | **Primary outcome:**<br>Recurrent cerebral infarction<br><br>**Secondary outcome:**<br>Coronary heart disease (CHD), death | Mean duration of follow-up was 20.3 months.<br><br>There were 148 cases of ischemic stroke in the low-dose group vs. 152 in the high-dose group. There was no significant difference between groups in the relative 2-year risk (8.1% vs. 8.4%, RR=1.0, 95% CI 0.8-1.3).<br><br>There were 18 cases of fatal or disabling ischemic stroke in the low-dose group vs. 12 in the high-dose group. There was no significant difference between groups in the relative 2-year risk (1.0% vs. 1.2%, RR=1.1, 95% CI 0.6-1.2).<br><br>There were no significant reductions in the risks of ischemic stroke or CHD; or ischemic stroke, CHD or death associated with high-dose supplementation.<br><br>Mean total homocysteine fell over the study for patients in both groups, but the decrease at 2 years |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | was greater by 2.3 µg in the high-dose group.<br><br>There were no significant differences in minor adverse events between groups.<br><br>There was a significant association between baseline homocysteine levels (classified as low, medium and high) and stroke recurrence in the low-dose group (p=0.02), but not in the high-dose group (p=0.24).<br><br>When analyzed as a continuous variable, a 3-µmol/L lower total homocysteine level was associated with a 10% lower risk of stroke (p=0.05) |
| **Spence et al. 2005**<br><br>**Canada**<br><br>**Sub-group analysis of VISP trial** | NA | 2,155 patients hypothesized to benefit the most from vitamin therapy (GFR > 10th percentile for calculated GFR [>46.18] and with serum B12 levels 25th to 95th percentiles (250 to 637 pmol/L). Mean age was 66 years, 63% male. Mean baseline total homocysteine level at randomization was 12.6 µg. | As above | **Primary outcome:**<br>Recurrent cerebral infarction<br><br>**Secondary outcome:**<br>Coronary heart disease (CHD), death | The sub group included 58.6% of patients randomized.<br><br>The risk of ischemic stroke was not reduced significantly among patients in the high-dose group in either unadjusted or adjusted analysis (age, sex, BP, smoking and vit $B_{12}$ level) adj HR=0.91, 95% CI 0.67-1.24, p=0.56.<br><br>The risk of the combined outcome of stroke and CHD was not reduced significantly among patients in the high-dose group in either unadjusted or adjusted analysis (adj HR=0.84, 95% CI 0.66-1.06, p=0.14.<br><br>The risk of the combined outcome of stroke, death and CHD was reduced significantly among patients in the high-dose group in the unadjusted analysis (HR=0.79, 95% CI 0.63-1.00, p=0.049), but not in the adjusted analysis (HR=0.80, 95% CI 0.63-1.01, p=0.056).<br><br>Patients with a baseline $B_{12}$ level ≥ the median, randomized to high-dose group vitamin had the best overall outcome, and those with B12 <the median randomized to the low-dose group had the worst (p<0.02 for combined stroke, death, and coronary events and p<0.03 for stroke and coronary events). |

CA: concealed allocation; ITT: intention-to-treat

## Interventions to Increase Fruit & Vegetable Consumption

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Hartley et al. 2013**<br><br>**UK**<br><br>**Cochrane review** | NA | 10 RCTs including 1,730 adults who were at increased risk for stroke because of dyslipidemia, smoking or hypertension.<br><br>Studies in which 25% of subjects had CVD at baseline (including those who had experienced a previous MI, stroke or had angina) and where more than 25% of the participants had type 2 diabetes, were excluded.<br><br>Four of the 10 trials recruited only female participant.<br><br>Participants included: women with metabolic syndrome (n=2), healthy post-menopausal women with a family history of breast cancer (n=1), obese individuals (n=1), patients with a history of colorectal adenomatous (n=1), pre-metabolic or healthy individuals (n=1), healthy individuals (n=3). | Interventions included: i) specific dietary advice to increase fruit and vegetable consumption (n=4) and ii) the provision of fruit and vegetables (n=6), to increase consumption.<br><br>Treatment interventions included the consumption of: 25 g/day of soy (n=1), 130 g/day of cooked pinto beans (n=1), half a grapefruit three times a day (n=1), addition of raw garlic on a sandwich (n=1) a high tomato diet (n=1) and 750 mL/week (n=1)<br><br>In trials that provided additional fruits and vegetables, the intervention period lasted 3 or 6 months with final assessment at the end of the intervention period. In trials that provided dietary advice, the treatments ranged from a single session to 4 sessions with a dietitian with follow-up of 6 or 12 months. None of the included studies had interventions that provided fruit and | Systolic & diastolic blood pressure (SBP, DBP), serum cholesterol & triglycerides (TG).<br><br>Due to short intervention and follow-up periods, stroke events were not reported. | **Advice to increase fruit and vegetables**<br>Change in SBP from baseline: mean difference (MD) = -3.00, 95% CI -4.92, -1.09, p= 0.0021). Results from 2 trials included.<br><br>Change in DBP from baseline: MD= -0.90, 95% CI -2.03, 0.24, p= 0.12. Results from 2 trials included.<br><br>Change in total cholesterol from baseline: MD= -0.01, 95% CI -0.11, 0.09, p= 0.81. Results from 2 trials included.<br><br>Change in TG from baseline: MD= 0.10, 95% CI -0.06, 0.27, p= 0.20. Results from 3 trials included.<br><br>**Provision of fruits and vegetables**<br>Change in SBP from baseline: mean difference (MD) = 1.00, 95% CI 0.45, 1.55, p= 0.0038). Results favour control condition. Results from 1 trial included.<br><br>Change in DBP from baseline: MD= 1.50, 95% CI 1.18, 1.82, p<0.0001. Results favour control condition. Results from 1 trial included.<br><br>Change in total cholesterol from baseline: MD= -0.10, 95% CI -0.24, 0.04 p= 0.17. Results from 2 trials included.<br><br>Change in TG from baseline: MD= % -0.01, 95% CI 0.03, 0.01, p= 0.32. Results from 3 trials included. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | vegetables and gave advice. | | |
| **Howard et al. 2006**<br><br>**USA**<br><br>**RCT** | CA: ☑<br><br>Blinding:<br>Patient ☒<br>Assessor ☑<br><br>ITT: ☑ | 48,835 postmenopausal women, aged 50 to 79 years (mean=62.3 years) whose dietary intake of fat was ≥32% of total calories at baseline.<br><br>Exclusions: prior breast or colorectal cancer, other cancers except nonmelanoma skin cancer, medical conditions with predicted survival less than 3 years, type I diabetes, many meals eaten away from home.<br><br>Participants were well-matched for stroke risk factors. Current smokers 6.7%, hypertension 43%, hypercholesterolemia 12%, history of stroke or CVD <2%, metabolic syndrome 36%. | Participants were randomized to the intervention group (n=19,541) or control group (n=29,294)<br><br>Participants in the intensive behavior modification group participated in 18 group sessions during the first year and quarterly sessions thereafter, designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d. Additional individual contact through email or telephone was used to reinforce the message.<br><br>Participants in the control group received healthy diet-related education materials only. | Fatal and nonfatal coronary heart disease (CHD), fatal and nonfatal stroke, and total CVD (combined CHD and stroke). | Mean follow-up was 8.1 years.<br><br>By year 6, relative to those in the control group, participants in the intervention group had reduced their mean fat intake by 8.2%, saturated fat intake by 2.9% and had increased their daily fruit and veg consumption by an average of 1.1 servings.<br><br>At 3 years, relative to those in the control group, participants in the intervention group had significantly reduced their mean BMI (-0.49), diastolic blood pressure (mean -0.31 mm Hg), total chol (mean -3.26 mg/dL) and increased total carotenoids (mean 0.04 µg/mL).<br><br>The intervention was not associated with a significant decrease in stroke risk.<br><br>All stroke: HR=1.02, 95% CI 0.90-1.17<br>Fatal stroke: HR=0.94, 95% CI 0.65-1.35<br>Non-fatal stroke: HR=1.04, 95% CI 0.90-1.19<br><br>Ischemic stroke: HR=1.03, 95% CI 0.87-1.22<br>Hemorrhagic stroke: HR=0.88, 95%CI 0.64-1.20<br><br>Total CVD: HR=0.96, 95% CI 0.89-1.03<br><br>Losses to follow-up or withdrawals: intervention group n=917, control group n=1,163 |

CA: concealed allocation; ITT: intention-to-treat

## Interventions to Decrease Fat Consumption

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Hooper et al. 2015**<br><br>**UK** | NA | 15 RCTs (59,000), including adults (≥18 years) at any risk of cardiovascular disease (with or without existing | Same approach as Hooper et al. 2012, with the focus on saturated fat. | **Primary outcomes:**<br>All-cause mortality, CVD mortality (deaths from MI, stroke, or sudden death), combined CVD events. | Following a reduced saturated fat diet was not associated with reductions in the risks of any of the outcomes except combined CV events<br><br>Total mortality: RR= 0.97, 95% CI 0.90-1.05, |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Cochrane review** | | cardiovascular disease), who were taking/not taking lipid-lowering medication.<br><br>. | Interventions included dietary advice, supplementation of fats, oils or modified or low-fat foods, or a provided diet, vs. control group that could include usual diet, placebo or a control diet.<br><br>Intended duration of the dietary intervention was at least two years | **Secondary outcomes:**<br>Additional health events | p=0.47, 55,858 participants, 11 RCTs. Mean duration of follow-up was 56 months<br><br>CV mortality: RR=0.95, 95% CI 0.80-1.12, p=0.5110 RCTs, 53,421 participants. Mean duration of follow-up was 53 months<br><br>All stroke: RR= 1.00, 95% CI 0.89 to 1.12, p=0.97 Results from 7 RCTs, 50,952 participants included. Mean duration of follow-up was 59 months<br><br>Non-fatal MI: RR= 0.95, 95% CI 0.80-1.13, p=0.57 7 RCTs, 52,834 participants. Mean duration of follow-up was 55 months<br><br>Combined CV events: RR=0.83, 95% CI 0.72- 0.96, p=0.01. 11 RCTs, 53,300 participants. Mean duration of follow-up was 52 months |
| **Hooper et al. 2012**<br><br>**UK**<br><br>**Cochrane review** | NA | 48 RCTs, including adults (≥18 years) at any risk of cardiovascular disease (with or without existing cardiovascular disease).<br><br>9 studies recruited participants with cardiovascular disease, 12 recruited those at increased risk of CVD, 25 recruited those from the general population without specific CVD risk factors and 2 studies included participants at both high and low CVD risk. | Interventions to reduce or modify fat or cholesterol intake compared with usual diet and was at least 6 months in length. A low-fat diet was considered to be one that aimed to reduce fat intake to < 30% or more from fat, and at least partially replace the energy lost with carbohydrates (simple or complex), protein or fruit and vegetables. A modified fat diet was considered one that aimed to include 30% or more energy from total fats, and included higher levels of mono-unsaturated or poly-unsaturated fats than a 'usual' diet. | **Primary outcomes**<br>Total cardiovascular mortality and combined cardiovascular events | Following a reduced fat or modified fat diet was not associated with reductions in total mortality, or fatal/non-fatal stroke<br><br>Total mortality: RR=0.98, 95% CI 0.93- 1.04, p=0.53. Results from 21 trials (n=71,790) included.<br><br>Stroke: RR= 0.99, 95% CI 0.89- 1.11, p=0.87 Results from 11 trials (n= 59,853) included<br><br>Following a reduced fat or modified fat diet was associated with reductions total cardiovascular events (RR=0.86, 95% 0.77-0.96, p= 0.0068). Results from 21 trials (n= 65,508) included. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | Interventions included: provision of dietary advice (n=35), provision of dietary advice plus some dietary supplementation (e.g., oils or margarines, n=9), provision of most food eaten by participants (n=16) | | |

## Effect of Dietary Sodium Reduction on Blood Pressure

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Aburto et al. 2013**<br><br>**UK**<br><br>**Systematic review & meta-analysis** | NA | 56 studies were included (5,508 subjects), 1,478 with hypertension, and 3,263 without.<br><br>14 cohort studies and 5 RCTs examined all-cause mortality, CVD, stroke or CHD<br><br>37 RCTs measured blood pressure, renal function or catecholamines | Cohort studies: measured sodium intake for a duration of at least 1 year and reported an outcome of interest. Duration of follow-up ranged from 3.8 to 22 years.<br><br>RCTs: compared decreased sodium intake with higher sodium intake with a between-group difference of 40 mmol/day with a duration of 4 weeks to 36 months and measured sodium intake using 24-hour urinary sodium excretion.<br><br>Interventions included dietary advice, education, counselling, or provision of foods with | Blood pressure, all-cause mortality, CVD, stroke, CHD, adverse effects, catecholamine levels, renal function | SBP: Mean difference= -3.39, 95% CI -4.31 to -2.46 (results from 36 studies included). Significant reductions of -1.38 and -4.06 for subgroups of subjects without HTN and with HTN<br><br>DBP: MD= -1.54, 95% CI -2.11 to -0.98 (results from 36 studies included). Significant reduction of -2.26 for subgroup of subjects with HTN<br><br>In trials where the relative sodium reduction of subjects in the intervention group was <1/3 of the control group, (8 studies), there were significant reduction in both SBP (MD= -1.45, 95% CI -2.29 to -0.60) and DBP (MD= -0.74, 95% CI -1.28 to -0.19)<br><br>In trials where the relative sodium reduction of subjects in the intervention group was ≥1/3 of the control group, (30 studies), there were significant reduction in both SBP (MD= -3.79, 95% CI -4.82 to -2.75) and DBP (MD= -1.68, 95% CI -2.34 to -1.02). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | a reduced sodium content | | Both mean SBP and DBPs were significantly reduced in patients who were taking concomitant drug therapy (-4.55, 95% CI -6.59 to -2.51 and -2.05, 95% CI -3.19 to -0.91, 6 studies) and those not taking drugs (-3.66, 95% CI -4.85 to -2.47 and -1.70, 95% CI -2.37 to -1.04, 27 studies).<br><br>Increased sodium intake was associated with an increased risk in all stroke (RR= 1.25, 95% CI 1.08 to 1.43, 10 studies) and combined fatal and non-fatal events (RR=1.13, 95% CI 1.01 to 1.26, 8 studies). The authors note that the findings related to stroke occurrence are based on studies of low and very low quality. |
| **He et al. 2013**<br><br>**UK & China**<br><br>**Cochrane review** | NA | 34 RCTs (n=3,230 subjects). 23 trials were a crossover and 11 were parallel group design<br><br>The mean age of participants ranged from 22 to 73 years. Subjects in 22 trials were hypertensive and in 12, were normotensive. | Comparison of trials in which subjects were randomized to a diet that moderately restricted sodium intake (2.3-7.0 g/day or 40-120 mmol/day urinary sodium excretion) or usual intake for a minimum of 4 weeks.<br><br>Subjects could not receive additional pharmacological therapy for hypertension. | Change in systolic and diastolic blood pressure at end of treatment. | Study durations were 4 weeks (n=19), 5-8 weeks (n=10), 3-6 months (n=2).>6 months (n=3).<br><br>**Overall**<br>In subjects in the control group, the median 24-hour urinary sodium excretion was 160 (range: 125-200) mmol or the equivalent of 9.4 (range: 7.3-11.7) grams of salt intake/day. Median blood pressure at baseline was 141/86 mm Hg.<br><br>The change in urinary sodium excretion from control condition to reduced salt intake was -75 (range: -40 to 118) mmol or a dietary reduction of 4.4 (range: 2.3-6.9) g/day.<br>The mean change in SBP was -4.18 mm Hg (95% CI -5.18 to -3.18), p<0.01. Results from 35 trials included.<br>The mean change in DBP was -2.06 mm Hg (95% CI -2.67 to -1.45), p<0.0001. Results from 37 trials included.<br>In meta-regression, a 100 mmol reduction in 24-hour urinary sodium was associated with a 5.8 mm Hg decrease in SBP (95% CI 2.5-9.2), p<0.001.<br><br>**Hypertension Trials**<br>The median 24-hour urinary sodium excretion |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | was 162 mmol (125-191 mmol) equivalent to a salt intake of 9.5 g/day. The median blood pressure was 148/93 mm Hg. The pooled estimate of the change in 24-hour sodium from the usual to the reduced salt intake was -75 mmol (range -53 to -117mmol) or -4.4 g/day (range (-3.1 to -6.8) grams Na /day<br><br>The mean change in SBP was -5.39 mm Hg (95% CI -6.62 to -4.150, p< 0.00001). Results from 21 trials included.<br><br>The mean change in DBP was -2.82 mm Hg (95% CI -3.54 to -2.11), p<0.0001. Results from 23 trials included.<br><br>In meta-regression, a 100 mmol reduction in 24-hour urinary sodium was associated with a 10.8 mm Hg decrease in SBP (95% CI 3.5-18.2), p<0.01.<br><br>**Normotensive Trials**<br>The median 24-hour urinary sodium excretion was 153 mmol (128-200 mmol) equivalent to a salt intake of 8.9 g/day. The median blood pressure was 148/93 mm Hg. The pooled estimate of the change in 24-hour sodium from the usual to the reduced salt intake was -75 mmol (range -40 to -118mmol) or -4.4 g/day (range (-2.3 to -6.89 grams Na /day<br><br>The mean change in SBP was -2.42 mm Hg (95% CI -3.56 to -1.29, p<0.0001). Results from 14 trials included.<br>The mean change in DBP was -1.00 mm Hg (95% CI -1.85 to -0.15), p<0.0001). Results from 14 trials included. |
| **Stolarz-Skrzypek et al. 2011**<br><br>**Belgium**<br><br>**Observational** | NA | 3,681 participants without cardiovascular disease (CVD), were included from the EPOGH and FLEMENGHO studies. | Baseline measurements included blood pressure, 24-hour urine collection, weight, medical history, demographics. 1-3 follow-up visits were | Incident hypertension, changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) | Median follow-up was 6.5 years for participants of the hypertension cohort and 6.4 years for those in the blood pressure cohort.<br><br>There were 552 cases of incident hypertension. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **study** | | Following ascertainment of the outcome portion of the study (described above), 2,856 participants agreed to the follow-up portion of the study and comprised a blood pressure cohort (1,499) and a hypertension cohort (2,096).<br><br>All the participants in the hypertension cohort were normotensive. Mean age was 38.6 years. 54.1% were female.<br><br>The mean age of participants in the blood pressure cohort was 38.3 years. 52.4% were female. 9.9% of participants had hypertension at baseline | conducted. | | There was no significant increase in the development of incident hypertension across sodium excretion tertiles (p=0.93)<br>Low: adjusted HR=1.00 (95% CI 0.87 to 1.16)<br>Medium: adjusted HR=1.02 (95% CI 0.89 to 1.16) High: adjusted HR= 0.98 (95% CI 0.86 to 1.12)<br><br>In the blood pressure cohort, the mean annual change in SBP and DBP were 0.37 and 0.47 mm Hg (p<0.001 for both)<br><br>Untreated HTN had increased from 9.9% to 19.9% at follow-up.<br><br>Absolute SBP increased by 1.71 mm Hg /each 100 mmol/ day increment of urinary sodium excretion (95% CI 0.786-2.637, p<0.001).<br><br>Absolute DBP increased by 0.379 mm Hg /each 100 mmol/ day increment of urinary sodium excretion (95% CI -0.313-1.070, p<0.12). |
| **Whelton et al. 1998**<br><br>**USA**<br><br>**RCT**<br>***A Randomized Controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE)*** | CA: ☑<br><br>Blinding:<br>Patient ☒<br>Assessor ☑<br><br>ITT: ☑ | 975 healthy participants, aged 60 to 80 years, with SBP < 145 mmHg and DBP < 85 mmHg while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diuretic agent. Individuals taking 2 antihypertensive medications were also eligible if they were successfully weaned off one of them during the screening phase.<br><br>Mean age was 66 years, 53% male | 390 nonobese participants were randomized to a 3-phase, (intensive, extended and maintenance) diet/exercise program, using small group and individual counseling sessions or usual care. Participants in the intervention group learned about sources of sodium, sodium alternatives and ways to adapt a low-salt diet to their own lifestyle, with the goal of achieving and maintaining a dietary sodium intake of ≤80 mmol/day, measured by | **Primary outcome:**<br>Occurrence of high blood pressure (SBP>190 mm Hg or DBP>110 mm Hg at a single visit), at one or more study follow-up visits, after withdrawal of antihypertensive medication and a cardiovascular event<br><br>Final follow-up was conducted at 30 months | Withdrawal of antihypertensive agents was attempted after 3 months.<br><br>At final follow-up, the mean reduction in SBP was greater for participants in the sodium reduction group compared with usual care (-3.4±0.8 vs. -0.8±0.8, p<0.001).<br><br>At final follow-up, the mean reduction in DBP was greater for participants in the sodium reduction group compared with usual care (-1.9±0.5 vs. -0.8±0.5, p<0.001).<br><br>Overall, the risk of the primary outcome over the study period was significantly lower among participants in the sodium reduction group (HR=0.69, 95% CI 0.59-0.81, p<0.001).<br><br>Among the obese participants, the risk of the primary outcome over the study period was significantly lower among participants in the |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | 24-hour urine collection. 585 obese participants were randomized to a reduced sodium intake and/or weight loss group | | sodium reduction group (HR=0.70, 95% CI 0.57-0.87, p<0.001).<br><br>There were 145 cardiovascular events over the study period, including 4 strokes and 17 TIAs. There were no differences between study groups in the risk of any of these events. |

CA: concealed allocation; ITT: intention-to-treat

## Dietary Sodium Intake and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including high-sodium diets, defined as > 5g/day) in high-income countries and low-income and middle-income countries. | Stroke burden (expressed as DALYs) | Globally, 22.6% (95% uncertainty interval 12.5%-33.0%) of the stroke burden was attributed to diets high in sodium.<br><br>In high income countries, 17.8% (95% uncertainty interval 9.2%-26.6%) of the stroke burden was attributed to diets high in sodium.<br><br>**In Canada, 12.6% (95% uncertainty interval 4.6%-24.3%) of the stroke burden was attributed to diets high in sodium**<br><br>Globally, during the study period, there was an increase of 33.4% (95% UI 32.1%, 35.8%) in the burden of stroke related to high sodium diets. |
| **Cook et al. 2014**<br><br>**USA**<br><br>**Prospective observational study** | NA | 2,275 participants from Trials of Hypertension Prevention (TOHP) phases I and II, recruited over 1897-1995, aged 30-54 years, with prehypertension who received no active treatment (i.e. control group). | Associations between urinary sodium excretion, (averaged across 3-7, 24-hr urine collections) over the study period (18 months in TOHP I, 3-4 yrs TOHP II), and cardiovascular risk over 10-15 years of follow-up. Models were adjusted for | Cardiovascular disease or CVD-associated mortality | There were 193 CVD events or death (including 22 strokes).<br><br>The reference category for sodium excretion was 3600-4800 mg/day.<br><br>The risks of the primary outcome among the sodium excretion groups for Model 1 were:<br><2300 mg/day: HR=0.92, 95% CI 0.53-1.60<br>2300-<3600 mg/day: HR=0.80, 95% CI |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | age, sex, race other treatment assignments (Model 1) and additional confounders in Models 2 and 3. | | 0.56-1.13)<br>≥4800 mg/day: HR=1.11, 95% CI 0.75-1.64, p for trend =0.18.<br><br>Per 1000 mg/day increase in sodium excretion HR=1.13, 95% CI 1.00-1.27, p=0.044. |
| **Graudal et al. 2014**<br><br>**Denmark**<br><br>**Meta-analysis** | NA | 23 cohort studies (n=274,683) including all individuals (healthy and those with diseases, all ages, sex and race). Studies in which participants had been advised to reduce their sodium consumption were excluded. | The relationship between sodium intake and cardiovascular events was examined. Sodium intakes from participants in individual studies were classified as low sodium (mean usual intake <115 mmol), usual sodium (mean daily intake of 115–215 mmol) and high sodium (mean daily intake >215 mmol). Sodium intake was assessed using 24-hour urine secretions, spot urine secretions, or dietary anamnesis (dietary recalls, food frequency questionnaires). | **Primary outcome:**<br>All-cause mortality, cardiovascular disease events<br><br>**Secondary outcomes:**<br>Stroke, heart disease<br><br>In most studies, analyses were adjusted for sex, age, body mass index, smoking, alcohol, diabetes, CVD, BP, HTN, use of diuretics, intake of total energy, potassium, cholesterol, and education. | Usual sodium intake was associated with a significantly lower risk of all-cause mortality compared with low-sodium intake (HR=0.91, 95% CI 0.82-0.99, p=0.04).<br><br>Usual sodium intake was associated with a significantly lower risk of all-cause mortality and cardiovascular events, combined compared with low-sodium intake (HR=0.90, 95% CI 0.82-0.99, p=0.02).<br><br>Usual sodium intake was not associated with a lower risk of stroke events or stroke mortality, combined compared with low-sodium intake (HR=1.04, 95% CI 0.96-1.13, p=0.33).<br><br>High-sodium intake was associated with a significantly higher risk of all-cause mortality compared with usual sodium intake (HR=1.16, 95% CI 1.03-1.30, p=0.01).<br><br>High-sodium intake was associated with a significantly higher risk of all-cause mortality and cardiovascular events, combined compared with high-sodium intake (HR=1.12, 95% CI 1.02-1.24, p=0.02).<br><br>High-sodium intake was associated with a significantly increased risk of stroke events or stroke mortality, combined compared with usual-sodium intake (HR=1.18, 95% CI 1.05-1.33, p=0.006 |
| **Mozaffarian et al. 2014**<br><br>**International** | NA | Data from national surveys, Cochrane reviews, prospective cohort studies, controlled trials, dietary | Data from various sources were used to: estimate global sodium consumption, estimate | See methods | In 2010, the mean global level of sodium intake was estimated to be 3.95 g/day.99% of all adults in the world had estimated sodium intakes exceeding the WHO recommendations of 2.0 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Survey data analysis** | | recommendations and data from the Global Burden of Disease study were used. | the effects of reduced sodium intake on blood pressure, calculate the effects of blood pressure levels on mortality, establish a reference level for sodium intake, and to examine the relationship between CVD mortality and sodium intake above the reference level. | | g/day.<br><br>Mean global systolic blood pressure was 134, 95% CI 124-144 mm Hg.<br><br>To estimate CVD mortality attributed to excessive sodium intake, a reference level of 2.0‡2.0 g sodium/day was used.<br><br>Each reduction in sodium intake of 2.3 g/day was associated with a reduction of 3.82 mm Hg.<br><br>Worldwide, an estimated 1.65, 95% CI 1.0-2.2 million deaths were attributed to sodium intake above the reference level, of which 685K (42%) were caused by stroke.<br><br>9.5% of all CVD was attributed to sodium consumption. |
| **O'Donnell et al. 2014**<br><br>**International**<br><br>***Prospective observational study (PURE)*** | NA | 156,424 participants aged 35-70 years, living in 17 countries, were recruited (starting in 2003) to the prospective Urban Rural Epidemiological (PURE) study.<br><br>For this analysis, a morning midstream urine sample was available from 101,945 persons. Mean age was 51 years, 42.5% male, 41.5% of participants were hypertensive | The association between dietary sodium intake (estimated from urinary sodium and potassium excretion) and health outcomes was explored, adjusted for age, sex, education, ancestry (Asian vs. non-Asian), ETOH use (former vs. current vs. non), diabetes, BMI, history of CVD, and smoking status) in the primary analysis | Composite of death/major cardiovascular events<br><br>Mean length of follow-up was 3.7 years. | The primary outcome occurred in 3317 (3.3%) participants<br><br>The reference category for estimated sodium excretion was 4.00-5.99 g/day. (x 2.5 to convert to estimated sodium intake).<br><br>The risks of the primary outcome among the sodium excretion groups were:<br>**<3.0 g/day: OR=1.27, 95% CI 1.12-1.44**<br>3.00-3.99 g/day: OR=1.01, 95% CI 0.93-1.09)<br>6.00-6.99 g/day: OR=1.05, 95% CI 0.94-1.17<br>**≥7.00 g/day: OR=1.15, 95% CI 1.02-1.30**<br><br>The pattern of results was similar when additional confounders were controlled for (LD:HDL, dietary factors/blood pressure, excluding CVD at baseline, excluding cancer and restricted to very low-risk cohort).<br><br>The risks of al-cause mortality among the sodium excretion groups were:<br>**<3.0 g/day: OR=1.39, 95% CI 1.12-1.72**<br>**3.00-3.99 g/day: OR=0.82, 95% CI 0.69-0.99** |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | 6.00-6.99 g/day: OR=1.13, 95% CI 0.93-1.37<br>≥7.00 g/day: OR=1.16, 95% CI 0.95-1.43<br><br>The risks of all stroke among the sodium excretion groups were:<br>**<3.0 g/day: OR=1.38, 95% CI 1.15-1.66**<br>3.00-3.99 g/day: OR=1.09, 95% CI 0.96-1.24<br>6.00-6.99 g/day: OR=1.02, 95% CI 0.89-1.18<br>**≥7.00 g/day: OR=1.25, 95% CI 1.07-1.48**<br><br>Higher urinary potassium excretion (>3 g/day) was associated with reduced risks of all-cause mortality (OR= 0.62, 95% CI 0.49- 0.77), major cardiovascular events (OR= 0.87, 95% CI 0.72-1.06) and cardiovascular death (OR= 0.48, 95% CI 0.32- 0.71).<br><br>In sub group analysis, the risk of the primary outcome was increased significantly for persons with HTN and estimated sodium excretion >6 g/day (OR= 1.17, 95% CI 1.04- 1.31) vs. no HTN and estimated sodium excretion > 6g/day (OR=0.89, 95% CI 0.78- 1.03), p for interaction=0.02.<br><br>There were no other significant interactions among sub groups. |
| **Stolarz-Skrzypek et al. 2011**<br><br>**Belgium**<br><br>**Observational study** | NA | 3,681 participants without cardiovascular disease (CVD), who were included in the EPOGH and FLEMENGHO studies. The mean age of participants was 40.9 years. 52.7% were female. 25.8% had hypertension at baseline. | Baseline measurements included blood pressure, 24-hour urine collection, weight, medical history, demographics. 1-3 follow-up visits were conducted | Mortality, fatal and non-fatal cardiovascular events | Median follow-up of 7.9 years.<br><br>There were 219 deaths (84 cardiovascular and 135 noncardiovascular). Of these, there were 20 fatal and 13 non-fatal strokes.<br><br>Across sodium excretion tertiles (low: mean 106 mmol, medium: mean 165 mmol, high: 250 mmol), there was no increased risk of all-cause mortality (p=0.10).<br>Low: adjusted HR=1.14, (95% CI 0.87-1.50)<br>Medium: adjusted HR=0.94 (95% CI 0.75-1.18)<br>High: adjusted HR=1.06 (95% CI 0.84-1.33)<br><br>There was a decrease in cardiovascular mortality with increasing sodium excretion (p=0.02) |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | Low: adjusted HR=1.56 (95% CI 1.02-2.36), p=0.04<br>Medium: adjusted HR=1.05 (95% CI 0.72-1.53)<br>High: adjusted HR=0.95 (95% CI 0.66-1.38)<br><br>There was no increase in the risk of fatal/non-fatal stroke (p=0.64)<br>Low: adjusted HR=1.07 (95% CI 0.57-2.00)<br>Medium: adjusted HR=1.29 (95% CI 0.75-2.200<br>High: adjusted HR=0.78 (95% CI 0.45-1.33)<br><br>There was no increase in stroke mortality risk in subgroup analysis examining age (<60 years and ≥60 years) |
| **Strazzullo et al. 2009**<br><br>**Italy**<br><br>**Systematic review & meta-analysis** | NA | 13 prospective cohort studies (n=177,025) in which dietary sodium intake was estimated at baseline and subjects were followed for at least 3 years.<br><br>11 studies included both men and women while 2 only included men. | Sodium intake was estimated using a 24-hour recall (n=3), 24-hr urine collection (n=4), food frequency questionnaire (n=3), household survey questionnaire (n=1) and multiple methods (n=2). | Risk of stroke, risk of cardiovascular disease.<br><br>Classification of salt intake varied across studies (continuous variable, quartiles, quintiles), therefore, where possible, the authors compared "higher" versus "lower" intakes based on the categories in which salt intake differed by an average of 100 mmol (6 grams/day) | Follow-up ranged from 3.5 to 19 years.<br><br>Higher salt intake was associated with increased risk of stroke (RR=1.23, 95% CI 1.06 to 1.43, p=0.007). Results from 10 studies included<br><br>Higher salt intake was associated with a trend towards increased risk of cardiovascular disease (RR=1.14, 95% CI 0.99 to 1.32, p=0.07). Results from 9 studies included. |

## Interventions Designed to Reduce Sodium intake

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Adler et al. 2014**<br><br>**UK**<br><br>**Cochrane** | NA | 8 RCTs including 3 in healthy, normotensive individuals (n= 3518), 2 in persons with hypertension and 3 in mixed populations of | Trials examined interventions designed to reduce dietary salt intake, either by advice from health professionals (n=6) or provision of low-sodium | **Primary outcomes:**<br>All-cause mortality, cardiovascular mortality, cardiovascular morbidity<br><br>**Secondary outcomes:** | Dietary sodium reduction was not associated with a reduced risk of all-cause mortality at end of trial: RR= 0.96, 95% CI 0.83-1.10. (Results from 7 trials included). There was not associated risk reduction when trials of normotensive (n=3) or hypertensive (n=4) persons were examined separately. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **review** | | normo- and hypertensives, who were both treated and untreated for HTN. | salt substitution (n=2) versus usual care, control or placebo diet, or no intervention.<br><br>Sodium reduction goals varied from 70-100 mmol/day urinary sodium | Changes in SBP and DBP, urinary salt excretion (or other method of estimation of salt intake), Health-related quality of life<br><br>Trial durations ranged from 7 to 36 months with additional follow-up ranging from 30 months to 11.5 years. | Dietary sodium reduction was not associated with a reduced risk of all-cause mortality at end of follow-up in trials of normotensive persons (RR= 0.90, 95% CI 0.58-1.40, results from 3 trials included), nor in trials with hypertensive persons (RR= 0.99, 95% CI 0.87-1.14, results from 5 trials included).<br><br>Dietary sodium reduction was associated with a reduced risk of cardiovascular events at the end of follow-up: RR= 0.77, 95% CI 0.63-0.95. Results from 6 trials included). However, when the trials of normotensive and hypertensive persons were examined separately, there was a non-significant risk reduction.<br><br>There was a significant reduction in SBP (mean difference= -1.79, 95% CI -3.23 to -0.36, results from 6 trials) and DBP (mean difference= -1.17,95% CI -2.08 to -0.2, results from 5 trials) |
| **Taylor et al. 2011**<br><br>**UK**<br><br>**Systematic review & meta-analysis** | NA | 7 RCTs (n=6,491) that included adults who were both normotensive and hypertensive. Mean age ranged from 39 to 75 years. In 2 studies 100% of subjects were male.<br><br>Subjects were on antihypertensive medications in 3 trials. | Intervention group received group or individual counseling and behaviour change programs to reduce dietary sodium (n=6) or ate high potassium (low sodium) prepared foods. Average duration was 6 months (n=2), 18 months (n=1), 31 months (n=1), 36 months (n=20 and was unclear in one study. Sodium excretion goals were set at <70-100 mmol/day.<br><br>Subjects in the control group did not receive dietary instruction (n=3) or were given general guidelines for healthy eating (n=1), attended | All-cause mortality at end of trial, cardiovascular disease, systolic blood pressure (SBP), diastolic blood pressure (DBP)<br><br>Follow-up ranged from 6 months to 12.7 years. | All-cause mortality at end of trial:<br>Among subjects who were normotensive at baseline: RR=0.67, 95% CI 0.40 to 1.12, p=0.13. Results from 3 trials included.<br><br>Among subjects who were hypertensive at baseline: RR=0.97, 95% CI 0.83 to 1.13, p=0.72. Results from 2 trials included.<br><br>All-cause mortality at end of follow-up:<br>Normotensive: RR=0.90, 95% CI 0.58 to 1.40, p=0.64. Results from 3 trials included.<br>Hypertensive: RR=0.96, 95% CI 0.83 to 1.11, p=0.61. Results from 3 trials included.<br><br>CVD mortality at longest follow-up<br>Normotensive: no data<br>Hypertensive: RR=0.69, 95% CI 0.45 to 1.5, p=0.08. Results from 2 trials included<br><br>CVD events at longest follow-up<br>Normotensive: RR=0.71, 95% CI 0.42 to1.20, p=0.20. Results from 2 trials included |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | group meetings without dietary counseling (n=1), received same dietary advice as subjects in treatment arm + additional 40 mmol sodium/day (n=1) or ate prepared foods containing usual salt (high sodium). | | Hypertensive: RR=0.84, 95% CI 0.57 to 1.23, p=0.38. Results from 2 trials included.<br><br>SBP at end of trial<br>Normotensive: Mead difference= -1.11, 95% CI -2.34 to 0.11 mm Hg, p=0.007. Results from 3 trials included<br>Hypertensive: MD=-4.14, 95% CI -5.84 to -2.43 mm Hg, p<0.0001. Results from 2 trials included.<br><br>DBP at end of trial<br>Normotensive: MD= -0.80, 95% CI -1.37 to -0.23 mm Hg, p=0.006. Results from 3 trials included<br>Hypertensive: MD= -3.74, 95% CI -0.41 to 0.93 mm Hg, p=0.12. Results from 2 trials included.<br><br>Urinary sodium was reduced by 34 mmol in normotensives and 39 mmol in hypertensives. |
| **Hooper et al. 2004**<br><br>**UK**<br><br>**Cochrane review** | NA | 11 RCTs including 3 trials in normotensives (n=2,326), 5 in untreated hypertensives (n=387) and 3 in treated hypertensives (n=801)<br>Subjects in all studies were adult (≥16 years)<br>Persons who were institutionalized, acutely ill or pregnant, were excluded.<br><br>Most trials included both men and women. | Comparison of interventions designed to reduce dietary sodium intake that lasted at least 6 months compared with placebo or no intervention. Studies that included multiple risk factor intervention programs that included a salt reduction component, were excluded.<br><br>Interventions: comprehensive diet and behavior change programs including individual or group counseling sessions, with provision of written materials, and/or instruction on reducing sodium in cooking or provision of low salt diets. Programs lasted several | Mortality, cardiovascular mortality, systolic blood pressure (SBP), diastolic blood pressure (DBP) | Follow-up ranged from 6 months to 7 years.<br>At the end of follow-up, there were 17 deaths (1 from stroke)<br><br>Mortality: RR= 0.90, 95% CI 0.36- 2.24, p=0.82. Results from 4 studies included.<br><br>Cardiovascular mortality: RR= 0.82, 95% CI 0.56-1.21, p=0.32. Results from 2 studies included.<br><br>SBP: Mean difference= -1.12, 95% CI -1.83, -0.41, p=0.0020. Results from 4 studies with 13 to 60 months of follow up were included.<br><br>DBP: MD= -0.62, 95% CI -1.54, 0.31, p=0.19. Results from 4 trials with 13 to 60 months of follow up were included.<br><br>Urinary sodium excretion. Mean difference= - 35.5 mmol/ 24 hours, 95% CI -47.2 to -23.9, p<0.0001. Results from 4 studies that assessed outcome 13 to 60 months following initiation of intervention were included. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | months. Treatment goals were urinary sodium excretion of 70-100 mmol/day. | | |

## Physical Exercise and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **O'Donnell et al. 2016**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 2**<br><br>**Case-control study** | NA | Participants were recruited from 32 countries from 2007-2015.<br><br>Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women.<br><br>13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Persons were considered to be physically active (PA) if they engaged in moderate (walking, cycling, gardening) or strenuous (jogging, football, swimming) leisure activity for 4 hours or more per week | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) | Regular physical activity was associated with a reduced risk of stroke<br><br>Total stroke: OR=0.60, 99% CI 0.52-0.70, PAR 35.8%, 99% CI 27.7-44.7%<br><br>Ischemic stroke: OR=0.63, 99% CI 0.53-0.74, PAR 33.4%, 99% CI 24.2-44.0%<br><br>Hemorrhagic stroke: OR=0.63, 99% CI 0.48-0.81, PAR 34.6%, 99% CI 21.3-50.7%<br><br>The results were similar for men and women in sub group analysis (PAR: men 37.3%, 99% CI 28.1-47.5% and women PAR 32.4%, 99% CI 18.4-50.4%) |
| **O'Donnell et al. 2010**<br><br>**Canada (International)**<br><br>**INTERSTROKE** | NA | Participants were recruited from 22 countries from 2007-2010.<br><br>Cases were 3,000 persons admitted to | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)<br><br>Results were adjusted for | Regular physical activity was associated with a reduced risk of total or ischemic stroke<br><br>Total stroke: OR=0.69, 99% CI 0.53-0.90, PAR 28.5%, 99% CI 14.5-48.5%<br><br>Ischemic stroke: OR=0.68, 99% CI 0.51-0.91, PAR |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Phase 1**<br><br>**Case-control study** | | hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women<br><br>3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | collected using questionnaires, physical examinations and blood and urine samples. Persons were considered to be physically active (PA) if they engaged in moderate (walking, cycling, gardening) or strenuous (jogging, football, swimming) activity for 4 hours or more per week | age, sex, and region | 29.4%, 99% CI 14.5-50.5%<br><br>Hemorrhagic stroke: OR=0.70, 99% CI 0.44-1.13, PAR 27.6%, 99% CI 6.8-66.6% |
| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including low physical activity, defined as average weekly work, home, transport-related, and recreational physical activity of less than 8000 metabolic equivalent of task-min) in high-income countries and low-income and middle-income countries. | Stroke burden (expressed as DALYs) | Globally, 7.7% (95% uncertainty interval 5.6%-9.2%) of the stroke burden was attributed to low physical activity.<br><br>In high income countries, 11.2% (95% uncertainty interval 8.3%-13.1%) of the stroke burden was attributed to low physical activity.<br><br>**In Canada, 10.9% (95% uncertainty interval 7.4%-14.6%) of the stroke burden was attributed to low physical activity**<br><br>Globally, during the study period, there was an increase of 39.2% (95% UI 36.1%-41.8%) in the burden of stroke related to low physical activity. |
| **Pandey et al. 2016**<br><br>**USA**<br><br>**Retrospective** | NA | 19,815 participants of the Cooper Centre Longitudinal Study (CCLS) who had undergone a comprehensive | Cardiorespiratory fitness (CRF) was measured during a baseline examination, using a treadmill exercise and classified according to | Stroke rate, stroke risk<br><br>Models were adjusted for fitness, baseline age, sex, BMI, cholesterol, diabetes, smoking SBP, and age | After 129,436 person-years of follow-up, there were 808 hospitalizations for stroke (683 men, 125 women)<br><br>Stroke rate/1,000 person-years<br>**Men**<br>Low fitness: 9.4 (95% CI 8.2-10.9) |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **study** | | examination from 1970-2009, without a history of stroke, and who were eligible for coverage under Medicare from 1999-2009. | age and sex norms into quintiles representing low (Q1) intermediate (Q2-3) and high fitness levels (Q4-5). Inpatient Medicare claims for hospitalization associated with stroke were linked with the CCLS participants and the association between midlife CRF (measured as metabolic equivalents) and incident stroke was assessed. | difference between first and recurrent stroke) | Intermediate: 6.8 (95% CI 6.0-7.6)<br>High: 5.2 (95% CI 4.5-6.0)<br><br>**Women**<br>Low fitness: 9.2 (95% CI 6.6-12.8)<br>Intermediate: 4.5 (95% CI 3.4-6.0)<br>High: 3.4 (95% CI 2.5-4.6)<br><br>Risk of stroke<br>Low fitness: Reference<br>Intermediate: HR=0.75, 95% CI 0.62-0.91, p=0.003<br>High: HR=0.61, 95% CI 0.49-0.76, p<0.0001<br>Per 1 MET higher fitness: HR=0.92, 95% CI 0.88-0.96, p<0.0001. |
| **Armstrong et al. 2015**<br><br>**UK**<br><br>**Prospective study** | NA | 1.1 million women, aged 50-64 years, without previous history of vascular disease or invasive cancer, who were participants of the Million Women Study, investigating how various reproductive and lifestyle factors affect women's health.<br><br>The mean age was 56 years, mean BMI was 26.0 | The associations between the frequency, duration and type of physical activity (PA) and the risk of incident CVD were examined.<br><br>PA was assessed at baseline and 3 years later using a self-reported questionnaire. The results were used to estimate metabolic equivalent (MET) hours for walking, gardening, cycling, strenuous activity, and housework. | Incident CHD, CVD (including SAH, ICH and ischemic stroke) and DVT<br><br>Analyses were adjusted for BMI, age, smoking, alcohol, region and SES and excluded the first4 years of follow-up | Mean duration of follow-up was 9 years. During this time there were 17,822 cardiovascular events.<br><br>Compared with women who rarely/never engaged in **strenuous activity** (reference group), those who did so once a week, 2-3 x/week and 4-6 x/week had significantly reduced risk of CVD. There was no risk reduction for those who exercised strenuously, daily.<br><br>Compared with women in the reference group, those who engaged in **any activity** (1x/week, 2-3x/week, 4-6x/week or daily had a significantly reduced risk of CVD.<br><br>Compared with women in the reference group, those who engaged in **strenuous activity**, those who did so once a week, and 2-3 x/week had a significantly reduced risk of ICH. There was no significant risk reduction for those in the 4-6 x/week and daily strenuous exercise groups.<br><br>Compared with women in the reference group, those who engaged in any **strenuous activity** (1x/week, 2-3x/week, 4-6x/week or daily had a significantly reduced risk of ischemic stroke.<br><br>Compared with women in the reference group, those who engaged in **any activity** (1x/week, 2-3x/week, 4-6x/week or daily had a significantly reduced risk of |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | ischemic stroke. |
| **McDonnell et al. 2013**<br><br>***Reasons for Geographic and Racial Differences in Stroke study (REGARDS)***<br><br>**Australia & US**<br><br>**Prospective cohort study** | NA | 30,239 US residents, aged ≥45 years (mean 65 years). 58% had hypertension and 21%, diabetes | To assess physical activity level, participants were asked the question: *"How many times per week do you engage in intense PA, enough to work up a sweat?"* Possible responses were: 1 (no times per week), 2 (1 to 3 times per week, and 3 (4 or more times per week)<br><br>Participants were contacted every 6 months by phone. | Incident stroke/TIA<br><br>Analyses were adjusted for i) age, sex, race, and age–race interaction, ii) then for income and education and iii) then for stroke risk factors (diabetes mellitus, hypertension, body mass index, alcohol use, and smoking status). | Mean follow-up was 5.7 years.<br><br>There were 918 confirmed strokes and cases of TIA.<br><br>Compared with persons exercising ≥4x/week, the risk of stroke was increased in persons who engaged in no physical activity (partially adjusted HR= 1.20, 95% CI, 1.02–1.42)<br><br>The risk was no longer significant after adjusting for traditional stroke risk factors (HR=1.14, 95% CI 0.95-1.37)<br><br>Compared with persons exercising 1-3x/week, the risk of stroke was increased in persons who engaged in no physical activity (partially adjusted HR=1.16, 95% CI, 0.98–1.42). |
| **Sattelmair et al. 2010**<br><br>**USA**<br><br>**Prospective follow-up of RCT** | NA | 39,315 healthy women who had been participants of the Women's Health Study (1992-1995).<br><br>The mean age at baseline was 54 years. 55% were post-menopausal, 29% had a history of hypertension, 3.4%, diabetes and 32%, high cholesterol. | At baseline, participants were asked to estimate the amount of time they spent weekly during the past year on 8 groups of recreational activities.<br><br>There were 8 response categories, ranging from 0-≥7 hours.<br><br>Physical activity (PA) information was updated at 36, 72, and 96 months during the trial, at the end of the trial (mean of 125 months) and 24 months later.<br><br>Weekly energy expenditures were estimated and grouped (<200, 200 to 599, 600 to 1499, or ≥1,500 kcal/week | Incidence of fatal and non-fatal stroke.<br><br>Analyses were partially and fully adjusted for potential confounders including i) age and treatment group, ii) + smoking, alcohol, saturated fat, fruit and vegetable, and fiber intake, postmenopausal hormone therapy, menopausal status, parental history of myocardial infarction, and migraine aura, iii) + BMI, history of diabetes, history of elevated cholesterol, and history of hypertension. | Mean duration of follow-up was 11.9 years.<br><br>There were 579 total strokes (473 ischemic, 102 hemorrhagic and 4 of unknown etiology).<br><br>Increasing amount of time spent in PA was not associated with decreased total stroke risk (p for trend=0.21).<br><br>Compared with reference category (<200 Kcals/week)<br>200-599 Kcals/week: fully adjusted RR=1.16, 95% CI 0.91-1.48<br>600-1499 Kcals/week: fully adjusted RR=0.93, 95% CI 0.72-1.20<br>≥1500 Kcals/week: fully adjusted RR=0.89, 95% CI 0.68-1.17<br><br>In fully adjusted models, similar results were reported for ischemic and hemorrhagic stroke. There was no significant decrease in stroke risk.<br><br>Women who engaged in vigorous PA did not have a reduced risk or total stroke, ischemic stroke or |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | of physical activity. | | hemorrhagic stroke (p for trend=0.99, 0.84, 0.64, respectively) in fully adjusted models.<br><br>Among women who did not engage in vigorous physical activity, those who walked ≥2 hours per week had a 30% lower risk of any stroke than women who did not walk (fully adjusted RR=0.70 95% CI, 0.52 to 0.94). Women who reported walking at a brisk pace (4.8 km/hour) also had a 37% lower risk (fully adjusted RR=0.63, 95% CI, 0.44 to 0.91) compared with women who did not walk. |
| **Willey et al. 2009**<br><br>**USA**<br><br>**Prospective cohort study** | NA | 3,298 participants of the Northern Manhattan Study. Mean age was 69 years at baseline. 63% were female. 74% were diagnosed with hypertension, 22% had diabetes | Physical activity (PA) was assessed using an in-person questionnaire. The duration and frequency of PA during the preceding 2-week period was recorded and enquires were made as to whether this level of PA was typical. PA was categorized as light, moderate and heavy intensity based on metabolic equivalents (MET), which was used to calculate energy expenditure. | Incident ischemic stroke<br><br>Analysis was adjusted for: age, sex, race/ethnicity, education, insurance status, hypertension, diabetes, moderate alcohol intake, and tobacco use. | Median duration of follow-up was 9.1 years.<br><br>There were 238 incident ischemic strokes<br><br>In the fully adjusted models, the risk of stroke associated with PA was:<br>Any vs. none: HR=0.86, 95% CI 0.66-1.13<br>Light vs. none: HR=0.94, 95% CI 0.71-1.25<br>Moderate/heavy vs. none: HR=0.65, 95% CI 0.43-0.98<br>Moderate/heavy vs. light/none: HR=0.68, 95% CI 0.46-0.99<br><br>There was an interaction between moderate to heavy PA and sex whereby increased PA was protective for stroke in men (adjusted HR=0.37, 95% CI 0.18-0.77), but not for women.<br><br>When PA was expressed in terms of Kcals/week, a 500 Kcal/week increase was not associated with decreased stroke risk in those engaged/not engaged in moderate to heavy PA. |
| **Lee et al. 2003**<br><br>**USA**<br><br>**Systematic review & meta-analysis** | NA | 23 studies (18 cohort and 5 case-control), published from 1966-2002, were included.<br><br>Studies included females only (n=3), males only (n=10) and both sexes (n=10). Mean baseline age varied widely among | Physical activity (PA) intensity was classified as low, moderate and high | Incident stroke<br><br>Common covariates adjusted for in the analyses of the included studies were: age, smoking status, dietary intake, alcohol intake, BMI, history of hypertension, high cholesterol, and diabetes | In the prospective studies, the mean follow-up of included studies ranged from 2-26 years.<br><br>Compared with low PA, high PA was associated with a reduced risk of total stroke (adjusted RR=0.73, 95% CI 0.67-0.79, p<0.001). Results from 23 studies included. Increased PA was also associated with reduced risk of ischemic and hemorrhagic strokes (RR= 0.79, 95% CI 0.69-0.91, p<0.001-results from 6 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | studies. | | mellitus | studies included and RR=0.66, 95% CI 0.49-0.91, p<0.001-results from 3 studies included).<br><br>Result patterns were similar for the comparison of low vs. moderate PA. Increased PA significantly reduced the risk of total stroke, ischemic stroke and hemorrhagic stroke. |

## Weight and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **O'Donnell et al. 2016**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 2**<br><br>**Case-control study** | NA | Participants were recruited from 32 countries from 2007-2015.<br><br>Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women.<br><br>13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Waist-to-hip ratio was expressed in tertiles, based on the overall control data. Cut-off points used were 0.91 and 0.97, for men and 0.86 and 0.93, for women. | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) | Increasing waist-to-hip ratio was associated with increased risk of stroke (T1=reference)<br><br>**T2 vs. T1**<br>All stroke: OR=1.24, 99% CI 1.11-1.39<br>Ischemic stroke: OR=1.31, 99% CI 1.14-1.49<br>Hemorrhagic stroke: OR=1.16, 99% CI 0.98-13.9<br><br>**T3 vs. T1**<br>All stroke: OR=1.44, 99% CI 1.27-1.64; PAR 18.6%, 99% CI 13.3-25.3%<br>Ischemic stroke: OR=1.44, 99% CI 1.25-1.67; PAR 20.4%, 99% CI 14.3-28.2%<br>Hemorrhagic stroke: OR=1.33, 99% CI 1.09-1.62; PAR 13.1%, 99% CI 6.4-25.1%<br><br>In sub group analyses, PARs were higher for women (T2+T3 vs. T1: 25.8%, 99% CI 18.3-35.1% compared with men 12.7%, 99% CI 6.4-23.7%) |
| **O'Donnell et al. 2010**<br><br>**Canada** | NA | Participants were recruited from 22 countries from 2007-2010.<br>Cases were 3,000 | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population | Increasing weight-to-hip ratio was associated with increased risk of stroke (T1=reference)<br><br>**T2 vs. T1**<br>All stroke: OR=1.42, 99% CI 1.18-1.71, PAR 26.5%, |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **(International)**<br><br>**INTERSTROKE Phase 1**<br><br>**Case-control study** | | persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women<br>3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Waist-to-hip ratio was expressed in tertiles, based on the overall control data. Cut-off points used were 0.91 and 0.96, for men and 0.86 and 0.93, in women. | attributable risk (PAR)<br><br>Results were adjusted for age, sex, and region | 99% CI 18.8-36.0%<br><br>Ischemic stroke: OR=1.34, 99% CI 1.10-1.64<br><br>Hemorrhagic stroke: OR=1.62, 99% CI 1.22-2.23<br><br>**T3 vs. T1**<br>All stroke: OR=1.65, 99% CI 1.39-1.99<br><br>Ischemic stroke: OR=1.69, 99% CI 1.38-2.07<br><br>Hemorrhagic stroke: OR=1.41, 99% CI 1.02-1.93 |
| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including high BMI, defined as >23.0) in high-income countries and low-income and middle-income countries | Stroke burden (expressed as DALYs) | Globally, 23.5% (95% uncertainty interval 20.7%-26.1%) of the stroke burden was attributed to a high BMI.<br><br>In high income countries, 28.4% (95% uncertainty interval 25.7%-29.71%) of the stroke burden was attributed to a high BMI.<br><br>**In Canada, 28.4% (95% uncertainty interval 24%-33%) of the stroke burden was attributed to a high BMI.**<br><br>Globally, during the study period, there was an increase of 46.4% (95% UI 46.1%-48.3%) in the burden of stroke related to a high BMI. |
| **Twig et al. 2016**<br><br>**Israel**<br><br>**Retrospective study** | NA | 2.3 million adolescents, aged 16-19 years, included in a national database (1967-2010). Mean age was 17.3 years, 60% were male | BMI was calculated using measured height and weight. Additional information was collected on SES, education and origin of birthplace. BMI was grouped by percentile (<5$^{th}$, 5$^{th}$-24$^{th}$, 25$^{th}$-49$^{th}$, 50$^{th}$-74$^{th}$, 75$^{th}$-84$^{th}$, 85$^{th}$-94$^{th}$ and ≥95$^{th}$). Follow up ceased in 2011. Underlying cause of death | **Primary outcomes:**<br>Deaths attributed to coronary heart disease, stroke, sudden death and death from unknown cause<br><br>Analyses were adjusted for age, birth year, sex, SES, country of origin, education level and height. | During 42,297,007 person-years of follow-up, there were 32,127 deaths, including 528 from stroke.<br><br>Mean age at time of death from stroke was 46 years.<br><br>Compared with the reference category (BMI percentile 5$^{th}$ -24$^{th}$), the risk of death from stroke was significantly increased in the 3 highest BMI categories:<br>75$^{th}$-85$^{th}$: HR=1.42, 95% CI 1.03-1.97, p=0.034<br>85$^{th}$-94$^{th}$: HR=1.81, 95% CI 1.30-2.51, p<0.01<br>≥95$^{th}$: HR=2.64, 95% CI 1.72-4.08, p<0.001 |

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| | | | was coded using ICD 9th and 10th. | | The pattern of risk was similar for the outcomes of all-cause mortality and total cardiovascular death, although the risk was significantly increased in the 4 highest BMI categories (i.e ≥50th percentile). |
| **Li et al. 2015**<br><br>**USA**<br><br>**Prospective cohort study** | NA | 29,554 participants of the Louisiana State University Hospital-Based Longitudinal Study with newly diagnosed type 2 DM and with no previous history of stroke or CHD. | BMI was calculated using measured height and weight at baseline and at yearly intervals during follow-up and was evaluated using 5 categories, and as a continuous variable. | Stroke<br><br>Analyses were adjusted for age, sex, smoking, income, type of insurance, and other risk factors (LDL cholesterol, systolic blood pressure, HbA1c, estimated glomerular filtration rate, history of atrial fibrillation, the use of antihypertensive drugs, glucose-lowering agents, and cholesterol lowering agents | Mean duration of follow-up was 8.3 yrs.<br><br>There were 2821 ischemic strokes and 109 ICH.<br><br>There was a significant, inverse association between stroke risk and increasing BMI.<br><br>Using baseline BMI:<br>18.5–24.9: Reference<br>25–29.9: HR=0.81, 95% CI 0.72-0.92<br>30–34.9: HR=0.77, 95% CI 0.68-0.87<br>35–39.9 HR=0.70, 95% CI 0.61-0.80<br>≥40: HR=0.64, 95% CI 0.56-0.74<br>The same pattern of results remained when BMI measurements obtained over the study period (mean of 15) were averaged and when BMI from the last visit were used.<br><br>The same pattern of results was observed for ischemic stroke and ICH.<br><br>When BMI was analyzed as a continuous variable, each increase in one increment above the ref category was associated with a decrease in stroke risk (HR=0.983, 95% CI 0.978-0.988).<br><br>There were significant interactions for: the use of glucose-lowering agents indicated a higher stroke risk among patients using oral hypoglycemic agents or not using hypoglycemic agents vs. those using insulin; and HbA1c levels indicated a higher risk among patients with HbA1c levels <7% vs. ≥7%. |
| **Joshy et al. 2014**<br><br>**Australia**<br><br>**Prospective** | NA | 266, 777 men and women aged ≥45 yrs included in the 45 and Up Study with no previous history of CVD. | BMI was calculated using self-reported height and weight and categorized as: 15–18.49 (underweight); 18.5– | First hospitalization for CVD, including IHD, stroke and heart failure<br><br>Analyses were adjusted for age, sex, region of residence, | Median duration of follow-up was 3.4 yrs, during which time there were 9,594 hospital admissions for CVD.<br><br>Among the BMI groups, there was no significant |

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| **cohort study** | | Median age was 58 yrs.60% of participants were overweight or obese | 19.99, 20–22.49 and 22.5–24.99 (normal weight); 25–27.49 and 27.5–29.99 (overweight); 30–32.49 and 32.5–50 kg (obese) | household income, education, smoking, alcohol intake and health insurance. | increase in the risks for hospitalizations due to stroke<br>BMI 15.0-19.99: HR=1.17, 95% CI 1.17-1.53<br>BMI 20.0-22.49: HR=1.00 (ref)<br>BMI 22.5-24.99: HR=1.08, 95% CI 0.90-1.29<br>BMI 25.0-27.49: HR=1.07, 95% CI 0.90-1.29<br>BMI 27.5-29.99 HR=1.14, 95% CI 0.94-1.38<br>BMI 30.0-32.49 HR=1.23, 95% CI 0.98-1.53<br>BMI 32.5-50 HR=1.04, 95% CI 0.82-1.32<br><br>The risks for all hospitalization due to hospitalizations for all CVD were significantly increased across all BMI groups compared with the ref group. |
| **Wu et al. 2014**<br><br>**Taiwan**<br><br>**Prospective study** | NA | 77,541 participants aged ≥65 yrs included in the Taipei Geriatric Health Examination Database.<br><br>Mean age was 73.1 yrs. 38.7% of participants were overweight or had, grade1, or 2-3 obesity. | BMI was calculated at baseline using height and weight, obtained during annual physical exam.<br><br>BMI was classified as underweight (BMI<18.5), normal weight (18.5≤BMI<25, reference category), overweight (25≤BMI<30), grade 1 obesity (30≤BMI<35), and grade 2–3 obesity (BMI≥35). | All-cause and CVD-associated mortality at 5 yrs.<br><br>Analyses were adjusted for age, sex, marital status, education, smoking, alcohol, exercise blood sugar, blood pressure and triglycerides. | Mean duration of follow-up was 3.3 yrs.<br><br>There were 3,842 (5%) deaths, of which 877 were CVD-associated deaths.<br><br>The HRs for CVD-associated mortality among the BMI groups were:<br>Underweight HR=1.79, 95% CI 1.39-2.29<br>Normal weight: ref<br>Overweight HR=0.83, 95% CI 0.71-0.97<br>Grade 1 obesity: HR=0.71, 95% CI 0.49-1.05<br>Grade 2-3 obesity HR=2.24, 95% CI 4.52<br>Grades 1 and 2-3 combined: HR=0.88, 95% CI 0.63-1.23. |
| **Saito et al. 2011**<br><br>**Japan**<br><br>**Prospective cohort study** | NA | 90,879 men and women aged 45-74 years with no history of stroke, cancer or ischemic heart disease. | BMI was calculated at baseline using self-reported height and weight and categorized into 6 groups (<19, 19.0-20.9, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, ≥30.0). Weight change over a 5-year period was also collected and categorized into 5 groups to capture weight loss (≥10%, 3-10%), stable (change <3%) and weight gain (3-10%, ≥10%). | The Hazard Ratio (HR) associated with all stroke, hemorrhagic and ischemic stroke and SAH and BMI and weight change for both men and women.<br><br>Analysis was adjusted for age, smoking status, education, alcohol intake, sports/physical activity, medications and history of diabetes or hypertension. | There were 2019 incident stroke events during the median 7.9 years of follow-up.<br><br>While higher baseline BMI and weight change over time was not a risk factor associated with any stroke they were significant risk factors in women. Baseline BMI >27.0 was associated with increased risk of total stroke and ischemic stroke. Baseline BMI ≥30.0 was associated with an increased risk of ICH (HR=2.50, 95% CI 1.47-4.24). Higher BMI was not a significant risk factor for SAH.<br><br>A ≥10% increase in weight in women was associated with increased risk of total stroke (HR=1.49, 95% CI 1.11-2.00) and ischemic stroke (HR=1.63, 95% 1.08-1.12). |

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| **Bazzano et al. 2010**<br><br>**US & China**<br><br>**Prospective cohort study** | NA | 154,736 Chinese men and women ≥ 40 years | Height and weight were measured at baseline, using a standardized protocol.<br><br>Weight categories included a BMI of <18.5, 18.5-24.9 (reference), 25.0-29.9, and ≥30 | Incidence of fatal and non-fatal stroke<br><br>Analysis were adjusted for age, gender, physical inactivity, urbanization, geographic region, cigarette smoking, education, and alcohol consumption | Mean duration of follow-up was 8.3years.<br><br>There were 7,489 incident strokes, 3,924 of which were fatal<br><br>The risk of stroke increased with increased BMI (p for linear trend<0.0001)<br><18.5: HR=0.86, 95% CI 0.80-0.93<br>25.0-29.9: HR=1.43, 95% CI 1.36-1.52<br>≥30: HR=1.72, 95% CI 1.55-1.91<br><br>The risk of ischemic stroke increased with increased BMI (p for linear trend<0.0001)<br><18.5: HR=0.76, 95% CI 0.66-0.86<br>25.0-29.9: HR=1.60, 95% CI 1.48-1.72<br>≥30: HR=1.89, 95% CI 1.66-2.16<br><br>The risk of hemorrhagic stroke increased with increased BMI (p for linear trend<0.0001)<br><18.5: HR=1.00, 95% CI 0.89-1.13<br>25.0-29.9: HR=1.18 95% CI 1.06-1.31<br>≥30: HR=1.54, 95% CI 1.27-1.87<br><br>The risk of fatal stroke increased with increased BMI (p for linear trend<0.0001)<br><18.5: HR=0.94, 95% CI 0.86-1.03<br>25.0-29.9: HR=1.15, 95% CI 1.05-1.25<br>≥30: HR=1.47, 95% CI 1.26-1.72 |
| **Hu et al. 2007**<br><br>**Finland**<br><br>**Prospective cohort study** | NA | 49,996 men and women, aged 25-74 years, at baseline, with no history of stroke or coronary heart disease.<br><br>(Participants were part of the WHO MONICA cohort).<br><br>Mean age at baseline was 45 years | BMI, waist circumference and waist-hip measures were obtained at baseline.<br><br>Body mass index was evaluated categorically (<18.5, 18.5-24.9 [reference], 25.0-29.9 and ≥30) and as a continuous variable. Waist circumference and waist-hip ratio were evaluated as sex-specific quartiles and, as a | Incident stroke (sex-specific total and by subtype)<br><br>Analysis were adjusted for age and study year (1972 vs. 1977), smoking, physical activity, educational level, family history of stroke, and alcohol consumption, systolic blood pressure, total cholesterol level, and history of diabetes mellitus | Mean duration of follow-up was 9.5 years.<br><br>There were 3,228 strokes (2,554 ischemic and 674 hemorrhagic).<br><br>The risk of all stroke and ischemic were increased in men with increasing BMI (p for trend <0.003 and <0.001, respectively), but not for hemorrhagic stroke (p for trend =0.98)<br>All stroke (BMI):<br><18.5: HR=0.80, 95% CI 0.20-3.21<br>25.0-29.9; HR=1.13, 95% CI 1.10-1.27<br>≥30: HR=1.32, 95% CI 1.14-1.53<br><br>The risk of all stroke and ischemic were increased in |

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| | | | continuous variable. | | women with increasing BMI (p for trend =0.04 and 0.02, respectively), but not for hemorrhagic stroke (p for trend =0.16).<br>All stroke (BMI):<br><18.5: HR=1.87, 95% CI 1.12-3.14<br>25.0-29.9; HR=1.02, 95% CI 0.90-1.16<br>≥30: HR=1.12 95% CI 0.97-1.29<br><br>Increased waist circumference was associated with an increased risk of total and ischemic stroke in men (p for trend<0.01 and <0.02, respectively) but not for hemorrhagic stroke (p for trend=0.53)<br>All stroke (by quartile with 1 as reference)<br>Q2: HR=1.31, 95% CI 0.89-1.91<br>Q3:HR=1.03, 95% CI 0.70-1.51<br>Q4: HR=1.57 95% CI 1.01-2.25<br><br>Increased waist circumference was not associated with increased risk of total (p for trend =0.96), ischemic (p for trend =0.65) or hemorrhagic stroke (p for trend=0.76) in women.<br><br>Increased waist-hip ratio was associated with an increased risk of total and ischemic stroke in men (p for trend<0.01 and <0.01, respectively) but not for hemorrhagic stroke (p for trend=0.41)<br>All stroke (by quartile with 1 as reference)<br>Q2: HR=0.96, 95% CI 0.64-1.44<br>Q3:HR=1.22, 95% CI 0.83-1.79<br>Q4: HR=1.55 95% CI 1.06-2.26<br><br>Increased waist-hip ratio was not associated with increased risk of total (p for trend =0.71), ischemic (p for trend =0.75) or hemorrhagic stroke (p for trend=0.86) in women. |
| **Jood et al. 2004**<br><br>**Sweden**<br><br>**RCT with follow-up** | NA | 7,402 males from the intervention group in the Multifactor Primary Prevention Study, which recruited participants from 1970-73. Those with previous stroke or MI were excluded. Average | Height and weight were measured at baseline, along with other lifestyle and stroke risk factor data. Patients were followed until 1998.<br><br>There were 6 BMI | Incident stroke, fatal stroke<br><br>In fully adjusted models, covariates included: age, smoking status, leisure time physical activity, parental history of stroke, psychological stress, | There were 875 incident strokes during follow-up (495 ischemic, 144 hemorrhagic and 234 of unknown etiology).<br><br>Increasing BMI was associated with increasing stroke risk (p for trend< 0.05)<br><br>Compared with baseline BMI group (20-22.49): |

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| | | age at baseline was 51.6 years. | categories: < 20.0, 20.0 to 22.49, 22.5 to 24.99, 25.0 to 27.49, 27.5 to 30.0, and >30.0 kg/m2 | occupation, diabetes, systolic blood pressure, treatment for hypertension, and serum cholesterol. | 22.5-24.99: HR=1.14,95% CI 0.89-1.45<br>25-27.49: HR=1.9, 95% CI 0.93-1.52<br>27.5-30.0: HR=1.31, 95% CI 1.00-1.71<br>>30: HR=1.52, 95% CI 1.13-2.06<br><br>A similar pattern of results was reported for ischemic stroke (p for trend<0.05) and unspecified stroke (p for trend<0.050, but not for hemorrhagic stroke (p for trend=0.85). |

## Alcohol Consumption and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **O'Donnell et al. 2016**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 2**<br><br>**Case-control study** | NA | Participants were recruited from 32 countries from 2007-2015.<br><br>Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women.<br><br>13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Alcohol use was classified as: never or former, low intake, moderate intake, and high (>14 drinks/week in women or >21 drinks/ week in men) or episodic heavy (>5 drinks in one episode at least once/month) intake | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) | Low or moderate ETOH intake was associated with significantly higher odds of stroke compared with former/never drinkers<br><br>All stroke: OR=1.14, 99% CI 1.01-1.28,<br>Ischemic stroke: OR=1.07, 99% CI 0.93-1.23<br>Hemorrhagic stroke: OR=1.43, 99% CI 1.17-1.74<br><br>High or heavy episodic drinking was associated with significantly higher odds of stroke compared with former/never drinkers<br><br>All stroke: OR=2.09, 99% CI 1.64-2.67, PAR 5.8%, 99% CI 3.49-9.7%<br>Ischemic stroke: OR=2.14, 99% CI 1.62-2.82; PAR 4.6%, 99% CI 20.-10.0%<br>Hemorrhagic stroke: OR=2.44, 99% CI 1.64-3.63; PAR 9.8%, 99% CI 6.4-14.8%<br><br>PARs were higher for men vs. women (light/moderate drinking vs former/never: 1.20%, 99% CI 1.05-1.37% vs. 0.92%, 99% CI 0.70-1.21) |
| **O'Donnell et al. 2010** | NA | Participants were recruited from 22 countries from | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic | Moderate alcohol consumption was associated with reduced risk of ischemic stroke and increased risk of hemorrhagic stroke compared with never/former |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| **Canada (International)**<br><br>**INTERSTROKE Phase 1**<br><br>**Case-control study** | | 2007-2010.<br>Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women<br>3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA) | ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Alcohol intake was classified as never/former drinker, moderate drinker (1-30 drinks/month), >30 drinks/month or binge drinker (>5 drinks/day at least once/month). | stroke (ICH) and population attributable risk (PAR)<br><br>Results were adjusted for age, sex, and region | drinkers.<br><br>All stroke: OR=0.90, 99% CI 0.72-1.11, PAR 3.8%, 99% CI 0.9-14.4%<br><br>Ischemic stroke: OR=0.79, 99% CI 0.63-1.00<br><br>Hemorrhagic stroke: OR=1.52, 99% CI 1.07-2.16<br><br>>30 drinks/month or binge drinking was associated with an increased risk of stroke compared with never/former drinkers.<br><br>All stroke: OR=1.51, 99% CI 1.18-1.92<br><br>Ischemic stroke: OR=1.41, 99% CI 1.09-1.82<br><br>Hemorrhagic stroke: OR=2.01, 99% CI 1.35-2.99 |
| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including any alcohol consumption) in high-income countries and low-income and middle-income countries | Stroke burden (expressed as DALYs) | Globally, 7.0% (95% uncertainty interval 5.6%-8.0%) of the stroke burden was attributed to alcohol use.<br><br>In high income countries, 9.6% (95% uncertainty interval 8.1%-10.7%) of the stroke burden was attributed to alcohol use.<br><br>**In Canada, 7.7% (95% uncertainty interval 4.8%-10.2%) of the stroke burden was attributed to alcohol use.**<br><br>Globally, during the study period, there was an increase of 32.4% (95% UI 31.1%-35.1%) in the burden of stroke related to alcohol use. |
| **Zheng et al. 2015**<br><br>**China**<br><br>**Systematic review & meta-analysis** | NA | 23 prospective cohort studies (n=489,696). Mean baseline age varied widely among studies. Duration of follow-up ranged from 5-20 yrs | The risk of cardiovascular outcomes and ETOH consumption were explored. | Coronary disease, total mortality, cardiac death, stroke and ischemic stroke. | Compared with the lowest or no ETOH groups, the risk of stroke was not significantly increased in **men** as ETOH consumption increased<br>Low: RR=0.89, 95% CI 0.79-1.00<br>Moderate: RR=0.91, 95% CI 0.81-1.02<br>Heavy: RR=1.19, 95% CI 0.93-1.52<br><br>The risk of ischemic stroke was decreased among |

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| | | | | | men who were light drinkers (RR=0.83, 95% CI 0.69-0.99).<br><br>Compared with the lowest or no ETOH groups, the risk of stroke was not significantly increased in **women** as ETOH consumption increased<br>Low: RR=0.89, 95% CI 0.79-1.06<br>Moderate: RR=0.79, 95% CI 0.69-0.91 (protective)<br>Heavy: RR=1.37, 95% CI 0.92-2.04<br><br>The risk of ischemic stroke was decreased among women who were light and moderate drinkers (RR=0.79, 95% CI 0.68-0.92 and RR=0.81, 95% CI 0.67-0.96). |
| **Zhang et al. 2014**<br><br>**China**<br><br>**Systematic review & meta-analysis** | NA | 27 prospective studies including 1,425,513 adult participants. 14 studies included only men, 3 included only women, 9 included both sexes and in one study the sex distribution was not reported | The risk of cardiovascular outcomes and ETOH consumption were explored across 4 exposure categories (no intake, low intake <15 g/day moderate 15-30 g/day and heavy).<br><br>Information on ETOH intake was obtained using self-administered questionnaires and food frequency questionnaires. | Total stroke, hemorrhagic stroke, ischemic stroke and stroke mortality | Duration of follow-up ranged from 6-35 years.<br><br>Compared with no intake, the risks of total stroke given increasing levels of ETOH intake were:<br>**Low ETOH: RR=0.85, 95% CI 0.75-0.95**<br>Moderate ETOH: RR=1.01, 95% CI 0.93-1.09<br>**Heavy ETOH: RR=1.20, 95% CI 1.01-1.43**<br><br>Compared with no intake, the risks of hemorrhagic stroke given increasing levels of ETOH intake were:<br>Low: RR=0.96, 95% CI 0.74-1.24<br>Moderate: RR=1.21, 95% CI 0.85-1.73<br>Heavy: RR=1.29, 95% CI 0.98-1.71<br><br>Compared with no intake, the risks of ischemic stroke given increasing levels of ETOH intake were:<br>**Low: RR=0.81, 95% CI 0.74-0.90**<br>Moderate: RR=0.89, 95% CI 0.78-1.02<br>Heavy: RR=0.96, 95% CI 0.77-1.19<br><br>Compared with no intake, the risks of stroke-related mortality given increasing levels of ETOH intake were:<br>**Low: RR=0.67, 95% CI 0.53-0.85**<br>Moderate: RR=0.93, 95% CI 0.81-1.06<br>Heavy: RR=0.95, 95% CI 0.78-1.15<br><br>The relationship between ETOH dose and stroke risk was j-shaped, with ETOH intake of 0-20 g/day |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | associated with a significant reduction and intakes above 40 g/day increasing the risk. |
| **Tikk et al. 2014**<br><br>**Germany**<br><br>**Prospective cohort study** | NA | 23,927 participants of the EPIC-Heidelberg cohort, aged 40-64 yrs. Mean age at baseline was 53 yrs (men) and 49 yrs (women) | The associations between risk of stroke and various lifestyle factors (BMI, waist circumference, physical activity, smoking lifetime mean alcohol consumption and DASH diet) were explored. ETOH consumption was based on questionnaire completed at baseline<br><br>Analyses were adjusted for lifestyle risk factors noted above. | Incident stroke | Mean duration of follow-up was 12.7 years, during which time there were 551 stroke events.<br><br>Men: The risk of stroke was not significantly increased among those who drank increasing amounts of ETOH:<br><12 g/day: HR=1.00 (ref)<br>12-24 g/day: HR=1.00, 95% CI 0.76-1.31<br>25-59 g/day: HR=0.88, 95% CI 0.66-1.16<br>≥60g/day: HR=1.30, 95% CI 0.91-1.86<br><br>Women: The risk of stroke was not significantly increased among those who drank increasing amounts of ETOH:<br><6 g/day: HR=1.00 (ref)<br>6-11 g/day: HR=1.09, 95% CI 0.76-1.56<br>12-23 g/day: HR=1.01, 95% CI 0.64-1.59<br>≥24 g/day: HR=1.31, 95% CI 0.73-2.34 |
| **Jimenez et al. 2012**<br><br>**US**<br><br>**Cohort study** | NA | 83,578 women aged 30-55 years at baseline (1980).<br><br>Exclusion Criteria included “greatly decreased” alcohol consumption in the past 10 years, consumption of >45 g/day of alcohol, and history of stroke, cancer, or cardiovascular disease at baseline. | Participants completed a food frequency questionnaire in 1980, 1984, 1986, and every 4 years until 2006. Alcohol consumption was categorized as grams consumed per day (one standard serving of beer=13g, wine=11g, and spirits=14g). | Risk of total, ischemic, and hemorrhagic stroke. Analyses were adjusted for age, smoking, physical activity, BMI, history of heart disease, family history of heart disease, history of diabetes, bilateral oophorectomy, post-menopausal status, use of hormone therapy, high cholesterol, multivitamin use, aspirin use, 6-nutrient diet score, education, spouse’s education, and marital status. | There were 2171 incident strokes over 1 695 324 person-years follow-up.<br><br>Compared to non-drinkers, moderate alcohol consumption (>0 to 14.9 g/day) was associated with a significant reduction in total stroke. However, when analyzed separately, neither ischemic nor hemorrhagic stroke was significantly associated with alcohol consumption at any level of consumption.<br><br>Total stroke:<br>>0-4.9 g/day: HR 0.83 (95% CI 0.75 to 0.92)<br>5.0-14.9: HR 0.79 (95% CI 0.70 to 0.90)<br>15.0-29.9: HR 0.87 95% CI (0.72 to 1.05)<br>30-45: HR 1.06 (95% CI 0.86 t o1.30)<br><br>Ischemic stroke:<br>>0-4.9: HR 0.88 (95% CI 0.76 to 1.02)<br>5.0-14.9: HR 0.86 (95% CI 0.72 to 1.02)<br>15.0-29.9: HR 0.82 (95% CI 0.63 to 1.07)<br>30-45: HR 1.17 (95% CI 0.89 to 1.54) |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | Hemorrhagic stroke:<br>>0-4.9: HR 0.82 (95% CI 0.63 to 1.06)<br>5.0-14.9: HR 0.76 (95% CI 0.56 to 1.03)<br>15.0-29.9: HR 0.88 (95% CI 0.58 to 1.35)<br>30-45: HR 0.97 (95% CI 0.58 to 1.60) |
| **Patra et al. 2010**<br><br>**Canada**<br><br>**Systematic review & meta-analysis** | NA | 26 studies (cohort n=17 and 9 case-control), published from 1980-2009, were included. | The relationship between ischemic or hemorrhagic stroke and alcohol consumption (any vs. abstinence) was examined, as was a dose-response relationship.<br><br>When number of drinks was reported, the conversion to grams was based on conversion factors that varied from 8-12 grams/serving. | Sex-specific stroke mortality and morbidity | The risk of both hemorrhagic and ischemic stroke was j-shaped in women and linear in men.<br><br>Risk of ischemic stroke (women)<br>1 drink/day vs. none: mortality: RR= 0.66, 95% CI 0.55-0.79, morbidity: RR=0.82, 95% CI 0.74-0.92, 7 drinks/day vs. none: mortality: RR=2.31, 95% CI 1.70-3.13, morbidity: RR=1.44, 95% CI 1.19-1.74.<br><br>Risk of hemorrhagic stroke (women)<br>1 drink/day vs. none: mortality: RR=0.89, 95% CI 0.52-1.52, morbidity: RR=0.69, 95% CI 0.54-0.89, 7 drinks/day vs. none: mortality: RR=3.66, 95% CI 2.16-6.19, morbidity: RR=2.03, 95% CI 1.19-1.74.<br><br>Risk of ischemic stroke (men)<br>1 drink/day vs. none: mortality: RR= 0.86, 95% CI 0.81-0.93, morbidity: RR=0.87, 95% CI 0.81-0.93, 7 drinks/day vs. none: mortality: RR=1.36, 95% CI 1.23-1.5, morbidity: RR=1.32, 95% CI 1.18-1.47.<br><br>Risk of hemorrhagic stroke (men)<br>1 drink/day vs. none: mortality: RR=1.09, 95% CI 1.06-1.12, morbidity: RR=1.10, 95% CI 1.06-1.14 7 drinks/day vs. none: mortality: RR=1.79, 95% CI 1.48-2.15, morbidity: RR=1.91, 95% CI 1.47-2.47. |
| **Reynolds et al. 2003**<br><br>**USA**<br><br>**Systematic review and meta-analysis** | NA | 35 studies (19 cohort and 16 case control), published from 1966-2002, were included. Sample sizes in the cohort studies ranged from 1,621-107,137. The number of cases in the case-control studies ranged from 89-677.<br><br>Studies included men and | To standardize alcohol consumption, the different units of alcohol reported among studies were converted to grams/day and then categorized into 5 groups (grams/day): none (reference), <12, 12-23, 24-60 and >60, where 12 grams =1 drink.<br><br>Self-administered | Total stroke incidence, ischemic and hemorrhagic stroke.<br><br>Most studies controlled for age, BMI, smoking status, hypertension | Mean duration of follow-up in cohort studies ranged from 4 to 30 years.<br><br>There was a significant j-shaped association between alcohol consumption and risk of total stroke (p for trend=0.002) and ischemic stroke (p for trend=0.004) and a linear relationship with hemorrhagic stroke (p for trend =0.004).<br><br>Risk of total stroke among consumption groups, compared with abstainers: |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | women (n=21), women (n=2) and men (n=12). Age at baseline varied widely among studies. | questionnaires and in-person interviews were used to obtain consumption data. | | <12 g/day: RR=0.83, 95% CI 0.75-0.91<br>12-24 g/day: RR=0.91, 95% CI 0.78-1.06<br>24-60 g/d: RR=1.10, 95% CI 0.97-1.24<br>>60 g/d: RR=1.64, 95% CI 1.39-1.93<br>Results from 35 studies included<br><br>Risk of ischemic stroke among consumption groups, compared with abstainers:<br><12 g/day: RR=0.80, 95% CI 0.67-0.96<br>12-24 g/day: RR=0.72, 95% CI 0.57-0.91<br>24-60 g/d: RR=0.96, 95% CI 0.79-1.18<br>>60 g/d: RR=1.69, 95% CI 1.34-2.15<br>Results from 15 studies included<br><br>Risk of hemorrhagic stroke among consumption groups, compared with abstainers:<br><12 g/day: RR=0.79, 95% CI 0.60-1.05<br>12-24 g/day: RR=0.98, 95% CI 0.77-1.25<br>24-60 g/d: RR=1.19, 95% CI 0.80-1.79<br>>60 g/d: RR=2.18, 95% CI 1.48-3.20<br>Results from 12 studies included<br><br>Risk patterns were similar between men and women, with increasing intake associated with a j-shaped increase in stroke risk. |

## Birth Control, Hormone Replacement Therapy and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***i) Birth Control*** | | | | | |
| **Lidegaard et al. 2012**<br><br>**Denmark**<br><br>**Prospective cohort study** | NA | 1,626,158 women aged 15-49 years, with no history of cardiovascular disease or cancer, recruited from 1995-2009. | Hormonal contraception was classified by estrogen dose (50 µg, 30 to 40 µg, or 20 µg of ethinyl estradiol or progestin only contraceptive), progestin type, route of administration, and | Incidents of thrombotic events, myocardial infarction<br><br>Analysis were adjusted for age, calendar year, length of schooling, educational level (ongoing or completed), and status with respect to hypertension, heart disease, | Duration of follow-up was 15 years.<br><br>There were 3,311 thrombotic strokes (1,633 were classified as ischemic stroke). There were 34 fatal strokes.<br><br>Current use of ethinyl estradiol at a dose of 30 to 40 µg was associated with an increased risk of thrombotic stroke, compared with nonusers |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | duration of use (<1 year, 1 to 4 years, or >4 years).<br><br>The reference group comprised nonusers (never or former users) | diabetes, and hyperlipidemia | Risk according to progestin type:<br>Norethindrone: RR=2.17, 95% CI 1.49-3.15<br>Levonorgestrel: RR=1.65, 95% CI 1.39-1.95<br>Norgestimate: RR= 1.52, 95% CI 1.21-1.91<br>Desogestrel: RR=2.20, 95% CI 1.79-2.69<br>Gestodene: RR= 1.80, 95% CI 1.58-2.04<br><br>The risk of thrombotic stroke associated with current use of ethinyl estradiol at a dose of 50 µg, compared with nonusers was:<br>Risk according to progestin type:<br>Norethindrone: RR=1.27, 95% CI 0.66-2.45<br>Levonorgestrel: RR=2.26, 95% CI 1.59-3.20<br><br>Current use of ethinyl estradiol at a dose of 20 µg was associated with an increased risk of thrombotic stroke, compared with nonusers<br>Risk according to progestin type:<br>Desogestrel: RR=1.53, 95% CI 1.26-1.87<br>Drospirenone: RR=2.20, 95% CI 1.79-2.69<br>Gestodene: RR= 0.88, 95% CI 0.22-3.53<br><br>Current use of progestin only was not associated with increased stroke risk.<br><br>Vaginal ring use was associated with an increased stroke risk: RR=2.49, 95% CI 1.41-4.41. |
| **Yang et al. 2009**<br><br>**Sweden**<br><br>**Cohort Study** | NA | 45,729 women who participated in the Women's Lifestyle and Health Study, aged 30-49 years with no prior history of stroke or MI | Data was collected reproductive history (age at menarche, menstrual cycle length at age 30, age at first birth, breastfeeding and duration of breastfeeding) and oral contraceptive (OC) use (ever/current/former use, duration of use, type of OC (high vs. low-dose combined estrogen/progestin vs. progestin only) | Risk of nonfatal ischemic and hemorrhagic stroke associated with oral contraceptive use.<br><br>Analysis was adjusted for smoking, BMI, ETOH consumption, physical activity, diabetes and hypertension. | There were 285 incident cases of stroke over an average 12.9 years of follow up.<br><br>Compared with never OC users, the risk of fatal or nonfatal ischemic stroke among current or former OC users was not significantly increased (RR=1.1, 95% CI 0.7-1.6 and 0.9, 95% CI 0.6-1.4, respectively).<br><br>Compared with never OC users, the risk of fatal or nonfatal hemorrhagic stroke among current or former OC users was not significantly increased (RR=0.4, 95% CI 0.1-2.1 and 1.6, 95% CI 0.8-3.2, respectively). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***ii) Hormone-Replacement Therapy*** | | | | | |
| **Renoux et al. 2010**<br><br>**Canada & Germany**<br><br>**Nested case-control study** | NA | 15,710 cases and 59,985 controls, between the ages of 50-79 years without a history of stroke, recruited from the UK General Practice Registry Research database, fulfilling quality criteria.<br><br>Cases were women who had sustained a first stroke during the study period (1987-2006).<br><br>Controls were matched (4:1) on the basis of age (± 1 year), at the point of the case's diagnosis, the general practice attended and the year of start in the practice.<br><br>The mean age for cases and controls was 70 years at index event. | All prescriptions for any hormone replacement therapy (HRT) issued during the year before the index date (date of stroke for cases, and in the year before the same index date for matched controls).<br><br>HRT products were categorised by type (estrogens only, estrogens + progestogen, progestogen only, and tibolone); route (oral and transdermal), dose (oral low dose: 0.625 mg of equine oestrogen or ≤ 2 mg of estradiol and oral high dose: >0.625 mg of equine oestrogen or >2 mg of estradiol; transdermal low/high dose: ≤50 µg and > 50 µg of estrogen) and duration of treatment based on the number of tablets or patches prescribed. | Incident stroke<br><br>Analysis was adjusted for BMI, smoking status, alcohol misuse, diabetes, hyperlipidemia, hypertension, atrial fibrillation, cardiovascular disease, transient ischaemic attack, hysterectomy or oophorectomy, and aspirin or other non-steroidal anti-inflammatory drug use in the year before the index date. | Mean duration of follow-up was 6.7 years.<br><br>1,214 (7.7%) cases and 4,124 (6.9%) controls had received at least one HRT prescription in the year before the index date.<br><br>The incident rate ratio (RR) of stroke associated with HRT use during the previous year, using nonusers as the reference group, was:<br>Transdermal: RR=0.95, 95% CI 0.75-1.20<br>Estrogen only: RR=1.02, 95% CI 0.78-1.34<br>Estrogen/progestogen: RR=0.76, 95% CI 0.47-1.22<br><br>Oral : RR=1.28, 95% CI 1.15-1.42<br>Estrogen only: RR=1.35, 95% CI 1.16-1.58<br>Estrogen/progestogen: RR=1.24, 95% CI 1.08-1.41<br><br>High dose transdermal patch use was associated with an increased risk of stroke. RR=1.89, 95% CI 1.15-3.11. Low dose transdermal use was not associated with increased risk.<br><br>Both high and low dose oral HRT was associated with an increased risk of stroke (RR=1.25, 95% CI 1.12-1.40 and RR=1.48, 95% CI 1.16-1.90.<br><br>Use of oral HRT for >1 year was associated with increased risk of stroke (RR=1.35, 95% CI 1.20-1.52), but not for a duration of ≤1 year.<br><br>There was no increase in stroke risk associated with duration of transdermal HRT (≤1 year or > 1 year) |
| **Hendrix et al. 2006**<br><br>**USA**<br><br>**RCT**<br>***Women's Health*** | CA: ☑<br><br>Blinding:<br>Patient ☑<br>Assessor ☑ | 10,739 women, aged 50-79 yrs who had undergone a hysterectomy, with or without an oophorectomy, with no | Women were randomized to receive conjugated equine estrogen (CEE) 0.625 mg/d (Premarin, n=5310) or placebo (n=5429) for the duration | Stroke | Mean duration of follow-up was 7.1 yrs. There were 295 strokes<br><br>At study termination 54% of participants had stopped taking their study medication |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***Initiative (WHI)*** **Estrogen only study** | ITT: ☑ | history of any cancer (except nonmelanoma skin cancer) within the past 10 years, or heart attack or stroke within the past 6 months, with predicted survival of 3 or more years, | of the study | | The risk of total stroke was significantly increased in the CEE group (HR=1.37, 95% CI 1.09-1.73)<br><br>The risk of ischemic stroke was significantly increased in the CEE group (HR=1.55, 95% CI 1.19-2.01), but not for hemorrhagic stroke (HR=0.64, 95% CI 0.35-1.18).<br><br>The risks of ischemic stroke remained significantly increased after adjustment for adherence to study medication, SBP, statin and aspirin use. |
| **Wassertheil-Smoller et al. 2003**<br><br>**USA**<br>**WHI (Estrogen+ progesterone trial)**<br><br>**RCT** | CA: ☑<br><br>Blinding:<br>Patient ☑<br>Assessor ☑<br><br>ITT: ☑ | 16,608 post-menopausal women, with an intact uterus aged 50-79 yrs who had undergone a hysterectomy, with or without an oophorectomy, with no history of any cancer (except nonmelanoma skin cancer) within the past 10 years, or heart attack or stroke within the past 6 months, with predicted survival of 3 or more years,<br><br>Mean age at baseline was 63 years. 74.3% of participants had never used hormones previously. | Women were randomized to receive conjugated equine estrogen (CEE) 0.625 mg/d + 2.5 mg of medroxyprogesterone acetate, (n=8605) or placebo (n=8102) for the duration of the study | **Secondary outcome:**<br>Stroke | Mean duration of follow-up was 5.6 years (range was 3.7-8.6 years).<br><br>There was a total of 258 strokes.<br><br>The risk of total stroke was significantly increased in the CEE + progestin group (HR=1.31, 95% CI 1.02-1.68)<br><br>The risk of ischemic stroke was significantly increased in the CEE + progestin group (HR=1.44, 95% CI 1.09-1.90), but not for hemorrhagic stroke (HR=0.82, 95% CI 0.43-1.56).<br><br>Among women who had never used hormones previously the risk of total stroke was significantly increased in the CEE + progestin group (HR=1.37, 95% CI 1.03-1.82) |
| **Simon et al. 2002**<br><br>**USA**<br><br>**RCT**<br>***Heart and Estrogen/Progestin Replacement Study (HERS)*** | CA: ☑<br><br>Blinding:<br>Patient ☑<br>Assessor ☑<br><br>ITT: ☑ | 2,763 postmenopausal women 55-75 years with existing CHD.<br><br>Mean age at baseline was 67 years. 76% of participants had never used hormones previously. | Women were randomized to receive conjugated equine estrogen (CEE) 0.625 mg/d + 2.5 mg of medroxyprogesterone acetate, (n=1380) or placebo (n=1383) for the duration of the study | **Secondary outcomes:**<br>Stroke, TIA | Mean duration of follow-up was 4.1 years.<br><br>There were 165 stroke events (in 149 participants), 139 nonfatal and 26 fatal.<br><br>The risk of stroke was not significantly elevated for any stroke (HR=1.23, 95% CI 0.89-1.70), TIA (HR=0.90, 95% CI 0.57-1.42) or combined stroke/TIA (HR=1.09, 95% CI 0.84-1.43). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | The risks of fatal, nonfatal, ischemic or hemorrhagic stroke were also not significantly increased with hormonal therapy. |
| **Grady et al. 2002**<br><br>**USA**<br>**HERS II**<br><br>**RCT** | CA: ☑<br><br>Blinding:<br>Patient ☑<br>Assessor ☑<br><br>ITT: ☑ | As per HERS | Additional follow-up from HERS I | **Secondary outcomes:**<br>Stroke, TIA | Mean duration of follow-up was 6.8 years. There was a total of 331 stroke/TIAs.<br><br>The risk of stroke associated with hormonal therapy was not significantly elevated for any stroke/TIA (HR=1.09, 95% CI 0.75-1.57).<br><br>Combining the results from HERS I & II, the risk of stroke was not significantly elevated for any stroke/TIA (HR=1.09, 95% CI 0.88-1.35). |
| **Bath & Gray 2005**<br><br>**UK**<br><br>**Systematic review & meta-analysis** | NA | 28 RCTs (n=39,769) published from 1965-2004. 3 trials included men, with the aim of prevention vascular events. Mean age at randomization ranged from 49.5 to 82 years. | Trials compared hormone replacement therapy (HRT) using oral or transdermal routes with a control group. Trials examined estrogen only (n=12), estrogen + progesterone (n=16) | Fatal and non-fatal stroke | Duration of follow-up ranged from 0.7-6.8 years.<br><br>There were 534 stroke events among participants in the HRT group and 406 in the control group<br><br>The risk of all stroke, ischemic stroke, non-fatal stroke and stroke resulting in death or dependency, was increased among HRT users.<br>All stroke: OR=1.29, 95% CI 1.13-1.47, p=0.0002. Results from 28 trials included.<br>Ischemic stroke: OR=1.29, 95% CI 1.06-1.56, p=0.01 Results from 16 trials included<br>Hemorrhagic stroke; OR=1.07, 95% CI 0.65-1.75, p=0.79. Results from 17 trials included.<br>Fatal stroke: OR=1.28, 95% CI 0.87-1.88, p=0.21. Results from 22 trials included.<br>Non-fatal stroke: OR=1.23, 95% CI 1.06-1.44, p=0.007. Results from 21 trials included.<br>Death/dependency: OR=1.56, 95% CI 1.11-2.20, p=0.01. Results from 14 trials included. |

CA: concealed allocation; ITT: intention-to-treat

## Recreational Drug Use and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***i) Characteristics of illicit drug users who experience stroke*** | | | | | |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Desbois & Cacoub 2013**<br><br>**France**<br><br>**Systematic review** | NA | Studies that reported on cases of arterial complications associated with cannabis use.<br><br>23 case studies that examined stroke incidence, 17 studies that examined myocardial infarction and 23 studies examining arteritis, were identified | Descriptive summaries of included studies. | Ischemic stroke, MI and arteritis | Among the included studies there were 71 cases of ischemic stroke. Of these, 86.2% were male. The average age was 35.5 years (range: 15-63 years).<br>6 patients had known stroke factors (hypercholesterolemia, hypertension and factor V gene mutation).<br><br>55.3% of cases involved posterior cerebral circulation, 42.2% anterior, and 4.4%, both. 43% of patients presented with cerebral vasoconstriction syndrome.<br><br>>85% of cases were heavy users (i.e >1x/week)<br><br>There was a strong temporal relationship between cannabis use and stroke. 76.5% of patients were using cannabis at the time of symptom onset, or during the preceding 30 minutes. The remaining patients had used cannabis within the previous 24 hours of symptom onset. 18 patients had increased their cannabis use in the days preceding their stroke.<br><br>33.8% of patients had consumed other toxic substances including alcohol, cocaine and ecstasy. |
| **De los Rios et al. 2012**<br><br>**USA**<br><br>**Retrospective Study** | NA | All patients aged 18-54 years who had experienced a stroke during three, one-year periods who resided in 5 counties of Kentucky and Ohio, were identified. | Use of illicit drugs, smoking and alcohol were examined in each of the 3 time periods.<br><br>Exposure status for drug use (including cannabis, cocaine, crack and other) was based on patients' self-report or by results of urine or serum drug testing, when available. | Trends in drug and alcohol use of 3 time periods | The total number of persons aged 18-54 years who experienced a stroke increased over time, as did the proportion of young strokes.<br><br>1993-1994: Of the 2,735 strokes, 10.9% occurred in the young.<br>1999-2000: Of the 2,875 strokes, 13.1% occurred in the young.<br>1999-2000: Of the 2,697 strokes, 118.6% occurred in the young.<br><br>The number of patients who reported using illicit drugs increased over time (3.8% vs. 9.8% vs. 19.8%).<br><br>The number of patients who reported using |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | drugs or alcohol within 24 hours of symptom onset increased (1.4% vs. 6.3% vs. 12.8%). |
| **Toossi et al. 2010**<br><br>**USA**<br><br>**Retrospective Study** | NA | 96 patients who were admitted to a single institution from 1998-2008 who had experienced a stroke and who were current or previous users of cocaine.<br><br>Mean age was 50 years, 47% were male. | Description of stroke risk factors (including drug use), investigations performed and type of stroke. Comparisons between active and current cocaine users were conducted. | Stroke type and cause | 5,142 records were screened. Of these, 96 users of cocaine (61 active users and 35 previous users) were identified. There were 45 ischemic stroke/TIA, 26 ICH and 25 SAH.<br><br>23% of patients reported being current or former users of crack cocaine.<br><br>Of the ischemic stroke cases, 44% were due to large artery atherosclerosis, 11% were cardioembolic, and 22% were due to small vessel occlusion. 9% of strokes were due to other determined cause and 13% were of unknown etiology.<br><br>Current users were more likely to have suffered from ICH (37.7% vs. 8.6%, p=0.004). 26% of patients in both groups experienced an SAH.<br><br>The risk factors associated with ischemic stroke/TIA of current and previous users:<br>Hypertension: 62.2%<br>Tobacco use: 71.1%<br>Diabetes: 15.6%<br>Hyperlipidemia: 71.1%<br>Family history of stroke: 22.2%<br>Carotid stenosis: 26.7%<br>Atrial fibrillation: 4.4%<br>Abnormal ECG result: 28.9%<br><br>There were no significant differences between current and former cocaine users. |
| **Sloan et al. 1998**<br><br>**USA**<br><br>**Retrospective study**<br><br>**Baltimore-Washington Cooperative Young** | NA | 422 patients admitted to 46 regional hospitals, aged 15 to 44 years discharged with a primary or secondary diagnosis of first ischemic stroke in 1988 and 1991. | Charts were reviewed for evidence of risk factors (i.e., hypertension, diabetes mellitus, smoking, and angina pectoris/myocardial infarction). Recent drug use was recorded if there | Frequency of illicit drug use and its contribution towards stroke | There was evidence of recent drug use in 12.1% of patients and any drug use in 22.3% of patients.<br>The drugs used were: cocaine (49%), multiple (29.4%), heroin (7.8%), marijuana (5.9%), amphetamines (2%), phencyclidine (3.9%), and other (2%). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Stroke Study** | | Man age was 36 years, 48.6% were male. | was a history of drug use within 48 hours of stroke onset, convincing physical evidence of drug use (i.e., needle in vein when patient found), or a positive toxicology screen. | | In patients with any drug use and recent drug use, hypertension and diabetes mellitus were significantly less common (p = 0.004) and smoking was significantly more common (p = 0.006).<br><br>Of the patients with recent illicit drug use, drug use was identified as a probable cause in 4.7% of cases, and a probable cause in 7.3%. Among patients with drug use was identified as a possible stroke mechanism, more likely diagnoses included cardioembolic stroke (n=18), hematologic/collagen vascular (n=6), nonatherosclerotic vasculopathy (n=5) and atherosclerosis (n=3). |
| ***ii) Increased risk of stroke associated with illicit drug use*** | | | | | |
| **Falkstedt et al. 2017**<br><br>**Sweden**<br><br>**Cohort study** | NA | 49,321 Swedish men, conscripted into military service in 1969/70, when they were 18-20 years of age. | At conscription, all participants underwent a 2-day screening procedure, which included an extensive health examination (and stroke risk factors) and the completion of 2 questionnaires—one focusing on social and behavioral factors and the other on substance use. Participants were asked which drugs they had used, and the frequency of their use. They were also asked about tobacco and alcohol use.<br><br>National databases were used to track the incidence of fatal and nonfatal stroke from 1971-2009, when participants were aged | **Primary outcome:**<br>Risk of any stroke and ischemic stroke, controlling for BMI, SBP/DBP, cardiorespiratory fitness, migraine, diabetes mellitus, early parental CVD, socioeconomic status until young adulthood, and tobacco smoking and alcohol consumption. | There were 1,037 first-time strokes over the study period.<br><br>Among men <45 years, there was no significantly increased risk of stroke (n=192) associated with cannabis use, regardless of intensity of exposure (1-10 times, 11-50 or >50 times).<br><br>Only cigarette smoking was associated with increased stroke risk among men <45 years, which was dose-dependent.<br><br>Among all men, there was no significantly increased risk of any stroke or ischemic stroke associated with cannabis use, regardless of intensity of exposure (used 1-10 times, 11-50 or >50 times).<br><br>Cigarette smoking was associated with a dose-dependent increased stroke risk in all participants. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | 20-59 years. | | |
| **Cheng et al. 2016**<br><br>**USA**<br><br>**Case-control study** | NA | 1,090 cases were those aged 15-49 years, with first-ever ischemic stroke identified from 59 acute care hospitals (1992-2008). Mean age was 41 years, 53.6% were male.<br><br>1,154 controls, matched by age, sex and region of residence. Mean age was 38.6 years, 46.6% were male. | Participants were asked to recall whether they had ever used cocaine before the reference date (date of stroke for cases, date of interview for controls). Timing of use was also noted (acute use-within 24 hours of reference date; current use-with the previous month). Data on traditional risk factors for stroke were also obtained through interview. | **Primary outcome:**<br>Incidence of ischemic stroke<br><br>Analysis was adjusted for age, sex, ethnicity, and other stroke risk factors | Cases were more likely to have a history of diabetes and hypertension, and were more likely to be smokers and current ETOH users.<br><br>28.1% of cases and 25.7% of controls reported to have ever used cocaine. (p=0.95)<br><br>Cocaine use within 24 hours of the reference date was associated with a significantly increased risk of ischemic stroke (n=26 vs. 4; OR=6.4, 95% CI 2.2-18.6, p<0.001).<br><br>Smoking as the route of administration of cocaine was associated with a significantly increased risk of ischemic stroke among acute users (n=16 vs. 2; OR=7.9, 95% CI 1.8-35.0, p=0.006)<br><br>Frequent cocaine use (≥1/week) was also associated with significantly increased odds of ischemic stroke (n=65 vs. 23; OR=2.6, 95% CI 1.6-4.3, p<0.001). |
| **Rumalla et al. 2016**<br><br>**USA**<br><br>**Case-control study** | NA | Patients aged 15-54 years from the Nationwide Inpatient Sample admitted from 2004 to 2011 with a primary diagnosis of ischemic stroke | The risk of ischemic stroke among cannabis users (identified through ICD-9 codes, n= 11,320) was compared to stroke risk among non-users (n= 467,329) | **Primary outcome:**<br>Stroke risk | The incidence of ischemic stroke was significantly greater among marijuana users compared to non-users (RR=1.17, 95% CI: 1.15–1.20, p<0.0001), controlling for age, sex, race, payer status, Charlson's Comorbidity Index, substance abuse and cardiovascular risk factors. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | The greatest risk of stroke was among patients aged 25-34 years (RR=2.26, 95% CI: 2.13–2.38, p<0.0001).<br><br>After adjusting for demographics, other forms of substance abuse, and medical risk factors, marijuana use was associated with significantly greater odds of vasospasm (OR= 2.18, 95% CI 1.77–2.67, p< 0.0001). |
| **Barber et al. 2013**<br><br>**New Zealand**<br><br>**Case-control study** | NA | Cases: 160 patients, aged 18-55 years, admitted to a single institution with a diagnosis of ischemic stroke/TIA during 2009-2012 and who had provided a urine sample within 72 hours of admission.<br>Controls: 160 patients, matched for age, sex and ethnicity, who had been admitted to the Internal Medicine Service. | Relationship between cannabis use and stroke risk was explored using bivariate and logistic regression | **Primary outcome:**<br>Independent risk factors associated with stroke | 25 (15.6%) of stroke patients tested positive for cannabis. They were more likely to be male, Maori, tobacco users and to have worse outcomes at discharge (median mRS 3 vs. 1, p=0.036).<br><br>13 (8.1%) of control patients tested positive for cannabis.<br><br>The odds of stroke were significantly higher in cannabis users, after adjusting for age, sex, and ethnicity (OR=2.3, 95% CI 1.08-5.08); however, the association was no longer significant after adjusting for current tobacco use (OR=1.59, 95% CI 0.71-3.70). |
| **Westover et al. 2007**<br><br>**USA**<br><br>**Retrospective study** | NA | 1,935 patients aged 18-44 years discharged from all hospitals across Texas with a diagnosis of stroke in 2003 | The associations between illicit drug use and the risk of ischemic and hemorrhagic stroke were examined using logistic regression. | **Primary outcome:**<br>Independent risk factors associated with stroke | There were 998 cases of ischemic stroke and 937 cases of hemorrhagic stroke<br><br>Amphetamine use was associated with an increase in the risk of hemorrhagic stroke (OR=4.95, 95% CI 3.24-7.55), but not ischemic stroke (OR=1.04, 95% CI 0.42-2.55).<br><br>Amphetamine use was also associated with an increased risk of hemorrhagic stroke resulting in death (OR=2.63, 95% CI 1.07-6.50).<br><br>Cocaine use was associated with an increase in the risk of hemorrhagic stroke (OR=2.33, 95% CI 1.74-3.11), and ischemic stroke (OR=2.03, 95% CI 1.48-2.79). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | Cannabis use was associated with an increased risk of ischemic stroke (OR=1.76, 95% CI 1.15-2.71) but not hemorrhagic stroke (OR=1.36, 95% CI 0.90-2.06).<br><br>Across both stroke types, the increased risk of death associated with amphetamine use was higher than that of coagulation defects (OR=3.92, 95% CI 1.79-8.59 vs. 3.06 95% CI 1.89-4.95) and 3 times higher than that of hypertension. |
| **Qureshi et al. 2001**<br><br>**USA**<br><br>**Retrospective study** | NA | 10,085 individuals age 19-45 years who had been included in the Third National Health and Nutrition Examination Survey Mortality Follow-up Study (1988-1994). Mean age of the cohort was 30.9 years, 46.5% were male. | The relationship between cocaine use and MI and stroke were examined. The survey included a household interview, a medical examination in a mobile examination center, a brief household medical examination for those unable to travel to the center, and a phlebotomy to measure serum markers including glucose, cholesterol, high-density lipoproteins, triglycerides, and apolipoproteins A-1 and B. Lifetime cocaine use was classified as never, <10 times Infrequent users), 10-100 times (frequent users), or >100 times (regular users).<br><br>Persons were considered to have had a stroke or MI if they reported that they had been told by a physician that they had suffered from either event | **Primary outcome:**<br>Nonfatal MI and stroke<br><br>Analysis was adjusted for age, sex, race/ethnicity, educational attainment, hypertension, hyperlipidemia, diabetes mellitus, BMI, cigarette smoking, and insurance status. | 731 individuals (7.2%) reported infrequent use of cocaine, 532 (5.3%) reported frequent use.<br><br>There were 33 nonfatal strokes.<br><br>The odds of a nonfatal stroke associated with cocaine use were not increased significantly:<br>Nonusers: Reference OR=1.0<br>Infrequent users: OR=0.48, 95% CI 0.01-7.66<br>Frequent users: RR=0.49, 95% CI 0.01-7.69<br>Regular users: OR not reported |
| **Kaku & Lowenstein** | NA | Cases: 214 patients | The association between | **Primary outcome:** | The mean age of patients in both groups was 35 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **1990**<br><br>**USA**<br><br>**Case-control study** | | aged 15-44 years, admitted to a single institution with a diagnosis of stroke from 1979-1988.<br><br>Controls: 180 patients admitted emergently with asthma, appendicitis or cholecystitis, with documentation of drug abuse (present or absent) matched for age, sex and year of discharge. | recreational (illicit) drug use and the risk of stroke was examined using conditional logistic regression. The temporal relationship among drug users was also examined.<br><br>Exposure status for drug use was based on documentation provided in the medical chart. | Independent risk factors associated with stroke | years.<br><br>Stroke types were 34% ICH, 27% cerebral thrombosis, 25% SAH and 14% cerebral embolism.<br><br>Drug abuse was documented more frequently in stroke patients 34% vs. 8%. Among patients with stroke, cocaine, heroin and amphetamine were the most commonly used drugs. Mortality associated with stroke was 26% during the acute admission period.<br><br>The risk ratio for drug abuse was 6.5, 95% CI 3.1-13.6. The risk was highest during the first 6 hours after use and decreased over time. Among patients <35 years, drug abuse was a stronger predictor of stroke (RR=11.7, 95% CI 3.2-42.5) compared with those ≥35 years (RR=3.6, 95% CI 1.3-10.4) |

## Association between Smoking and Stroke Risk

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **O'Donnell et al. 2016**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 2**<br><br>**Case-control study** | NA | Participants were recruited from 32 countries from 2007-2015.<br><br>Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women.<br><br>13,472 controls were matched for age and sex and were recruited from the community or hospitals | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Smoking status was classified as current or never/former | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) | Smoking was associated with an increased risk of stroke.<br><br>All stroke: OR=1.67, 99% CI 1.49-1.87; PAR 12.4%, 99% CI 10.2-214.9%<br><br>Ischemic stroke: OR=1.93, 99% CI 1.69-2.21, PAR 15.1%, 99% CI 12.8-18.8%<br><br>Hemorrhagic stroke: OR=1.14, 99% CI 0.95-1.36, PAR 3.6%, 99% CI 0.9-13.0% |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | (in-patient or outpatient, unrelated to treatment for stroke or TIA) | | | |
| **O'Donnell et al. 2010**<br><br>**Canada (International)**<br><br>**INTERSTROKE Phase 1**<br><br>**Case-control study** | NA | Participants were recruited from 22 countries from 2007-2010.<br><br>Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women.<br><br>3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA). | All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples.<br><br>Smoking status was classified as current or never/former. | The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)<br><br>Results were adjusted for age, sex, and region | Smoking was associated with an increased risk of stroke compared with never/former smokers.<br><br>All stroke: OR=2.09, 99% CI 1.75-2.51, PAR 18.9%, 99% CI 15.3-23.1%<br><br>Ischemic stroke: OR=2.32, 99% CI 1.91-2.81, PAR 21.4%, 99% CI 17.5-25.8%<br><br>Hemorrhagic stroke: OR=1.45, 99% CI 1.07-1.96, PAR 9.5%, 99% CI 4.2-20.0% |
| **Feigin et al. 2016**<br><br>**International**<br><br>**Retrospective study** | NA | Population-based data from 188 countries from 1990 to 2013. | Data from the Global Burden of Disease Study 2013 was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors (including tobacco use, defined as previous or current use) in high-income countries and low-income and middle-income countries. | Stroke burden (expressed as DALYs) | Globally, 20.7% (95% uncertainty interval 18.2%-22.7%) of the stroke burden was attributed to tobacco use.<br><br>In high income countries, 18.1% (95% uncertainty interval 16.2%-19%) of the stroke burden was attributed to tobacco use.<br><br>**In Canada, 13% (95% uncertainty interval 10.6%-15.4%) of the stroke burden was attributed to tobacco use**<br><br>Globally, during the study period, there was an increase of 10.4% (95% UI 8.6%-13.7%) in the burden of stroke related to tobacco use. |
| **Peters et al. 2013**<br><br>**Australia & US** | NA | 81 prospective cohort studies, published from 1966-2013, including the results from, 3,980,359 | Dose-response relationship (<10, 10-20, >20) and stroke subtype (ischemic vs. hemorrhagic) were also | Combined fatal/nonfatal incident stroke, expressed as relative risk (RR) and a ratio of RR in | Duration of the included studies ranged from 6-40 years. There were 42,401 strokes. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Systematic review & meta-analysis** | | persons, reporting sex-specific risk of current smoker vs. nonsmokers. | examined. | women/men (RRR).<br><br>Variables adjusted for in the individual studies included: age, race, education blood pressure, diabetes, serum cholesterol, alcohol intake, physical activity. | The prevalence of current smoking ranged from 8% to 59% in men and from 1% to 51% in women. Most studies reported higher smoking rates among men.<br><br>The risk of stroke was higher in current smokers compared with nonsmokers.<br>Women: RR=1.83, 95% CI 1.58-2.12<br>Men: RR=1.67, 95% CI 1.49-1.88<br>The risk was not significantly different between the sexes (RRR=1.06, 95% CI 0.99-1.13, p=0.10).<br><br>The risk of stroke was higher in former smokers compared with never smokers:<br>Women: RR=1.17, 95% CI 1.12-1.22<br>Men: RR=1.08, 95% CI 1.03-1.13<br>The risk was not significantly different between the sexes (RRR=1.10, 95% CI 0.99-1.22)<br><br>The risk of stroke was higher in women who smoked >20 cigarettes/day compared with men:<br><10 cigs: RRR=0.94, 95% CI 0.67-1.22<br>10-20 cigs: RRR=0.91, 95% CI 0.67-1.22<br>>20 cigs: RRR=1.31, 95% CI 1.00-1.72<br><br>The risk of ischemic stroke was elevated significantly in both men and women who smoked, compared with nonsmokers, but the risk was not significantly different between the sexes (RRR=0.97, 95% CI 0.79-1.18, p=0.73).<br><br>The risk of hemorrhagic stroke was significantly increased in women who smoked compared with men who smoked (RRR=1.17, 95% CI 1.02-1.34, p=0.02). |
| **Robbins et al. 1994** | N/A | 22,071 male physicians enrolled as part of the Physicians' Health Study. | Smoking status was defined as never smoked, formally smoked, currently smoking | Occurrence of stroke.<br><br>**Timing of Assessment:** | During the study period, 312 non-fatal and 28 fatal strokes occurred. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **US**<br><br>**Observational study** | | Participants were aged 40-84 and did not have histories of stroke, TIA, or myocardial infarction at the time of study entry. | <20 cigarettes/day, and currently smoking ≥20 cigarettes/day. | Baseline, 6-month follow-up, and every 12-months until diagnosis of stroke, fatal event, or the end of the 10-year study period. | Compared with those who never smoked, the risk of non-fatal stroke occurrence was:<br>Significantly higher for those currently smoking ≥20 cigarettes/day (RR=2.52, 95% CI 1.75 to 3.61),<br>Significantly higher for those smoking <20 cigarettes/ day. (RR=2.02, 95% CI 1.23 to 3.31)<br>Higher for former smokers (RR=1.20, 95% CI 0.94 to 1.53)<br>Test for trend: p<0.001), adjusting for age and aspirin and beta-carotene use.<br><br>The risk for fatal stroke was not significantly increased for former (RR= 0.96; 95% CI 0.42 to 2.19) or current smokers (RR= 1.46; 95% CI 0.32 to 6.76). |

## Interventions to Promote Smoking Cessation

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| *Pharmacological Interventions +/- behavioural support* | | | | | |
| **Mullen et al. 2016**<br><br>**Canada**<br><br>**RCT** | CA: ☒<br><br>Blinding:<br>Patient ☒<br>Assessor☒<br><br>ITT: ☑ | 1,367 patients admitted to one of 14 hospitals, >17 years of age who smoked ≥1 cigarette per day in the 6 months prior to their hospitalization. Mean age was 52 years, 48% of patients were male, 32% of patients smoked >20 cigs/day. | Patients were randomized to participate in the 'Ottawa Model' for Smoking Cessation (OMSC), a systematic approach to tobacco dependence treatment delivered within healthcare settings that involves: identifying and documenting the smoking status of all patients; providing brief counselling and in hospital | **Primary outcome:**<br>All-cause mortality and all-cause hospital readmission<br><br>**Secondary outcomes:**<br>Smoking-related readmission; all-cause and smoking-related ED visits; and all-cause and smoking-related physician visits<br><br>Analysis was adjusted for baseline covariates: age, sex, income, number of cigarettes | **30-day outcomes:**<br>The risk of death was not reduced significantly in the OMSC group (HR=0.66, 95% CI 0.29-1.48, p=0.38); however, the incidence of rehospitalization was reduced significantly (HR=0.50, 95% CI 0.34-0.72, p<0.001).<br><br>**One-year outcomes:**<br>The cumulative incidences of death and all-cause rehospitalizations were significantly lower in the OMSC group |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | pharmacotherapy to smokers; and, offering follow-up support post hospitalization (n=726) or to a usual care group (n=641) that (most frequently) received self-help brochures | smoked per day, community size, resource usage prior to index event, and history of: acute MI, asthma, COPD, heart failure, diabetes, hypertension, mental illness, stroke/TIA. | (HR=0.55, 95% CI 0.36-0.82, p<0.001 and HR=0.72, 95% CI 0.61-0.86, p<0.001, respectively).<br><br>**Two-year outcomes:**<br>The cumulative incidences of death and all-cause rehospitalizations were significantly lower in the OMSC group (HR=0.60, 95% CI 0.42-0.85, p<0.001 and HR=0.79, 95% CI 0.68-0.92, p<0.001, respectively). |
| **Stead et al. 2015**<br><br>**UK**<br><br>**Cochrane Review** | NA | 47 RCTs (18,000+) examining the effectiveness of behavioural support as an adjunct to pharmacotherapy for smoking cessation as compared to a control condition that received pharmacotherapy and less intensive behavioural support.<br><br>Trials recruited people who smoked, in all settings and populations except pregnant women and adolescents. All participants had access to one or more of the following pharmacological agents: nicotine replacement therapy (NRT), varenicline, bupropion, and nortriptyline. | Participants were provided NRT in the majority of included trials. The intensity of behavioural support varied greatly for both intervention and control groups and was typically only slightly greater for those in the intervention arm than those in the control arm. | Abstinence from smoking after at least six months of follow-up. | 9 new trials have been added since the review was last updated (2012).<br><br>More intensive behavioural support was associated with a better chance of long-term abstinence from smoking when combined with pharmacotherapy, as compared to pharmacotherapy combined with less intensive behavioural support (RR= 1.17, 95% CI 1.11 to 1.24)<br><br>An increased number of sessions (≥4 vs. no sessions) was associated with a greater chance of successful low-term abstinence (RR=1.25; 95% CI 1.08 to 1.45; 6 trials). |
| **Stead & Lancaster 2012**<br><br>**UK**<br><br>**Cochrane review** | NA | 41 RCTs (n= 20,000) that included participants in all settings. The percentage of female participants typically varied from 35% to 65%. Two trials recruited only women. The average age ranged from early 40's to mid-50's.<br><br>Participants from healthcare | Comparison of trials that included behavioral support with the addition of the availability of pharmacotherapy vs. control receiving usual care or brief advice or less intensive behavioural support.<br><br>Most studies supplied nicotine replacement | Abstinence from smoking after at least six months of follow-up. | Combination therapy was associated with cessation of smoking at longest follow-up.<br><br>RR=1.82, 95% CI 1.66-2.00, p< 0.00001. Results from 40 studies (n=15,021) included.<br><br>In studies that recruited participants from healthcare settings, the probability of success was greater. RR=2.06, 95% CI 1.83-2.34. Results from 31 trials (n=9,396) included vs. RR= 1.53, 95% CI |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | settings included a broad range of health conditions, although none appeared to have recruited those with stroke or TIA.<br><br>Most trials included participants who smoked an average of >20 cigs/day. | therapy, (provided as patch or gum).<br><br>Behavioural support was typically provided by specialists in cessation counselling, but was also provided by peer counsellors, trained nurses and usual care providers. 4-8 contact sessions were provided; the duration of contact varied, but was typically >30 to <300 minutes. Forms of contact included telephone, mail, individual and group sessions. | | 1.33 to 1.76, (8 trials, n=4,906) that recruited participants from the community.<br><br>There was no association between number of sessions provided and success of quitting (1-3 vs. 4-8 vs. >8) or the planned duration of contact (total minutes) (up to 30 vs. 31-90 vs. 91-300 vs. >300). |
| **Cahill et al. 2013**<br><br>**UK**<br><br>**Cochrane review of reviews** | NA | 12 Cochrane reviews (including the results from 267 RCTs, 101,804 participants) which examined the effectiveness of pharmacological treatments to promote smoking cessation in adults (excluding pregnant women). | The main treatments examined included: nicotine replacement therapy (NRT), provided as gum (n=55), transdermal patch (n=43), oral nicotine tablet or lozenge (n=6), choice of product (n=5), intranasal nicotine spray (n=4), nicotine inhaler (n=4), one of oral spray (n=1), patch plus inhaler (n=1) and patch plus lozenge (n=1), bupropion, nortriptyline, and the nicotine receptor partial agonists, varenicline and cytosine.<br><br>Additional treatments included: antidepressants, anxiolytics, and selective type 1 cannabinoid receptor antagonists.<br><br>The control conditions included placebo, other | Sustained (at least 6 months) smoking cessation. | Pharmacotherapy was associated with increased odds of success (odds ratio, 95% Credible interval).<br><br>NRT vs. placebo: OR=1.84, 95% CI 1.71 to 1.99, based on 119 comparisons.<br><br>Combination NRT outperformed single formulations.<br>All forms of NRTs were superior to placebo.<br><br>Bupropion vs. placebo: OR=1.82, 95% CredI 1.60 to 2.06. 36 comparisons.<br>Varenicline vs. placebo: OR= 2.88, 95% CredI 2.40 to 3.47. 15 comparisons.<br><br>Bupropion vs. NRT: OR= 0.99; 95% CredI 0.86 to 1.13. 9 comparisons.<br><br>Varenicline was superior to single forms of NRT: OR= 1.57, 95% CredI 1.29 to 1.91.<br><br>Varenicline vs. bupropion: OR= 1.59, 95% CredI 1.29 to 1.96. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | pharmacological treatments, or combinations of treatments or usual care. | | Odds of serious adverse events (chest pains and heart palpitations) associated with NRT was: OR= 1.88, 95% CI 1.37-2.57. The corresponding event rate was 2.5% in the NRT group and 1.4% in the control group, reported in 15 trials.<br><br>Bupropion: the most common side effects were insomnia, occurring in 30% to 40% of patients, dry mouth (10%) and nausea. Typical drop-out rates due to adverse events ranged from 7% to 12%. The main serious adverse event was seizures, which may occur at a rate of around 1:1000 users.<br><br>Varenicline: the main adverse event was mild-moderate nausea, subsiding over time. The event rates for serious adverse events 2.1% in the varenicline arms and 2.0% in the placebo arms, reported in 14 trials. |
| **Edjoc et al. 2012**<br><br>**Canada**<br><br>**Systematic Review** | NA | 4 RCTs (n=354) including participants with cerebrovascular disease, a portion of whom were smokers (28%-54%). Trials were not excluded based on age or ethnicity of participants. | Trials evaluated the effectiveness of a smoking cessation intervention (medications +/- counselling) vs. usual care | Smoking Cessation (follow-ups ranged from 26 weeks to 42 months). | The overall smoking cessation rate was 23.9% (42/176) for participants randomized to receive an active smoking cessation intervention and 20.8% (37/178) for participants randomized to a control group, |
| *Non-pharmacological Interventions* | | | | | |
| **Lindson-Hawley et al. 2015**<br><br>**UK**<br><br>**Cochrane Review** | NA | 28 RCTs (n=16,803) examining the use of motivational interviewing (MI) for smoking cessation.<br><br>Trials included participants who were tobacco users, recruited from any setting. Pregnant women and adolescents were excluded. | Included trials based the active intervention on the principles and practice of MI. MI was provided in 1-4 sessions, with duration of 15-45 minutes per session. Control groups received brief advice, a low-intensity intervention, or routine care. | Abstinence from smoking after at least six months of follow-up. | Compared to brief advice or usual care, motivational interviewing was associated with a significantly greater likelihood of long-term smoking cessation (RR=1.26, 95% CI 1.16 to 1.36; 28 trials).<br><br>MI was associated with a significant treatment effect whether delivered in single (RR=1.26, 95% CI 1.15 to 1.40) or multiple sessions (RR=1.20, 95% CI 1.02 to 1.42). |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | Sessions of <20 and >20 minutes' duration were both associated with an increased likelihood of cessation (RR= 1.69, 95% CI 1.34-2.12 and RR= 1.20, 95% CI 1.08- 1.32, respectively). |
| **Rice et al. 2013**<br><br>**USA**<br><br>**Cochrane Review** | NA | 49 RCTs (17,000+) that recruited adult participants from any type of healthcare, or other setting. Trials that exclusively recruited pregnant participants were excluded. In 20 trials the intervention was provided while patients were in hospital, while in 24 trials participants were recruited from primary care or outpatient clinics. | Trials evaluated smoking cessation interventions delivered by nurses, including provision of advice, counselling, and strategies to help participants stop smoking vs. usual care or control | Abstinence from smoking after at least six months of follow-up. | Participants who were randomized to receive the nurse-delivered active intervention were significantly more likely to be abstinent from smoking at the longest point of follow-up (RR= 1.29; 95% CI 1.20 to 1.39; 35 trials, n=17,629).<br><br>High Intensity interventions: RR=1.26; 95% CI 1.17 to 1.36 (28 trials, n=13,613).<br><br>Low intensity interventions: RR= 1.27; 95% CI 0.99 to 1.62 (7 trials, n=4,016). |
| **Stead et al. 2013**<br><br>**UK & Bogota**<br><br>**Cochrane Review** | NA | 42 RCTs (31,000+) that recruited participants from any setting. Trials that exclusively recruited pregnant participants were excluded. | Trials evaluated smoking cessation advice delivered by a physician vs. usual care or no advice. | Abstinence from smoking after at least six months of follow-up. | Participants who received smoking cessation advice from a medical practitioner were significantly more likely to be abstinent from smoking at the longest point of follow-up (RR= 1.76; 95% CI 1.58-1.96, 26 trials, n=22,239)<br><br>Smoking cessation was associated with an increased likelihood of smoking cessation among sub groups including more vs. less intensive treatment, high-risk vs. unselected participants, and the use of aids as adjuncts to advice vs. no aids. |
| **Frandsen et al. 2012**<br><br>**Denmark**<br><br>**RCT** | CA: ☒<br><br>Blinding:<br>Patient ☒<br>Assessor☒<br><br>ITT: ☑ | 94 current daily smokers following acute stroke or TIA (59% men).<br><br>**Exclusion criteria:** severe stroke, decreased life expectancy related to concomitant disease, and any condition that precluded participation in a smoking | Participants were randomized to receive an intensive (n=49) or minimal (n=45) smoking cessation intervention. All participants received 30-minutes of nurse-delivered individual cessation counselling, an information booklet, and free nicotine patches for the | Smoking cessation at 6-months follow-up. | Self-reported smoking cessation rate was non-significantly higher in the intervention group (42.9% vs. 37.8%, p>0.05).<br><br>Using exhaled CO, smoking cessation was confirmed in 32.7% of participants in the intervention group and 28.9% in the control group (.>0.05).<br><br>Lost to follow-up: Intervention group=6/49 |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | cessation program. | duration of their hospital stay. Participants in the intervention group additionally received 6 cessation counselling sessions with an authorized instructor following hospital discharge, 5 telephone-based counselling sessions, and free nicotine patches. | | (12%). Control group=4/45 (9%). |

## Smoking Cessation Pharmacotherapy and Risk of Adverse Cardiovascular Events

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Mills et al. 2014**<br><br>**USA**<br><br>**Systematic Review & Meta-analysis** | N/A | 63 RCTs (n=30,508) including current smokers who were treated with NRT at any marketed dose or combination, bupropion at licensed doses, for any duration and which reported cardiovascular outcomes. | Trials examined smoking cessation therapy with nicotine replacement therapy (NRT; 21 trials), bupropion (27 trials), or varenicline (18 trials) vs. placebo or no treatment | All cardiovascular events and all major adverse cardiovascular events (defined as cardiovascular death or non-fatal stroke or myocardial infarction. | **All cardiovascular events:**<br>NRT: RR= 1.81, 95% CI 1.35 to 2.43.<br>Bupropion: RR= 1.03, 95% CI 0.71 to 1.50.<br>Varenicline: RR= 1.24, 95% CI 0.85 to 1.81.<br><br>**Major cardiovascular events:**<br>NRT: RR= 1.38, 95% CI 0.58 to 3.26.<br>Bupropion: RR= 0.57, 95% CI 0.31 to 1.04.<br>Varenicline: RR= 1.44, 95% CI 0.73 to 2.83.<br><br>The authors concluded that smoking cessation therapies did not appear to be associated with a significant increase in the risk of major cardiovascular events, but were associated with a significant increase in risk of less serious CV events. |
| **Prochaska & Hilton, 2012**<br><br>**USA**<br><br>**Systematic** | N/A | 22 RCTs (n=9232) including current smokers aged 18 years or older using varenicline and reporting cardiovascular outcomes. | Trials compared varenicline smoking cessation therapy vs. placebo control | Occurrence of ischemic or arrhythmic adverse cardiovascular events during treatment or within 30-days of treatment discontinuation. | The rate of treatment emergent cardiovascular events was 0.63% (n=34) for participants randomized to receive varenicline and 0.47% (n=18) for those randomized to a control group: risk difference = 0.27%, 95% CI -10% to 63%, |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Review & Meta-analysis** | | | | | p=0.15.<br><br>In a secondary analysis that only included the 14 trials in which at least one outcome event occurred, the risk of adverse cardiovascular events was not significantly increased among those receiving an active intervention (RR=1.40 (95%, CI 0.82 to 2.39, p=0.22), |

## Electronic Cigarettes

Electronic cigarettes ("e-cigarettes") contain propylene glycol (PG), vegetable glycerin, nicotine, and flavouring, and are promoted as a safer alternative to smoking regular cigarettes, and as an aid in tobacco cessation programs. However, evidence to support these claims is lacking and there is also debate whether e-cigarettes can act as a gateway to real smoking. Several health-related bodies, including the World Health Organization (2013), the Canadian Lung Association (2012) and the International Union against Tuberculosis and Lung Disease (2014) have released position statements cautioning/advising against the use of these products.

The use of electronic cigarettes has increased significantly in the past several years among both adolescents and adults. Results from the 2015 Canadian Tobacco, Alcohol and Drugs Survey indicated that in 2015, 26% of Canadians aged 15-19 years had tried an e-cigarette, Overall, 13% (3.9 million) of Canadians aged 15 years and older reported having ever tried an e-cigarette, an increase from 9% (2.5 million) reported in 2013. Among adults aged 25 years or older, 11% (2.6 million) adults aged 25 years and older had tried an e-cigarette.

Currently, e-cigarettes can be sold in Canada if they release vapour but do not contain nicotine, although devices can be sold with vapour cartridges that are easily exchanged for nicotine. E-cigarettes cannot be advertised as a healthy alternative to cigarettes. While the sale of e-cigarettes with nicotine is essentially banned in Canada, regulation is not actively enforced and there is much public confusion over the legal status of these products. New regulations have recently been proposed (November 2106). The Tobacco and Vaping Products Act will amend the *Tobacco Act,* to regulate vaping products as a separate class of products. The proposed Act will establish a new regulatory framework for vaping products, as part of a strategy to protect youth from nicotine addiction and tobacco use, allow adults to access vaping products as likely less harmful alternatives to tobacco use, and to protect the health and safety of Canadians.

Few controlled trials examining the effectiveness of e-cigarettes have been published. In fact, only a single randomized controlled trial has evaluated its role as an aid in cessation efforts in individuals wanted to quit smoking (Bullen et al. 2013). Based on the results of several trials, described below, it appears that the use of e-cigarettes is associated with significant reductions in the use of conventional cigarettes. There are limited data regarding safety.

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***i) RCTS examining effectiveness of the use of e-cigarettes to reduce/quit smoking*** | | | | | |
| **McRobbie et al. 2014**<br><br>**UK**<br><br>**Cochrane Review** | NA | 2 RCTs and 11 cohort studies including participants who were current smokers who may/may not have been motivated to quit. | Studies included electronic cigarettes (EC) vs. placebo ECs, ECs vs. alternative smoking cessation aids, including nicotine replacement therapy (NRT | **Primary outcome:**<br>Smoking cessation at longest follow-up (≥6 months following initiation of treatment)<br><br>**Secondary outcome:** | Participants using nicotine EC were more likely to quit smoking compared with those using placebo ECs (RR=2.29, 95% CI 1.05-4.96, p= 0.037). Results from 2 RCTs included. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | or no intervention, and ECs+ standard smoking cessation treatment (behavioural or pharmacological or both) with standard treatment alone. | >50% reduction in cigarette use at the longest follow-up point (≥6 months following initiation of treatment) | Participants using EC were no more likely to quit smoking compared with those using other forms of NRT (RR=1.26, 95% CI 0.68-2.34, p>0.05). Results from 1 RCTs included.<br><br>Participants using nicotine EC were no more likely to reduce their smoking compared with using placebo ECs (RR=1.31, 95% CI 0.1.02-1.68, p=0.037). Results from 2 RCTs included. (quitters excluded).<br><br>Participants using EC were significantly more likely to reduce smoking compared with those using other forms of NRT (RR=1.41, 95% CI 1.20-1.67). Results from 1 RCTs included. (quitters excluded).<br><br>The proportion of participants reporting adverse events was not significantly greater among those using nicotine EC vs placebo EC or other NRTs. |
| **Bullen et al. 2013**<br><br>**New Zealand**<br><br>**RCT** | CA: ☑<br><br>Blinding:<br>Patient ☒<br>Assessor ☑<br><br>ITT: ☑ | 657 participants ≥18 yrs, who smoked >10 cigs/day for previous year and who **wanted to stop smoking**. Mean age was 42 yrs, 62% female, mean number of years of continuous tobacco use was 25.<br><br>Exclusions: women who were pregnant, those currently on other cessation meds, those reporting stroke, heart attack or severe angina within previous 2 weeks, poorly controlled medical conditions or history of substance abuse | Participants were randomized to use e-cigarettes (16 mg nicotine/day, n=289), nicotine patches (21 mg/day, n=295) or placebo e-cigarettes (0 mg, n=73) from 1 week before, until 12 weeks after their chosen quit date. All participants had access to telephone-based behavioral support | **Primary outcome:**<br>Abstinence at 6 months after quit date (self-report and verified by breath CO <10 ppm).<br><br>**Secondary outcomes:**<br>7-day point prevalence of abstinence, continued abstinence at 1 and 3 months | Verified absences at 6 months were:<br>Nicotine e-cig: 7.3%<br>Nicotine patch: 5.8%<br>Placebo e-cig: 4.1%<br><br>The superiority of nicotine e-cigs over patches or placebo e-cigs could not be established due to lower than expected quit rates (10% was anticipated).<br>The results of pairwise comparisons:<br>Nicotine e-cigs vs. patch: RR=1.26, 95% CI 0.68-2.34, p=0.46<br>Nicotine e cigs vs. placebo e-cigs: RR=1.77, 95% CI 0.54-5.77, p=0.44.<br><br>At 1 month, a significantly higher percentage of nicotine e-cig users reported continuous abstinence vs. patch users (23.2% vs. 15.9%, p=0.03; RR=1.46, 95% CI 1.04-2.04). There was |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | no significant difference in abstinence at 1 month between nicotine e-cig users and placebo e-cig users (23.2% vs. 16.4%, p=0.21).<br><br>There were no significant differences in abstinence at 3 months (nicotine e-cigs vs. patch 13.1% vs. 9.2%, p=0.12 &nicotine e-cig vs. placebo e-cigs 13.1% vs. 6.8%, p=0.14.<br><br>At 6 months, nicotine e-cig users had reduced their mean daily tobacco use significantly more compared with the other 2 groups (9.7 vs. 7.7. vs. 1.9 cigs/day, p=0.002).<br><br>There were no significant differences in the total number of adverse events among groups (event rate: 0.8 events/person month in both nicotine e-cig and patch group & 0.9 events/person month in placebo e-cig group).<br><br>Losses to follow-up: nicotine e-cig: 17%, patches: 27%, placebo e-cig: 22%. |
| **Caponnetto et al. 2013**<br><br>***EffiCiency and Safety of an eLectronic cigareTte (ECLAT)***<br><br>**Italy**<br><br>**RCT** | CA: ☒<br><br>Blinding:<br>Patient ☑<br>Assessor ☑<br><br>ITT: ☑ | 300 participants aged 18-70 yrs who smoked ≥10 cigs/day for at least the previous 5 yrs, in good health and **not intending to quit smoking** (or wishing to do so) for the next 30 days. Mean age was 44 yrs, 63% male. On average, participants had smoked for 25 yrs.<br><br>Exclusions included pregnancy or breastfeeding, symptomatic CVD, ETOH abuse and nicotine replacement therapy | All participants used e-cigs, but were randomized to different doses units in the nicotine cartridges: 7.2 mg/cartridge x 12 weeks, (Group A, n=100); 7.2 mg for 6 weeks then 5.4 mg/cartridge for 6 weeks (n=100) or 0 mg nicotine x 12 weeks (n=100). Participants used the cartridges *ad libitum* up to 4/day. | **Primary outcome:**<br>Decline in tobacco use at 1 yr.<br><br>**Secondary outcomes:**<br>Self-reported abstinence (verified by exhaled CO ≤7 ppm)<br><br>Assessment were conducted at baseline, weeks 2, 4, 6, 8, 10, 12, 24 & 52 | The numbers (%) of patients who reported a reduction of ≤50% tobacco use since baseline were:<br>**6 weeks**<br>Group A: 24%, Group B: 26%, Group C: 25%<br>**24 weeks**<br>Group A: 17%, Group B: 19%, Group C: 15%<br>**52 weeks**<br>Group A: 10%, Group B: 9%, Group C: 12%.<br><br>Quit rates<br>**6 weeks**<br>Group A: 11%, Group B: 15%, Group C: 25% |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| | | | | | **24 weeks**<br>Group A: 12%, Group B: 10%, Group C: 5%<br>**52 weeks**<br>Group A: 13%, Group B: 9%, Group C: 4%.<br>(no p values reported)<br><br>At baseline, the mean number of cigs/day was 20. It had decreased to 13.9 cigs/day at week 52 (p<0.0001). There were significant reductions in the median number of cigs/day among groups at weeks 2, 6 & 8 (favouring groups A&B over group C).<br><br>There were no significant differences in adverse events at any time point, among groups (dry cough, mouth irritation, SOB, throat irritation, headache)<br><br>Losses to follow-up: Group A 35%, Group B 37%, Group C 45% |
| **Bullen et al. 2010**<br><br>**UK/NZ**<br><br>**Crossover RCT** | CA: ☒<br><br>Blinding:<br>Patient ☒<br>Assessor ☑<br><br>ITT: ☑ | 40 participants aged 18-70 yrs who smoked ≥10 cigs for the previous year, who smoked their first cig of the day within 30 minutes of waking and who were **not attempting to quit** nor intending to do so within the next 30 days. Mean age was 48 yrs. 47% male, average cig use was 20 /day<br><br>Exclusions: women who were pregnant or breast feeding, history of serious medical conditions or current use of any other smoking cessation product. | Participants were randomized to use 4 different products for 1 day, in random order: e-cigs (0 and 16 mg nicotine), nicotine inhaler and their own brand of cigs. They were instructed to only to use their assigned product for the day, but it could be used *ad libitum*. There was a 3-day washout period between treatments. Participants were instructed to abstain from smoking on study days | **Primary outcome:**<br>Withdrawal symptoms, desire to smoke<br><br>Assessments were conducted 5, 10, 15, 20, 25, 30, 40, 50 & 60 minutes counting from first puff of product. | Over the 60- minute assessment period, participants using the 16 mg nicotine e-cig reported significantly lower mean desire to smoke scores compared with those using 0 mg cartridges (-2.6 vs. -1.8 units on Likert scale, mean difference=-0.82 units, p=0.006. There were no significant differences in scores related to irritability, restlessness or difficulty concentrating.<br><br>There was no significant difference in mean desire to smoke score between 16 mg e-cig group and nicotine inhaler group (Mean difference: -0.10, 95% CI -1.16-0.95, p=0.99).<br><br>As an alternative to regular cigs, 58% preferred e-cigs, 25% preferred the inhaler and 13% liked neither.<br>16 mg e-cigs were associated in shorter |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
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| | | | | | interval to peak serum nicotine levels (19.6 min vs. 32 min for inhaler).<br><br>There were no serious adverse events. The most common adverse events were mouth/throat irritation (highest in nicotine inhaler group-88%), headache and nausea (≥18% in e-cig and inhaler groups)<br><br>Losses to follow-up: n=4 |
| ***ii) Observational studies examining the use of e-cigarettes to reduce/quit smoking*** | | | | | |
| **Polosa et al. 2011**<br><br>**Italy**<br><br>**Uncontrolled study** | NA | 40 healthy smokers aged 18-60 yrs who had smoked ≥15 cigs/day for at least the previous 10 yrs., who were **not attempting to quit** and had no desire to quit within the next 30 days. Mean age was 43 yrs, 65% male. Mean of 27 yrs smoking history.<br><br>Exclusions included recent MI, severe angina, high BP, symptomatic, DM and poorly controlled asthma | Participants were provided with e-cigs and cartridges (7.4 mg nicotine/cartridge) and instructed to use a maximum of 4 cartridges/day for the duration of the study period (12 weeks). | **Primary outcome:**<br>Smoking reduction (50%)<br><br>**Secondary outcomes:**<br>Smoking reduction (80%), quitters (sustained abstinence at 24 weeks, verified by exhaled CO ≤10 ppm).<br><br>There were 5 study visits at baseline, weeks 4, 8, 12 &24 | 27 participants attended the final follow-up visit. Of these, 13 had reduced cig use by ≤50%, reducing their daily cig use significantly from a median of 25 to 6 ($p<0.001$).<br><br>5 participants had reduced their cig use by ≥80%, reducing their daily cig use significantly from a median of 30 to 3 ($p=0.043$).<br><br>There were 9 quitters. Of these, 6 had continued their use of e-cigs during the follow-up period (weeks 12-24).<br><br>There were 5 smoking failures (those unable to quit/reduced tobacco use).<br><br>Mean cartridge use was 2/day.<br><br>Mouth/throat irritation, sore throat, dry cough, headache, nausea and dizziness were reported in >10% of participants at week 4, but declined throughout the study period. Only mouth and throat irritation were reported in >10% of participants. |
| **Etter & Bullen 2014**<br><br>**Switzerland/NZ** | NA | Subjects who had participated in an online survey posted on a smoking cessation website and who | The use of e-cigarette and tobacco usage was examined in follow-up surveys | Changes in e-cig and tobacco usage among smokers and ex-smokers. | 1,329 people completed the baseline survey. The one month and one-year response rates were 62% and 47%, respectively. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| **Observational study** | | agreed to follow-up at one month (n=477) and one year (n=367) | | | **1-month respondents**: Median age was 42 yrs. 72% were former smokers. 92% were using e-cigs to prevent relapse. 76% used e-cigs daily. Of the persons still smoking, the mean number of cigs/day was 18.2. 61.6% indicated that they were currently trying to quit smoking.<br><br>**1-year respondents**: Median age was 43 yrs. 76% were former smokers. 90% were using e-cigs to prevent relapse. 79% used e-cigs daily. Of the persons still smoking, the mean number of cigs/day was 16.3. 60.7% indicated that they were currently trying to quit smoking.<br><br>**Changes between baseline and follow-up**: 98% of vapors at baseline were still vaping at 1 month, 89% at 1 year.<br><br>Among daily smokers who were vaping at baseline, 91% and 72% were still vaping at 1 month and 1 year, respectively.<br><br>Among ex-smokers who were vaping daily at baseline, 99% and 92% were still vaping at 1 month and 1 year, respectively.<br><br>Among ex-smokers who were vaping daily at baseline, 6% relapsed to smoking daily or occasionally at 1 month and 1 year.<br><br>Among dual users, smoking cessation rates were 22% at 1 month and 46% at 1 year. Mean daily cigarette usage declined significantly from 11.3-6.0 cig/day from baseline to 1 month (p=0.006), but there was no significant change at 1 year. |

| Study/Type | Quality Rating | Sample Description | Method | Outcomes | Key Findings and Recommendations |
|---|---|---|---|---|---|
| ***iii) E-cigarettes to facilitate behavioral change*** | | | | | |
| **Wagener et al. 2013**<br><br>**USA**<br><br>**Uncontrolled study** | NA | 20 participants aged 18-55 yrs. who had not previously tried e-cigs, who had smoked ≥15 cigs/day for the previous year, **not currently trying to quit**, nor intending to quit within the next 30 days. Mean age was 40 yrs, 35% male, smoking an average of 18.6 cigs/day. Mean duration of smoking was 13 yrs.<br><br>Exclusions: women who were pregnant or breast feeding, history of cardiovascular distress, major psychiatric impairment | There were 3 phases of the study<br><br>**Baseline phase**: baseline visit and data collection, Exhaled CO measured to confirm smoking (≥10 ppm)<br><br>**Experimental phase:** consisted of 4 separate sessions, separated by 60 minutes in which participants sampled 3 different brands of e-cigs for 2-10 minutes in addition to their own brand of cigs (OBC), presented in random order. Nicotine levels of e-cigs were titrated to meet participants' preferences. Pre/post questionnaires related to product satisfaction, and readiness & confidence to quit were administered after each session.<br><br>**Ad libitum phase:** Participants were invited to take home a one-week's supply of the e-cig (+ nicotine cartridges) that they liked the most and to use as they wished, to be followed by a 10-minute survey (conducted by telephone) | **Primary outcome:** Product preferences, readiness and confidence to quit, product satisfaction | Participants preferred OBC to e-cigs. Mean scores: 8.6 vs 6.6 vs. 4.7 vs. 5.2 ($p<0.0001$)<br><br>There were no differences among groups in the mean scores associated with effectiveness to reduce urges/cravings (7.3 vs. 7.2 vs. 6.2 vs. 6.1, $p=0.335$).<br><br>Participants reported OBC more satisfying than e-cigs (mean scores: 8.7 vs. 6.6 vs. 5.2 vs. 5.0, $p<0.0001$)<br><br>From baseline to end of ad libitum phase, participants reported a significant increase in mean readiness to quit score ($p=0.006$) and a trend towards increased confidence to quit smoking ($p=0.053$).<br><br>While there was a 44% reduction in the use of OBC over the study period, there was no change in total tobacco use (e-cigs + OBC)<br><br>Losses to follow-up: n=4 |

# Reference List

B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. *Lancet Neurol 2010*;9(9):855-865.

Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ 2013;*346:f1326.

Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD009217. DOI: 10.1002/14651858.CD009217.pub3.

Agnoli C, Krogh V, Grioni S, Sieri S, Palli D, Masala G, Sacerdote C, Vineis P, Tumino R, Frasca G, Pala V, Berrino F, Chiodini P, Mattiello A, Panico S: A priori-defined dietary patterns are associated with reduced risk of stroke in a large Italian cohort. *J Nutr 2011;*141:1552-1558.

Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation 2015*; 131(8):721-729.

Barber PA, Pridmore HM, Krishnamurthy V, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. *Stroke 2013*;44:2327-29

Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. BMJ 2005;330:342.

Bazzano LA, Gu D, Whelton MR, et al.. Body mass index and risk of stroke among Chinese men and women. *Ann Neurol 2010*;67:11-20.

Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N: Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013;382:1629-1637.

Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M: Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control 2010*;19:98-103.

Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;5:CD009329.

Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R: EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 2013;8:e66317.

Cheng YC, Ryan KA, Qadwai SA, Shah J, Sparks MJ, Wozniak MA, et al. Cocaine Use and Risk of Ischemic Stroke in Young Adults. *Stroke 2016;*47(4):918-22.

Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation 2014*; 129(9):981-989.

de Los Rios F, Kleindorfer DO, Khoury J, et al. Trends in substance abuse preceding stroke among young adults: a population-based study. *Stroke 2012*;43:3179-83.

de Oliveira Otto MC, Mozaffarian D, Kromhout D, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr 2012*;96(2):397-404.

de Oliveira Otto MC, Nettleton JA, Lemaitre RN, et al. Biomarkers of dairy fatty acids and risk of cardiovascular disease in the Multi-ethnic Study of Atherosclerosis. *J Am Heart Assoc 2013*;2(4):e000092.

Desbois AC, Cacoub P. Cannabis-associated arterial disease. Ann Vasc Surg 2013;27:996-1005.

Du H, Li L, Bennett D, Guo Y, Key TJ, Bian Z, et al. Fresh Fruit Consumption and Major Cardiovascular Disease in China. *N Engl J Med 2016*;374(14):1332-43.

Edjoc RK, Reid RD, Sharma M. The effectiveness of smoking cessation interventions in smokers with cerebrovascular disease: a systematic review. *BMJ Open* 2012;2:e002022.

Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA: Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279-1290.

Etter JF, Bullen C: A longitudinal study of electronic cigarette users. *Addict Behav* 2014;39:491-494.

Falkstedt D, Wolff V, Allebeck P, Hemmingsson T, Danielsson AK. Cannabis, tobacco, alcohol use, and the Risk of Early Stroke. *Stroke* 2017;48(2):265-70.

Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol* 2016;15(9):913-24.

Frandsen NB, Sorensen M, Hyldahl TK, Henriken RM, Bak S. Smoking cessation intervention after ischemic stroke or transient ischemic attack. A randomized controlled pilot trial. *Nicotine Tob Res* 2012;14(4):443-447.

Fung TT, Stampfer MJ, Manson JE, et al. Prospective study of major dietary patterns and stroke risk in women. *Stroke 2004*;35:2014-19.

Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke 2001*;32:280 99.

Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA 2002*; 288(1):49-57.

Graudal N, Jurgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am *J Hypertens 2014*; 27(9):1129-1137.

Hartley L, Igbinedion E, Holmes J, et al. Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. *Cochrane Database Syst Rev 2013*;6:CD009874.

He FJ, Li J, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev 2013*;4:CD004937.

He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet 2006*;367:320-26.

He K, Merchant A, Rimm EB, et al. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ 2003*;327:777-82.

Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard BV, Kooperberg C, Rossouw JE et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006; 113(20):2425-2434.

Hooper L, Bartlett C, Davey SG, et al. Advice to reduce dietary salt for prevention of cardiovascular disease. *Cochrane Database Syst Rev 2004*;CD003656.

Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD011737. DOI: 10.1002/14651858.CD011737

Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2012;5:CD002137.

Howard BV, Van HL, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;295:655-66.

Hu D, Huang J, Wang Y, Zhang D, Qu Y. Dairy foods and risk of stroke: a meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis 2014*; 24(5):460-469.

Hu D, Huang J, Wang Y, Zhang D, Qu Y. Fruits and vegetables consumption and risk of stroke: a meta-analysis of prospective cohort studies. *Stroke 2014*; 45(6):1613-1619

Hu G, Tuomilehto J, Silventoinen K, et al. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med* 2007;167:1420-27.

Jimenez M, Chiuve SE, Glynn RJ, Stampfer MJ, Camargo CA, Jr., Willett WC, Manson JE, Rexrode KM: Alcohol consumption and risk of stroke in women. *Stroke* 2012;43:939-945.

Jood K, Jern C, Wilhelmsen L, et al. Body mass index in mid-life is associated with a first stroke in men: a prospective population study over 28 years. *Stroke* 2004;35:2764-69.

Joshy G, Korda RJ, Attia J, Liu B, Bauman AE, Banks E. Body mass index and incident hospitalisation for cardiovascular disease in 158 546 participants from the 45 and Up Study. *Int J Obes (Lond) 2014*; 38(6):848-856.

Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med* 1990;113:821-27

Kaplan RC, Tirschwell DL, Longstreth WT, Jr., Manolio TA, Heckbert SR, Lefkowitz D, El-Saed A, Psaty BM: Vascular events, mortality, and preventive therapy following ischemic stroke in the elderly. *Neurol* 2005;65:835-842.

Kiage JN, Merrill PD, Judd SE, He K, Lipworth L, Cushman M et al. Intake of trans fat and incidence of stroke in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort. *Am J Clin Nutr* 2014; 99(5):1071-1076.

Larsson SC, Orsini N. Fish consumption and the risk of stroke: a dose-response meta-analysis. *Stroke 2011*; 42(12):3621-3623.

Larsson SC, Virtamo J, Wolk A. Dairy consumption and risk of stroke in Swedish women and men. *Stroke 2012*;43:1775-80.

Larsson SC, Wallin A, Wolk A. Dietary Approaches to Stop Hypertension Diet and Incidence of Stroke: Results From 2 Prospective Cohorts. *Stroke 2016*;47(4):986-90.

Larsson SC, Wolk A. Dietary fiber intake is inversely associated with stroke incidence in healthy Swedish adults. *J Nutr 2014*;144(12):1952-1955.

Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. *Stroke 2003*;34:2475-81.

Li W, Katzmarzyk PT, Horswell R, Zhang Y, Zhao W, Wang Y et al. Body mass index and stroke risk among patients with type 2 diabetes mellitus. *Stroke 2015*; 46(1):164-169.

Li XY, Cai XL, Bian PD, Hu LR. High salt intake and stroke: meta-analysis of the epidemiologic evidence. *CNS Neurosci Ther 2012*; 18(8):691-701.

Lidegaard O, Lokkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med 2012*;366:2257-66.

Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database of Systematic Reviews 2015*, Issue 3. Art. No.: CD006936. DOI: 10.1002/14651858.CD006936.pub3.

Martinez-Gonzalez MA, Dominguez LJ, Delgado-Rodriguez M. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. *Br J Nutr 2014*; 112(2):248-259.

McDonnell MN, Hillier SL, Hooker SP, et al. Physical activity frequency and risk of incident stroke in a national US study of blacks and whites. *Stroke 2013*;44:2519-24.

McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database of Systematic Reviews 2014*, Issue 12. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub2.

Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. *Nutr Metab Cardiovasc Dis 2008*;18:283-90.

Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation 2010*;121:2271-83.

Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014;129:28-41.

Misirli G, Benetou V, Lagiou P, Bamia C, Trichopoulos D, Trichopoulou A. Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. *Am J Epidemiol* 2012; 176(12):1185-1192.

Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med 2014*; 371(7):624-634.

Mullen KA, Manuel DG, Hawken SJ, et al. Effectiveness of a hospital-initiated smoking cessation programme: 2-year health and healthcare outcomes. *Tob Control 2016*;0:1–7. doi:10.1136/tobaccocontrol-2015-052728

O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med 2014*; 371(7):612-623.

O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016;388(10046):761-775.

O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet 2010*;376:112-23.

Pandey A, Patel MR, Willis B, Gao A, Leonard D, Das SR, Defina L, Berry JD. Association Between Midlife Cardiorespiratory Fitness and Risk of Stroke The Cooper Center Longitudinal Study. *Stroke 2016*; 47:1720-1726.

Patra J, Taylor B, Irving H, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. *BMC Public Health 2010*;10:258.

Peters SA, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke 2013*;44:2821-28.

Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ* 2012;344:e2856.

Psaltopoulou T, Sergentanis TN, Panagiotakos DB, et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann Neurol 2013*;74(4) :580-91.

Qin LQ, Xu JY, Han SF, Zhang ZL, Zhao YY, Szeto IM. Dairy consumption and risk of cardiovascular disease: an updated meta-analysis of prospective cohort studies. *Asia Pac J Clin Nutr* 2015; 24(1):90-100.

Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. *Circulation 2001*;103(4):502-6.

Renoux C, Dell'aniello S, Garbe E, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519.

Reynolds K, Lewis B, Nolen JD, et al. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA 2003*;289:579-88.

Rice VH,Hartmann-Boyce J, Stead LF. Nursing interventions for smoking cessation. *Cochrane Database of Systematic Reviews 2013*; 8: CD001188.

Robinson AS, Manson JE, Lee IM, Satterfield S, Hennekens CH. Cigarette smoking and stroke ina cohort of U.S. male physicians. *Ann Intern Med* 1994;120:458-462.

Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *J Neurol Sci* 2016;364:191-196.

Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S: Body mass index, weight change and risk of stroke and stroke subtypes: the Japan Public Health Center-based prospective (JPHC) study. *Int J Obes 2011*;35:283-291.

Salehi-Abargouei A, Maghsoudi Z, Shirani F, et al. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases--incidence: a systematic review and meta-analysis on observational prospective studies. *Nutrition 2013*;29:611-18.

Sattelmair JR, Kurth T, Buring JE, et al. Physical activity and risk of stroke in women. *Stroke 2010*;41:1243-50.

Sharma S, Pakserescht M, Cruickshank K, et al. Adherence to the USDA dietary recommendations for fruit and vegetable intake and risk of fatal stroke among ethnic groups: a prospective cohort study. *BMC Neurol* 2013;13:120.

Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J et al. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation 2001*; 103(5):638-642.

Siri-Tarino PW, Sun Q, Hu FB, et al. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr 2010*;91:535-46.

Sloan MA, Kittner SJ, Feeser BR, et al. Illicit drug-associated ischemic stroke in the Baltimore-Washington Young Stroke Study. *Neurol 1998*;50:1688-93

Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr 2011*;93:158-71.

Spence JD, Bang H, Chambless LE, Stampfer MJ. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. *Stroke 2005*;36(11):2404-2409.

Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. *Cochrane Database of Systematic Reviews 2013*;5: CD000165.

Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews 2015*, Issue 10. Art. No.: CD009670. DOI: 10.1002/14651858.CD009670.pub3.

Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev 2012*;10:CD008286.

Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA 2011*;305:1777-85.

Strazzullo P, D'Elia L, Kandala NB, et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ 2009*;339:b4567.

Taylor RS, Ashton KE, Moxham T, et al. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). *Am J Hypertens* 2011;24:843-53.

Tikk K, Sookthai D, Monni S, Gross ML, Lichy C, Kloss M et al. Primary preventive potential for stroke by avoidance of major lifestyle risk factors: the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort. *Stroke 2014*; 45(7):2041-2046.

Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA 2004*;291(5):565-575.

Toossi S, Hess CP, Hills NK, et al. Neurovascular complications of cocaine use at a tertiary stroke center. *J Stroke Cerebrovasc Dis 2010*;19:273-78.

Tsivgoulis G, Psaltopoulou T, Wadley VG, Alexandrov AV, Howard G, Unverzagt FW et al. Adherence to a Mediterranean diet and prediction of incident stroke. *Stroke* 2015; 46(3):780-785.

Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. *N Engl J Med 2016;*374(25): 2430-2440.

Wagener TL, Meier E, Hale JJ, Oliver ER, Warner ML, Driskill LM, Gillaspy SR, Siegel MB, Foster S: Pilot investigation of changes in readiness and confidence to quit smoking after E-cigarette experimentation and 1 week of use. *Nicotine Tob Res* 2014;16:108-114.

Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA 2003*; 289(20):2673-2684.

Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Arch Gen Psychiatry* 2007;64:495-502.

Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Jr., Kostis JB et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998; 279(11):839-846.

Willey JZ, Moon YP, Paik MC, et al. Physical activity and risk of ischemic stroke in the Northern Manhattan Study. *Neurol 2009*;73:1774-79.

Wu CY, Chou YC, Huang N, Chou YJ, Hu HY, Li CP. Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. *PLoS One 2014;* 9(7):e102589.

Xun P, Qin B, Song Y, Nakamura Y, Kurth T, Yaemsiri S et al. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. Eur J Clin Nutr 2012; 66(11):1199-1207

Yang L, Kuper H, Sandin S, Margolis KL, Chen Z, Adami HO, Weiderpass E: Reproductive history, oral contraceptive use, and the risk of ischemic and hemorrhagic stoke in a cohort study of middle-aged Swedish women. *Stroke 2009*;40:1050-1058.

Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL et al. Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. *Int J Cardiol 2014*; 174(3):669-677.

Zheng YL, Lian F, Shi Q, Zhang C, Chen YW, Zhou YH et al. Alcohol intake and associated risk of major cardiovascular outcomes in women compared with men: a systematic review and meta-analysis of prospective observational studies. BMC Public Health 2015; 15(1):773.

* Publications not included in evidence tables, but cited in evidence summary

* Bushnell C, Arnan M, Han S. A new model for secondary prevention of stroke: transition coaching for stroke. *Front Neurol 2014*;5:219.

* Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. *Neurol 2010*; 74 (7): 588-593.

* Hedegaard U, Kjeldsen LJ, Pottegard A, Henriksen JE, Lambrechtsen J, Hangaard J, Hallas J. Improving medication adherence in patients with hypertension: a randomized trial. *Am J Med 2015*; 128 (12): 1351-61.

* Jurkiewicz MT, Marzolini S, Oh P. Adherence to a home-based exercise program for individual after stroke. *Top Stroke Rehabil 2001*; 18 (3): 277-84.

* MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly: which tools to use in clinical practice? *Drugs Aging 2005*; 33 (3): 231-255.

* Travis T. Patients perception of factors that affect adherence to dietary regimes for diabetes mellitus. *Diabetes Educ 1997*; 23 (2): 152-156.