CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Lifestyle & Risk Factor Management*

(Physical Activity, Weight Management, Oral Contraceptives, Hormone Replacement Therapy, Air Pollution, Behaviour Management)

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on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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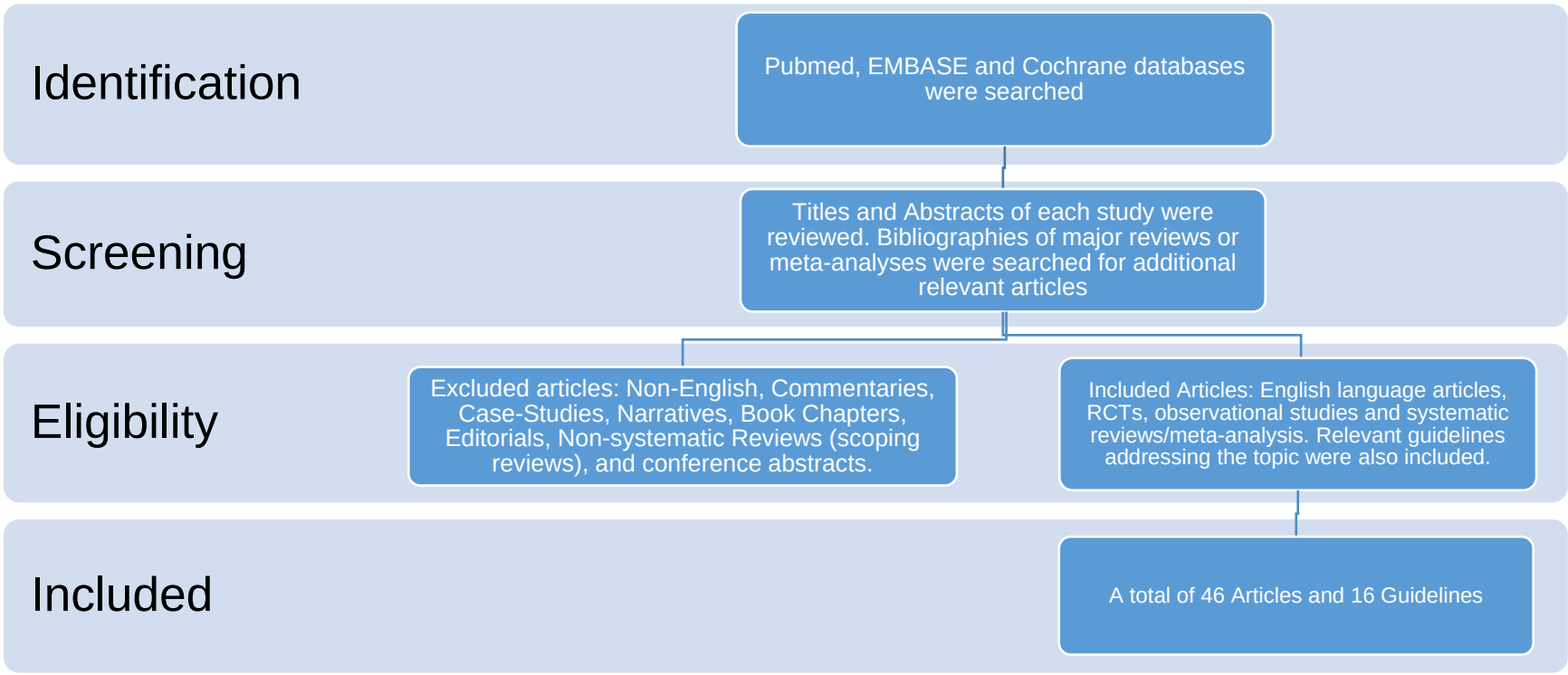
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“Stroke” and “lifestyle” or “body mass index” or “weight” or “waist circumference” or “exercise” or “contraceptive” or “hormone replacement therapy” or “air pollution” or “behavior modification”). 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
US Preventive Services Task Force. **Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults with Cardiovascular Risk Factors: US Preventive Services Task Force Recommendation Statement.** ***JAMA*. 2020;324(20):2069–2075.**	The USPSTF recommends offering or referring adults with cardiovascular disease (CVD) risk factors to behavioral counseling interventions to promote a healthy diet and physical activity. GRADE B.
Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO	Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline. Quality of evidence: moderate Strength of the recommendation: strong Physical activity may be recommended to adults with mild cognitive impairment to reduce the risk of cognitive decline. Quality of evidence: low Strength of the recommendation: conditional Interventions for mid-life overweight and/or obesity may be offered to reduce the risk of cognitive decline and/or dementia. Quality of evidence: low to moderate Strength of the recommendation: conditional
Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. **2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** ***Circulation*. 2019;140:e596–e646** **(selected)**	Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk. COE I; LOE B-NR In individuals with overweight and obesity, weight loss is recommended to improve the ASCVD risk factor profile. COE I; LOE B-R.
Tobe SW, Stone JA, Anderson T, et al. Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE)	**Secondary prevention**

Guideline	Recommendations
guideline for the prevention and management of cardiovascular disease in primary care: 2018 update. ***CMAJ* 2018; 190: E1192-e206** **(selected)**	Persons at risk of stroke and patients who have had a stroke should be assessed for vascular disease risk factors, lifestyle management issues (diet, sodium intake, exercise, weight, alcohol intake, smoking) and use of oral contraceptives or hormone replacement therapy. Persons at risk of stroke should receive information and counselling about possible strategies to modify their lifestyle and risk factors. Referrals to appropriate specialists should be made where required. They may provide more comprehensive assessments and structured programs to manage specific risk factors
Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, Harris KC, Nakhla M, Cloutier L, Gelfer M, Lamarre-Cliche M. **Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children.** ***Can J Cardiol* 2018 May 1;34(5):506-25.** **(selected)**	I. Health behaviour management Guidelines **A. Physical exercise** For nonhypertensive 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 (eg, 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 nonhypertensive or stage 1 hypertensive individuals, the use of resistance or weight training exercise (such as free weightlifting, fixed weight lifting, or handgrip exercise) does not adversely influence BP (Grade D). **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 of 18.5-24.9, 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 lose weight (Grade B). 3. Weight loss strategies should use a multidisciplinary approach that includes dietary education, increased physical activity, and behavioural intervention (Grade B). **H. Stress management** In hypertensive patients in whom stress might 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).
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Physical Activity** Practice point People with stroke or TIA should be advised and supported to undertake appropriate, regular physical activity as outlined in one of the following existing guidelines: • Australia's Physical Activity & Sedentary Behaviour Guidelines for Adults (18-64 years) OR • Physical Activity Recommendations for Older Australians (65 years and older) **Obesity**

Guideline	Recommendations
	Practice point People with stroke or TIA who are overweight or obese should be offered advice and support to aid weight loss as outlined in the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia
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)** 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 weightlifting, fixed weight lifting, or handgrip exercise) does not adversely influence BP (Grade D). 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 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). 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).
American Academy of Family Physicians (AAFP). Summary of recommendations for clinical preventive services. Leawood (KS), 2017.	The AAFP recommends offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD. (2014) (Grade: B recommendation). The AAFP recommends that primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose, or diabetes to behavioral counseling to promote a healthful diet and physical activity. (2016) (Grade: C recommendation). The AAFP recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. (2012) (Grade: D recommendation). The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening adolescents, adults, and pregnant women for illicit drug use. (2008) (Grade: I recommendation).

Guideline	Recommendations
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	**Physical activity** A- People with stroke or TIA should participate in physical activity for fitness unless there are contraindications. Exercise prescription should be individualised, and reflect treatment goals and activity recommendations. B- People with stroke or TIA should aim to be active every day and minimise the amount of time spent sitting for long periods. 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. 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. 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. 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. **Oral contraception** 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. **Hormone replacement therapy** 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. B-Post-menopausal women with ischaemic stroke or TIA should not be offered hormone replacement therapy for secondary vascular prevention.
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 **Guidelines for the prevention of stroke in patients with stroke and transient ischemic**	**Physical activity** • 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). • 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).

Guideline	Recommendations
attack: a guideline for healthcare professionals from the American heart association/American stroke association. ***Stroke 2014*;45:2160-2236.**	• 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. **Overweight/obesity** • All patients with TIA or stroke should be screened for obesity with measurement of BMI (Class I; Level of Evidence C). New recommendation 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). Homocysteinemia Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated (Class III; Level of Evidence C). New recommendation In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, 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).
Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Hypertension. **Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke*. 2014;45:3754–3832. (selected)**	1.Physical activity is recommended because it is associated with a reduction in the risk of stroke (Class I; Level of Evidence B). 2. Healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity at least 40 min/d 3 to 4 d/wk (Class I; Level of Evidence B). 1. Among overweight (BMI=25 to 29 kg/m^2) and obese (BMI >30 kg/m^2) individuals, weight reduction is recommended for lowering BP (Class I; Level of Evidence A). 2. Among overweight (BMI=25 to 29 kg/m^2) and obese (BMI >30 kg/m^2) individuals, weight reduction is recommended for reducing the risk of stroke (Class I; Level of Evidence B).
Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G.	Reduction in personal and peer exposure to airborne pollutants can be achieved through simple measures such as: Travel by walking, cycling, and public transportation should be preferred to car or motorbike. Avoid inefficient burning of biomass for domestic heating.

Guideline	Recommendations
Expert position paper on air pollution and cardiovascular disease. ***Eur Heart J.* 2014 Dec 9;36(2):83-93.**	Avoid walking and cycling in streets with high traffic intensity, particularly during rush hour traffic. Exercise in parks and gardens, but avoid major traffic roads. Limit time spent outdoors during highly polluted periods, especially infants, elderly, and those with cardiorespiratory disorders. Consider ventilation systems with filtration for homes in high pollution areas.
Eckel RH, Jakicic JM, Ard JD et al. **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.** ***J Am Coll Cardiol* 2014;63(25 Pt B):2960-2984.**	**Physical Activity** Lipids 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). Blood pressure 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. **Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***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.
Perk J, De BG, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. **European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and**	**Physical activity** Healthy adults of all ages should spend 2.5–5 h a week on physical activity or aerobic exercise training of at least moderate intensity, or 1–2.5 h a week on vigorous intense exercise. Sedentary subjects should be strongly encouraged to start light-intensity exercise programmes. Class I; Level A; GRADE Strong **Psychosocial factors** Multimodal behavioural interventions, integrating health education, physical exercise, and psychological therapy for psychosocial risk factors and coping with illness, should be prescribed. Class I; Level A; GRADE Strong

Guideline	Recommendations
Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). ***Atherosclerosis* 2012; 223:1–68.** **(selected)**	**Body weight** Weight reduction in overweight and obese people is recommended as this is associated with favourable effects on blood pressure and dyslipidaemia, which may lead to less CVD. Class I; Level A; GRADE Strong
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** ***Cerebrovasc Dis 2008*;25:457–507**	**Smoking** • It is recommended that cigarette smoking be discouraged (Class III, Level B) **Alcohol** • It is recommended that heavy use of alcohol be discouraged (Class III, Level B) Physical Activity • Regular physical activity is recommended (Class III, Level B)

Evidence Tables

Physical Activity and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lear et al. 2017 **International** **Prospective study** ***Prospective Urban Rural Epidemiology (PURE) study***	NA	130,843 participants without pre-existing CVD, aged 35-70 years. Most participants were recruited between 2003 and 2010. Mean age was 50.2 years 41.7% were men.	1-week total physical activity was assessed using the long-form International Physical Activity Questionnaire (IPAQ)15 and calculated as a total of occupation, transportation, housework, and recreational activity reported in metabolic equivalents (MET)×minutes per week. Physical activity was also reported in minutes per week of moderate intensity physical activity. Total physical activity was categorized as low (3000 MET×minutes per week) physical activity, corresponding to less than 150 minutes per week, 150–750 minutes per week, and more than 750 minutes per week of moderate intensity physical activity	**Primary outcomes**: All-cause mortality and major CVD (CVD mortality, incident MI, stroke, or heart failure), all-cause mortality and major CVD Estimates were adjusted for age, sex, wealth index, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.	Mean duration of follow-up was 6.9 years. There were 5,334 deaths in total (1,294 deaths from CVD and 4,040 deaths from non-CVD causes), 1,987 incident MIs, 2,086 incident strokes, and 386 cases of new heart failure. Higher levels of PA were associated with significant reductions in the risk of all outcomes. Combined all-cause mortality and major CVD Moderate vs. low: HR=0·85, 95% CI 0·80–0·91, p<0·0001 High vs. moderate: HR= 0·85, 95% CI 0·80–0·90, p<0·0001 High vs. low: HR= 0·73, 95% CI 0·68–0·77, p<0·0001. Similar patterns in risk reductions were reported for all-cause mortality and major CVD, separately.
O'Donnell et al. 2016 **Canada (International)**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447 persons admitted to	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alco hol intake, psychosocial factors, cardiac causes and	**Primary outcomes:** 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. Total stroke: OR=0.60, 99% CI 0.52-0.70, PAR 35.8%, 99% CI 27.7-44.7%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
INTERSTROKE Phase 2 **Case-control study**		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. 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)	ApoB:ApoA1) were 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) leisure activity for 4 hours or more per week		Ischemic stroke: OR=0.63, 99% CI 0.53-0.74, PAR 33.4%, 99% CI 24.2-44.0% Hemorrhagic stroke: OR=0.63, 99% CI 0.48-0.81, PAR 34.6%, 99% CI 21.3-50.7% The results were similar for men and women in subgroup 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 **Canada (International)** **INTERSTROKE Phase 1** **Case-control study**	NA	Participants were recruited from 22 countries from 2007-2010. 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 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. 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	**Primary outcome:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) Results were adjusted for age, sex, and region	Regular physical activity was associated with a reduced risk of total or ischemic stroke. Total stroke: OR=0.69, 99% CI 0.53-0.90, PAR 28.5%, 99% CI 14.5-48.5% Ischemic stroke: OR=0.68, 99% CI 0.51-0.91, PAR 29.4%, 99% CI 14.5-50.5% Hemorrhagic stroke: OR=0.70, 99% CI 0.44-1.13, PAR 27.6%, 99% CI 6.8-66.6%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Feigin et al. 2016 **International** **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.	**Primary outcome:** 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. In high income countries, 11.2% (95% uncertainty interval 8.3%-13.1%) of the stroke burden was attributed to low physical activity. **In Canada, 10.9% (95% uncertainty interval 7.4%-14.6%) of the stroke burden was attributed to low physical activity.** 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 **USA** **Retrospective study**	NA	19,815 participants of the Cooper Centre Longitudinal Study (CCLS) who had undergone a comprehensive examination from 1970-2009, without a history of stroke, and who were eligible for coverage under Medicare from 1999-2009.	Cardiorespiratory fitness (CRF) was measured during a baseline examination, using a treadmill exercise and classified according to 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.	**Primary outcome:** Stroke rate, stroke risk Models were adjusted for fitness, baseline age, sex, BMI, cholesterol, diabetes, smoking SBP, and age difference between first and recurrent stroke)	After 129,436 person-years of follow-up, there were 808 hospitalizations for stroke (683 men, 125 women) Stroke rate/1,000 person-years **Men** Low fitness: 9.4 (95% CI 8.2-10.9) Intermediate: 6.8 (95% CI 6.0-7.6) High: 5.2 (95% CI 4.5-6.0) **Women** Low fitness: 9.2 (95% CI 6.6-12.8) Intermediate: 4.5 (95% CI 3.4-6.0) High: 3.4 (95% CI 2.5-4.6) Risk of stroke Low fitness: Reference Intermediate: HR=0.75, 95% CI 0.62-0.91, p=0.003 High: HR=0.61, 95% CI 0.49-0.76, p<0.0001 Per 1 MET higher fitness: HR=0.92, 95% CI 0.88-0.96, p<0.0001.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Armstrong et al. 2015 **UK** **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. 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. 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.	**Primary outcome:** Incident CHD, CVD (including SAH, ICH and ischemic stroke) and DVT 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. 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. 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. 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. 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. 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 ischemic stroke.
McDonnell et al. 2013 ***Reasons for Geographic and Racial Differences in Stroke study (REGARDS)*** **Australia & US**	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,	**Primary outcome:** Incident stroke/TIA 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. There were 918 confirmed strokes and cases of TIA. 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) The risk was no longer significant after adjusting for traditional stroke risk factors (HR=1.14, 95% CI 0.95-1.37)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prospective cohort study			and 3 (4 or more times per week) Participants were contacted every 6 months by phone.		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 **USA** **Prospective follow-up of RCT**	NA	39,315 healthy women who had been participants of the Women's Health Study (1992-1995). 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. There were 8 response categories, ranging from 0-≥7 hours. 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. Weekly energy expenditures were estimated and grouped (<200, 200 to 599, 600 to 1499, or ≥1,500 kcal/week of physical activity.	**Primary outcome:** Incidence of fatal and non-fatal stroke. 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. There were 579 total strokes (473 ischemic, 102 hemorrhagic and 4 of unknown etiology). Increasing amount of time spent in PA was not associated with decreased total stroke risk (p for trend=0.21). Compared with reference category (<200 Kcals/week) 200-599 Kcals/week: fully adjusted RR=1.16, 95% CI 0.91-1.48 600-1499 Kcals/week: fully adjusted RR=0.93, 95% CI 0.72-1.20 ≥1500 Kcals/week: fully adjusted RR=0.89, 95% CI 0.68-1.17 In fully adjusted models, similar results were reported for ischemic and hemorrhagic stroke. There was no significant decrease in stroke risk. Women who engaged in vigorous PA did not have a reduced risk or total stroke, ischemic stroke or hemorrhagic stroke (p for trend=0.99, 0.84, 0.64, respectively) in fully adjusted models. 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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Willey et al. 2009 **USA** **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.	**Primary outcome:** Incident ischemic stroke 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. There were 238 incident ischemic strokes In the fully adjusted models, the risk of stroke associated with PA was: Any vs. none: HR=0.86, 95% CI 0.66-1.13 Light vs. none: HR=0.94, 95% CI 0.71-1.25 Moderate/heavy vs. none: HR=0.65, 95% CI 0.43-0.98 Moderate/heavy vs. light/none: HR=0.68, 95% CI 0.46-0.99 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. 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 **USA** **Systematic review & meta-analysis**	NA	23 studies (18 cohort and 5 case-control), published from 1966-2002, were included. Studies included females only (n=3), males only (n=10) and both sexes (n=10). Mean baseline age varied widely among studies.	Physical activity (PA) intensity was classified as low, moderate and high	**Primary outcome:** Incident stroke 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 mellitus	In the prospective studies, the mean follow-up of included studies ranged from 2-26 years. 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 studies included and RR=0.66, 95% CI 0.49-0.91, p<0.001-results from 3 studies included). 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
O'Donnell et al. 2016 **Canada (International)** **INTERSTROKE Phase 2** **Case-control study**	NA	Participants were recruited from 32 countries from 2007-2015. 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. 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. 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.	**Primary outcome:** 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) **T2 vs. T1** All stroke: OR=1.24, 99% CI 1.11-1.39 Ischemic stroke: OR=1.31, 99% CI 1.14-1.49 Hemorrhagic stroke: OR=1.16, 99% CI 0.98-13.9 **T3 vs. T1** All stroke: OR=1.44, 99% CI 1.27-1.64; PAR 18.6%, 99% CI 13.3-25.3% Ischemic stroke: OR=1.44, 99% CI 1.25-1.67; PAR 20.4%, 99% CI 14.3-28.2% Hemorrhagic stroke: OR=1.33, 99% CI 1.09-1.62; PAR 13.1%, 99% CI 6.4-25.1% In subgroup 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 **Canada (International)** **INTERSTROKE Phase 1** **Case-control study**	NA	Participants were recruited from 22 countries from 2007-2010. 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 3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or	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. Waist-to-hip ratio was expressed in tertiles, based on the overall control data. Cut-off	**Primary outcome:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) Results were adjusted for age, sex, and region	Increasing weight-to-hip ratio was associated with increased risk of stroke (T1=reference) **T2 vs. T1** All stroke: OR=1.42, 99% CI 1.18-1.71, PAR 26.5%, 99% CI 18.8-36.0% Ischemic stroke: OR=1.34, 99% CI 1.10-1.64 Hemorrhagic stroke: OR=1.62, 99% CI 1.22-2.23 **T3 vs. T1** All stroke: OR=1.65, 99% CI 1.39-1.99 Ischemic stroke: OR=1.69, 99% CI 1.38-2.07

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		outpatient, unrelated to treatment for stroke or TIA)	points used were 0.91 and 0.96, for men and 0.86 and 0.93, in women.		Hemorrhagic stroke: OR=1.41, 99% CI 1.02-1.93
Feigin et al. 2016 **International** **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	**Primary outcome:** 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. In high income countries, 28.4% (95% uncertainty interval 25.7%-29.71%) of the stroke burden was attributed to a high BMI. **In Canada, 28.4% (95% uncertainty interval 24%-33%) of the stroke burden was attributed to a high BMI.** 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 **Israel** **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 (<5th, 5th-24th, 25th-49th, 50th-74th, 75th-84th, 85th-94th and ≥95th). Follow up ceased in 2011. Underlying cause of death was coded using ICD 9th and 10th.	**Primary outcomes:** Deaths attributed to coronary heart disease, stroke, sudden death and death from unknown cause 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. Mean age at time of death from stroke was 46 years. Compared with the reference category (BMI percentile 5th -24th), the risk of death from stroke was significantly increased in the 3 highest BMI categories: 75th-85th: HR=1.42, 95% CI 1.03-1.97, p=0.034 85th-94th: HR=1.81, 95% CI 1.30-2.51, p<0.01 ≥95th: HR=2.64, 95% CI 1.72-4.08, p<0.001 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 **USA** **Prospective cohort study**	NA	29,554 participants of the Louisiana State University Hospital-Based Longitudinal Study with newly diagnosed type 2	BMI was calculated using measured height and weight at baseline and at yearly intervals during follow-up and was evaluated using 5	**Primary outcome:** Stroke Analyses were adjusted for age, sex, smoking, income, type of insurance, and other risk factors (LDL cholesterol,	Mean duration of follow-up was 8.3 yrs. There were 2821 ischemic strokes and 109 ICH. There was a significant, inverse association between stroke risk and increasing BMI.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		DM and with no previous history of stroke or CHD.	categories, and as a continuous variable.	systolic blood pressure, HbA1c, estimated glomerular filtration rate, history of atrial fibrillation, the use of antihypertensive drugs, glucose-lowering agents, and cholesterol lowering agents	Using baseline BMI: 18.5–24.9: Reference 25–29.9: HR=0.81, 95% CI 0.72-0.92 30–34.9: HR=0.77, 95% CI 0.68-0.87 35–39.9 HR=0.70, 95% CI 0.61-0.80 ≥40: HR=0.64, 95% CI 0.56-0.74 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. The same pattern of results was observed for ischemic stroke and ICH. 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). 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 **Australia** **Prospective cohort study**	NA	266, 777 men and women aged ≥45 yrs included in the 45 and Up Study with no previous history of CVD. Median age was 58 yrs.60% of participants were overweight or obese	BMI was calculated using self-reported height and weight and categorized as: 15–18.49 (underweight); 18.5–19.99, 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)	**Primary outcome:** First hospitalization for CVD, including IHD, stroke and heart failure Analyses were adjusted for age, sex, region of residence, household income, education, smoking, alcohol intake and health insurance.	Median duration of follow-up was 3.4 yrs, during which time there were 9,594 hospital admissions for CVD. Among the BMI groups, there was no significant increase in the risks for hospitalizations due to stroke BMI 15.0-19.99: HR=1.17, 95% CI 1.17-1.53 BMI 20.0-22.49: HR=1.00 (ref) BMI 22.5-24.99: HR=1.08, 95% CI 0.90-1.29 BMI 25.0-27.49: HR=1.07, 95% CI 0.90-1.29 BMI 27.5-29.99 HR=1.14, 95% CI 0.94-1.38 BMI 30.0-32.49 HR=1.23, 95% CI 0.98-1.53 BMI 32.5-50 HR=1.04, 95% CI 0.82-1.32 The risks for all hospitalization due to hospitalizations for all CVD were significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					increased across all BMI groups compared with the ref group.
Wu et al. 2014 **Taiwan** **Prospective study**	NA	77,541 participants aged ≥65 yrs included in the Taipei Geriatric Health Examination Database. 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. 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).	**Primary outcome:** All-cause and CVD-associated mortality at 5 yrs. 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. There were 3,842 (5%) deaths, of which 877 were CVD-associated deaths. The HRs for CVD-associated mortality among the BMI groups were: Underweight HR=1.79, 95% CI 1.39-2.29 Normal weight: ref Overweight HR=0.83, 95% CI 0.71-0.97 Grade 1 obesity: HR=0.71, 95% CI 0.49-1.05 Grade 2-3 obesity HR=2.24, 95% CI 4.52 Grades 1 and 2-3 combined: HR=0.88, 95% CI 0.63-1.23.
Saito et al. 2011 **Japan** **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. 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. 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. 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).
Bazzano et al. 2010 **US & China** **Prospective cohort study**	NA	154,736 Chinese men and women ≥ 40 years	Height and weight were measured at baseline, using a standardized protocol. 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 Analysis was adjusted for age, gender, physical inactivity, urbanization, geographic region, cigarette smoking, education, and alcohol consumption	Mean duration of follow-up was 8.3years. There were 7,489 incident strokes, 3,924 of which were fatal. The risk of stroke increased with increased BMI (p for linear trend<0.0001) <18.5: HR=0.86, 95% CI 0.80-0.93 25.0-29.9: HR=1.43, 95% CI 1.36-1.52 ≥30: HR=1.72, 95% CI 1.55-1.91

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The risk of ischemic stroke increased with increased BMI (p for linear trend<0.0001) <18.5: HR=0.76, 95% CI 0.66-0.86 25.0-29.9: HR=1.60, 95% CI 1.48-1.72 ≥30: HR=1.89, 95% CI 1.66-2.16 The risk of hemorrhagic stroke increased with increased BMI (p for linear trend<0.0001) <18.5: HR=1.00, 95% CI 0.89-1.13 25.0-29.9: HR=1.18 95% CI 1.06-1.31 ≥30: HR=1.54, 95% CI 1.27-1.87 The risk of fatal stroke increased with increased BMI (p for linear trend<0.0001) <18.5: HR=0.94, 95% CI 0.86-1.03 25.0-29.9: HR=1.15, 95% CI 1.05-1.25 ≥30: HR=1.47, 95% CI 1.26-1.72
Hu et al. 2007 **Finland** **Prospective cohort study**	NA	49,996 men and women, aged 25-74 years, at baseline, with no history of stroke or coronary heart disease. (Participants were part of the WHO MONICA cohort). Mean age at baseline was 45 years	BMI, waist circumference and waist-hip measures were obtained at baseline. 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 continuous variable.	Incident stroke (sex-specific total and by subtype) Analysis was 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. There were 3,228 strokes (2,554 ischemic and 674 hemorrhagic). 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) All stroke (BMI): <18.5: HR=0.80, 95% CI 0.20-3.21 25.0-29.9; HR=1.13, 95% CI 1.10-1.27 ≥30: HR=1.32, 95% CI 1.14-1.53 The risk of all stroke and ischemic were increased in women with increasing BMI (p for trend =0.04 and 0.02, respectively), but not for hemorrhagic stroke (p for trend =0.16). All stroke (BMI): <18.5: HR=1.87, 95% CI 1.12-3.14 25.0-29.9; HR=1.02, 95% CI 0.90-1.16 ≥30: HR=1.12 95% CI 0.97-1.29

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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) All stroke (by quartile with 1 as reference) Q2: HR=1.31, 95% CI 0.89-1.91 Q3:HR=1.03, 95% CI 0.70-1.51 Q4: HR=1.57 95% CI 1.01-2.25 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. 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) All stroke (by quartile with 1 as reference) Q2: HR=0.96, 95% CI 0.64-1.44 Q3:HR=1.22, 95% CI 0.83-1.79 Q4: HR=1.55 95% CI 1.06-2.26 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 **Sweden** **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 age at baseline was 51.6 years.	Height and weight were measured at baseline, along with other lifestyle and stroke risk factor data. Patients were followed until 1998. There were 6 BMI 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	Incident stroke, fatal stroke In fully adjusted models, covariates included: age, smoking status, leisure time physical activity, parental history of stroke, psychological stress, occupation, diabetes, systolic blood pressure, treatment for hypertension, and serum cholesterol.	There were 875 incident strokes during follow-up (495 ischemic, 144 hemorrhagic and 234 of unknown etiology). Increasing BMI was associated with increasing stroke risk (p for trend< 0.05) Compared with baseline BMI group (20-22.49): 22.5-24.99: HR=1.14,95% CI 0.89-1.45 25-27.49: HR=1.9, 95% CI 0.93-1.52 27.5-30.0: HR=1.31, 95% CI 1.00-1.71 >30: HR=1.52, 95% CI 1.13-2.06 A similar pattern of results was reported for ischemic stroke (p for trend<0.05) and unspecified stroke (p

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					for trend<0.050, but not for hemorrhagic stroke (p for trend=0.85).

Birth Control, Hormone Replacement Therapy, Transgender Hormone Therapy and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Hormonal Birth Control					
Roach et al. 2015 **Netherlands** **Cochrane review**	5 studies considered to be at low risk of bias, the remainder were high risk.	24 studies (22 case-control studies, one nested case-control study and one prospective study), including women aged 18-50 years.	The risks of MI and ischemic stroke were compared between combined oral contraception (COC) users and non-users.	Ischemic stroke and MI	COC users were at increased risk of MI or ischemic stroke compared with non-users (RR=1.6, 95% CI 1.3-1.9), MI (RR=1.6, 95% CI 1.2 to 2.1) and ischemic stroke (RR=1.7, 95% CI 1.5 to 1.9). Results from 24 studies included. The risk of MI or ischemic stroke increased with increasing doses of estrogen. 20 µg: RR=1.6, 95% CI 1.4 to 1.8 30 to 49 µg: RR=2.0, 95% CI 1.4 to 3.0 ≥ 50 µg: RR= 2.4, 95% CI 1.8 to 3.3 The results of 7 studies were included.
Lidegaard et al. 2012 **Denmark** **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 duration of use (<1 year, 1 to 4 years, or >4 years). The reference group comprised nonusers (never or former users)	Incidents of thrombotic events, myocardial infarction Analysis was adjusted for age, calendar year, length of schooling, educational level (ongoing or completed), and status with respect to hypertension, heart disease, diabetes, and hyperlipidemia	Duration of follow-up was 15 years. There were 3,311 thrombotic strokes (1,633 were classified as ischemic stroke). There were 34 fatal strokes. 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. Risk according to progestin type: Norethindrone: RR=2.17, 95% CI 1.49-3.15 Levonorgestrel: RR=1.65, 95% CI 1.39-1.95 Norgestimate: RR= 1.52, 95% CI 1.21-1.91 Desogestrel: RR=2.20, 95% CI 1.79-2.69 Gestodene: RR= 1.80, 95% CI 1.58-2.04

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The risk of thrombotic stroke associated with current use of ethinyl estradiol at a dose of 50 µg, compared with nonusers was: Risk according to progestin type: Norethindrone: RR=1.27, 95% CI 0.66-2.45 Levonorgestrel: RR=2.26, 95% CI 1.59-3.20 Current use of ethinyl estradiol at a dose of 20 µg was associated with an increased risk of thrombotic stroke, compared with nonusers. Risk according to progestin type: Desogestrel: RR=1.53, 95% CI 1.26-1.87 Drospirenone: RR=2.20, 95% CI 1.79-2.69 Gestodene: RR= 0.88, 95% CI 0.22-3.53 Current use of progestin only was not associated with increased stroke risk. Vaginal ring use was associated with an increased stroke risk: RR=2.49, 95% CI 1.41-4.41.
Yang et al. 2009 **Sweden** **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. 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. 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). 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).
ii) Risk of Stroke and Oral Contraceptive with Migraines					
MacClellan et al. 2007 **USA** **Case control study**	NA	386 women ages 15 to 49 years with first ischemic stroke and 614 age- and ethnicity-matched controls	The association between probable migraine (with/without visual aura) with ischemic stroke, was examined.	Risk of ischemic stroke	The odds of stroke were significantly higher among smokers (OR=1.5; 95% CI, 1.1 to 2.3), while the risk of stroke among oral contraceptive (OC) users was not (p=0.87); however, the combined odds of stroke given OC use and smoking were significantly higher (OR=7.0, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					CI 1.4 to 22.8), compared with non-smokers and non OC users.
Chang et al. 1999 **UK** **Case control study**	NA	Hospital-based study including 291 women aged 20-44 years with ischaemic, hemorrhagic, or unclassified arterial stroke and 736 age matched controls.	The association between self-reported history of headaches and stroke, was examined	Risks of ischemic and hemorrhagic stroke	Among women who were oral contraception users and who reported having migraines, the risk of ischemic stroke was increased significantly (OR=16.9, 95% CI 2.72 to 106). Among women who were low-dose oral contraception users and who reported having migraines, the risk of ischemic stroke was not increased significantly (OR=6.59, 95% CI 0.79 to 54.8). Among women who were oral contraception users and who reported having migraines, the risk of hemorrhagic stroke was not increased significantly
Schwartz et al. 1998 **USA** **Pooled analysis of 2 case control studies**	NA	Women 18-44 years randomly selected from the Kaiser Permanente and University of Washington studies who had an ischemic (n=175) or hemorrhagic stroke (n=198) and 1,191 controls	Among other analyses, the risk of ischemic stroke among those with migraine headache who were current users of oral contraceptives, was assessed.	Risk of ischemic stroke	Among 175 persons with incident ischemic stroke, 30% had a history of migraines. Among control subjects, 19.3% had a history of migraines. The odds of developing an ischemic stroke were significantly higher among women with a history of migraines who were current users of oral contraceptives (OR=2.08, 95% CI 1.19–3.65).
iii) Hormone-Replacement Therapy					
Carrasquilla et al. 2017 **Sweden** **Pooled analysis**	NA	88,914 postmenopausal women included in 5 national prospective studies, who reported data on HRT use and had no previous history of cardiovascular disease. Median age at baseline was 60 years. Median age at menopause was 50 years.	Women who reported current or previous use of HRT were categorized as ever users. Ever users who reported initiating HRT within the previous 12 months were categorized as incident users. Early initiation and late HRT initiation were defined using a 5-year cutoff as ≤5 and >5 years since menopause onset, respectively, or using a 10-year cutoff (≤10 and	Incident stroke (ischemic, hemorrhagic or unspecified) The adjusted models included age at baseline, level of education (primary school, high school, or university), smoking status (never, former, or current), BMI (<25, 25–29, or 30 kg/m^2), level of physical activity (low, moderate, or high), and age at menopause onset (41–46, 47–52, or 53–58 years)	Median duration of follow-up was 14.3 years. There were 6,371 first-time strokes, of which 1,080 were hemorrhagic. Compared with never use, estrogen only HRT was associated with a significantly longer stroke-free period (PD= 0.95, 95% CI 0.29-1.61). Compared with never use, HRT use within the previous 5 years was associated with a significantly longer stroke-free period (PD=0.67, 95% CI 0.06-1.29).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			>10 years, respectively). HRT was categorized as estrogen-only or combined (estrogen-progestin). The fifth and first percentile differences [PD] were calculated for total stroke and hemorrhagic stroke		Compared with never use, vaginal HRT was associated with a significantly longer stroke-free period (PD=1.13, 95% CI 0.06- 2.21). Compared with never use, initiation of HRT within 5- and 10-years of menopause was associated with a significantly longer stroke-free period (PD=1.00, 95% CI 0.42-1.57 and PD=0.71, 95% CI 0.18-1.24, respectively). The authors concluded that when iinitiated early in relation to menopause onset, HRT was not associated with increased risk of incident stroke, regardless of the route of administration, type of HT, active ingredient, or duration.
Canonico et al. 2016 **Nested case-control** **France**	N/A	Population source was 5,532,341 women aged 51 to 62 years with no prior history of cardiovascular disease or contraindication to hormone therapy included in the French National Health Insurance database from 2009 and 2011.	The final sample consisted of 3,144 women with ischemic stroke and 12,158 controls. Mean age was 56.6 years. Hospitalized cases of ischemic stroke were matched for age and zip code to controls. Each case was matched to ≤4 controls. Each woman was classified according to her hormone therapy exposure history at the index date – defined as the time of event for cases and the corresponding date for matched controls.	Ischemic stroke	Compared to non-users, the odds of ischemic stroke were significantly increased among oral estrogen users (OR=1.58; 95% CI: 1.01 to 2.49), but not among transdermal estrogen users (OR=0.83; 95% CI: 0.56 to 1.24) **By pharmacological classes of progestogens:** Progesterone use: OR=0.78; 95% CI: 0.49 to 1.26 Pregnanes use: OR=1.00; 95% CI: 0.60 to 1.367 Nortestosterones use: OR=1.26; 0.62 to 2.58 Norpregnanes use: OR=2.25; 95% CI: 1.05 to 4.81
Boardman et al. 2015 **UK** **Cochrane review**	Study quality was good with low risk of bias, generally	19 RCTs (n=40,410) including post-menopausal women. Mean age was 64 years.	Trials compared orally administered hormone therapy with placebo or no treatment.	**Primary outcomes:** Death from any cause, cardiovascular death, non-fatal MI, stroke, angina **Secondary outcomes:**	Duration of follow-up ranged from 7 months to 10 years. Hormone therapy did not increase the risk of all-cause mortality, nonfatal MI, angina or need for revascularization when used for primary or secondary CVD prevention

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Venous thromboemboli, pulmonary emboli (PE) Revascularisation	. **Primary prevention:** Hormone therapy did not reduce the risk of death from cardiovascular disease (RR= 0.81; 95% CI: 0.47 to 1.40 [n=3 trials]) but increased the risks of stroke (RR=1.32; 95% CI: 1.12 to 1.15 [n=4 trials]), and venous thromboembolism (RR=1.92, 95% CI 1.24 to 2.99; [n=6 trials]) **Secondary prevention:** Hormone therapy did not reduce the risks of death from cardiovascular disease or stroke (RR= 1.00; 95% CI: 0.78 to 1.29 [n=6 trials] and RR=1.09; 95% CI: 0.89 to 1.33 [n=5 trials]), but did increase the risk of venous thromboembolism (RR=2.02, 95% CI 1.13 to 3.62; [n=6 trials]) **Primary & secondary prevention combined:** The risk of stroke was increased significantly with hormone therapy (RR=1.24, 95% CI 1.10 to 1.41: [10 trials]), as were the risks of venous thromboembolism and PE (RR=1.92, 95% CI 1.36 to 2.69 and RR=1.81, 95% CI 1.32 to 2.48, respectively). **Hormone therapy commenced less than 10 years after the menopause.** Hormone therapy did not reduce the risks of death from cardiovascular causes (RR= 0.52; 95% CI: 0.29 to 0.96; [4 trials] of stroke (RR= 1.37; 95% CI: 0.80 to 2.34 [3trials]) **Hormone therapy commenced more than 10 years after the menopause.** Hormone therapy significantly increased the risk of Stroke (RR=1.21; 95% CI: 1.06 to 1.38 [n=8 trials]). The absolute risk increase for stroke was 6 per 1,000 women
Renoux et al. 2010	NA	15,710 cases and 59,985 controls, between	All prescriptions for any hormone replacement	Incident stroke	Mean duration of follow-up was 6.7 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada & Germany **Nested case-control study**		the ages of 50-79 years without a history of stroke, recruited from the UK General Practice Registry Research database, fulfilling quality criteria. Cases were women who had sustained a first stroke during the study period (1987-2006). 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. The mean age for cases and controls was 70 years at index event.	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). 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.	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.	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. The incident rate ratio (RR) of stroke associated with HRT use during the previous year, using nonusers as the reference group, was: Transdermal: RR=0.95, 95% CI 0.75-1.20 Estrogen only: RR=1.02, 95% CI 0.78-1.34 Estrogen/progestogen: RR=0.76, 95% CI 0.47-1.22 Oral : RR=1.28, 95% CI 1.15-1.42 Estrogen only: RR=1.35, 95% CI 1.16-1.58 Estrogen/progestogen: RR=1.24, 95% CI 1.08-1.41 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. 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. 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. There was no increase in stroke risk associated with duration of transdermal HRT (≤1 year or > 1 year)
Hendrix et al. 2006 **USA** **RCT** ***Women's Health Initiative (WHI)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	10,739 women, 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	Women were randomized to receive conjugated equine estrogen (CEE) 0.625 mg/d (Premarin, n=5310) or placebo (n=5429) for the duration of the study	Stroke	Mean duration of follow-up was 7.1 yrs. There were 295 strokes. At study termination 54% of participants had stopped taking their study medication The risk of total stroke was significantly increased in the CEE group (HR=1.37, 95% CI 1.09-1.73)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Estrogen only study		past 10 years, or heart attack or stroke within the past 6 months, with predicted survival of 3 or more years,			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). 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 **USA** **WHI (Estrogen+ progesterone trial)** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	16,608 post-menopausal women, with an intact uterus aged 50-79 yrs 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, 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:** Stroke	Mean duration of follow-up was 5.6 years (range was 3.7-8.6 years). There was a total of 258 strokes. The risk of total stroke was significantly increased in the CEE + progestin group (HR=1.31, 95% CI 1.02-1.68) 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). 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 **USA** **RCT** ***Heart and Estrogen/Progestin Replacement Study (HERS)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,763 postmenopausal women 55-75 years with existing CHD. 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:** Stroke, TIA	Mean duration of follow-up was 4.1 years. There were 165 stroke events (in 149 participants), 139 nonfatal and 26 fatal. 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). The risks of fatal, nonfatal, ischemic or hemorrhagic stroke were also not significantly increased with hormonal therapy.
Grady et al. 2002	CA: ☑ Blinding:	As per HERS	Additional follow-up from HERS I	**Secondary outcomes:** Stroke, TIA	Mean duration of follow-up was 6.8 years. There was a total of 331 stroke/TIAs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **RCT** ***HERS II***	Patient ☑ Assessor ☑ ITT: ☑				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). 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 **UK** **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. There were 534 stroke events among participants in the HRT group and 406 in the control group. The risk of all stroke, ischemic stroke, non-fatal stroke and stroke resulting in death or dependency, was increased among HRT users. All stroke: OR=1.29, 95% CI 1.13-1.47, p=0.0002. Results from 28 trials included. Ischemic stroke: OR=1.29, 95% CI 1.06-1.56, p=0.01 Results from 16 trials included Hemorrhagic stroke; OR=1.07, 95% CI 0.65-1.75, p=0.79. Results from 17 trials included. Fatal stroke: OR=1.28, 95% CI 0.87-1.88, p=0.21. Results from 22 trials included. Non-fatal stroke: OR=1.23, 95% CI 1.06-1.44, p=0.007. Results from 21 trials included. Death/dependency: OR=1.56, 95% CI 1.11-2.20, p=0.01. Results from 14 trials included.
iv) Cross-sex Hormone Therapy					
Nota et al. 2019 **The Netherlands** **Retrospective study**	NA	2,517 transwomen (median age 30 years) and 1,358 transmen (median age 23 years) who attended a gender clinic from 1972- 2015, who received transgender hormone treatment (THT), whose start date of THT was known, and who had at least 1 follow-up visit	Age-adjusted, standardized incidence ratios (SIRs) were calculated for the outcomes of interest, by comparing the expected outcomes of the reference population of Dutch or Norwegian general populations with those of the THT group	**Primary outcomes:** Venous thromboembolism (VTE), stroke, and myocardial infarction (MI)	**Transwomen** Total duration of follow-up was 22,830 years (mean of 9.07 years, median of 5.95 years). Compared with the reference group of women, the SIRs for all outcomes was significantly higher in transwomen (stroke, 2.42, 95% CI 1.65–3.42; MI, 2.64, 95% CI 1.81–3.72; VTE 5.52, 95% CI 4.36–6.90). Compared with the reference group of men, the SIRs for stroke and VTE were significant higher in transwomen (1.8 and 4.55, respectively)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Transmen Total duration of follow-up was 11,003 years (mean of 8.1 years, median of 4.1 years). Compared with the reference group of women, the SIRs for MI was significantly higher in transmen (3.69, 95% CI 1.94–6.42). Compared with the reference group of men, none of the SIRs, for any of the outcomes were significantly higher in transmen.
Getahun et al. 2018 **USA** **Retrospective study**	N/A	Cohorts of transfeminine (n=2,842) and transmasculine (n=2,118) persons with matched reference groups of cisgender men (n=48,686) and women (n= 48,775)	The potential increases in the risks of the primary outcomes in transgender men and women, were estimated relative to cisgender men and women.	**Primary outcomes:** Venous thromboembolism (VTE), ischemic stroke, and myocardial infarction (MI)	**Transfeminine group** The mean duration of follow-up was 4.0 years. The incidence of VTE was 5.5 per 1,000-person years (95% CI 4.3–7.0). Compared with the reference groups of cisgender men and women, the risks were significantly increased (HR=1.9, 95% CI 1.4–2.7 and HR= 2.0, 95% CI 1.4–2.8, respectively). The incidence of ischemic stroke was 4.8 per 1,000-person years (95% CI 3.7–6.3). Compared with the reference group of cisgender men, the risk of ischemic stroke was not significantly increased, but was compared with cisgender women (HR=1.9, 95% CI 1.3–2.6). In a subgroup of persons (n=853) for which the exact date of hormone therapy was initiated, the incidence of ischemic stroke was 3.8 per 1,000-person years (95% CI2.0–7.3) in persons who had been on hormone therapy for 0-6 years and 36.2 per 1,000 persons years (95% CI 18.1–72.4) in persons receiving hormone therapy for >6 years. The risk of ischemic stroke was significantly higher compared with both cisgender men and women (HR= 9.9, 95% CI 3.0–33.1 and HR=4.1, 95% CI 1.5–11.4, respectively.) **Transmasculine group**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The mean duration of follow-up was 3.6 years. The incidence of VTE was 3.1 per 1,000-person years (95% CI 2.0-4.6). Compared with the reference groups of cisgender men and women, the risk of VTE was not significantly increased. The incidence of ischemic stroke was 2.1 per 1,000-person years (95% CI 1.3-3.5). Compared with the reference groups of cisgender men and women, the risk of ischemic stroke was not significantly increased. In a subgroup of persons (n=585) for which the exact date of hormone therapy was initiated, the incidence of ischemic stroke was 1.7 per 1,000-person years (95% CI 0.4-6.7). The 0-2 and >6-year risk of ischemic stroke was not calculated.
Maraka et al. 2017 **USA** **Systematic review & meta-analysis**	Studies had a moderate risk of bias	29 studies included adolescent and adult transgender individuals who used sex steroids, (with/without gender reassignment surgery). The mean age of the male to female (MTF) group ranged from 19.3 to 43.7 years, and the mean age of the female to male (FTM) group ranged from 21.7 to 37.5 years	Studies examined changes in lipid profiles and increased risks of cardiovascular events after exposure to cross-sex hormone therapy (estrogen, antiandrogens and gonadotropin-releasing hormone (GnRH) agonists in MTF persons and testosterone in FTM persons). Studies were included if they provided a pre-post intervention comparison of participants followed up for ≥ 3 months and studies that compared cross-sex hormones vs. control for ≥ 3 months.	**Primary outcomes:** Changes in lipid profiles, Venous thromboembolism (VTE), stroke, MI and mortality	Exposure and duration of follow-up ranged from 3 months to 41 years. **Female-to-male (n=1,500):** There was a significant increase in mean serum TG levels at 3 to 6 months of therapy (9 mg/dL; 95% CI: 2.5 to 15.5 mg/dL) and at ≥24 months (21.4 mg/ dL; 95% CI: 0.1 to 42.6 mg/dL), but not at 12 months, compared with baseline. There were significant increases in mean LDL-chol at 12 and ≥24 months, with significant decreases in HDL chol at 3-6 months, 12 months and ≥24 months. During follow-up, there were 13 deaths, no strokes, 1 MI and 1 VTE. **Male to female (n=3,231)** There were no significant changes in serum TG, LDL chol, HDL chol or total chol. During follow-up, there were 139 deaths, 56 VTEs, 8 strokes and 14 MIs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Asscheman et al. 2011 **The Netherlands** **Prospective cohort study**	NA	966 male-to-female (MtF) and 365 female-to-male (FtM) transsexuals, who started cross-sex hormones before July 1, 1997. Mean age at baseline of MtF was 31.4 years and 26.1 years for FtM.	All-cause and cause-specific mortality rates in subjects receiving cross-sex hormone treatment were estimated. MtF transsexuals received treatment with different high-dose estrogen regimens and cyproterone acetate 100 mg/day. FtM transsexuals received parenteral/oral testosterone esters or testosterone gel. After surgical sex reassignment hormonal treatment was continued with lower doses.	**Primary outcome:** Standardized mortality ratio (SMR)	Median duration of follow-up was 18.5 years. **MtF** Mean duration of hormone therapy was 19.4 years. 86.7% had sex reassignment surgery. There were 122 deaths (12.6%). SMR was significantly increased compared with the reference (general) population. (SMR=1.51, 95% CI 1.47–1.55). The most frequently cited causes of death were cancer, suicide/illicit drug use, and cancer. There were 5 deaths due to stroke, which was not significantly higher compared with the general population. (SMR= 1.26, 95% CI 0.93–1.64); however, among the 4 persons who died before age 65 the SMR for fatal stroke was 2.11 (95% CI 1.32–3.21) **FtM** Mean duration of hormone therapy was 18.8 years. 94% had sex reassignment surgery. There were 12 deaths (3.4%). SMR was not significantly increased compared with the reference (general) population. (SMR=1.12, 95% CI 0.89-1.59). Cancer was the most frequent cause of death. There were no fatal strokes.

Air Pollution & Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Yang et al. 2019 **China**	All studies scored 6 or 7 on the Ottawa Newcastle	35 studies, published from 2004-2018, including 53 cohorts with 21.09 million participants. Of the cohorts,	The associations between air pollutants ($PM_{2.5}$, PM_{10}, NO_2, or O_3) with the risk of CVD disease, were	Total CVD events, CVD incidence, CVD mortality, total stroke events, stroke incidence, stroke mortality, total IHD	Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a significantly increased risk of total CVD events (RR= 1.12, 95% CI 1.05–1.19), CVD incidence (RR= 1.12,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & meta-analysis	Scale	17 were from America, 6 from Canada, 18 from Europe, 8 from China, 2 from Japan, 1 from Korea, and 1 from multiple areas (China, Ghana, India, Mexico, Russia, and South Africa).	examined.	events IHD incidence, or IHD mortality	95% CI 1.05–1.19), and CVD mortality (RR= 1.11,95% CI 1.08–1.14). Each 10 µg/m^3 increase in $PM_{2.5}$ was associated with a significantly increased risk of stroke (RR=1.12, 95% CI 1.02–1.16), and stroke mortality (RR=1.11, 95% CI 1.07–1.14). There was no significantly increased risk of stroke associated with increased concentrations of PM_{10}, NO_2, or O_3.
Stafoggia et al. 2017 **Europe** ***The European Study of Cohorts for Air Pollution Effects (ESCAPE) Project***	NA	99,446 participants from 11 existing cohort studies from Finland, Sweden, Denmark, Germany, and Italy. Individuals were enrolled at different periods, ranging from 1992 to 2007. Mean ages at baseline ranged from 44-74 years. The percentage of women ranged from 48%-65%	The association between long-term exposure to multiple air pollutants and the incidence of stroke in European cohorts, was assessed. Exposures included particulate matter ≤ 2.5 µm in diameter ($PM_{2.5}$), coarse PM (PM 2.5 and 10 µm), PM_{10} (PM ≤ 10 µm), $PM_{2.5}$ absorbance, nitrogen oxides, and traffic indicators Models were adjusted for age, sex, year of enrollment, marital status, education level, occupation status, smoking status, area-level variables (mean income at municipality level	Incident stroke	There were 3,086 strokes. The median $PM_{2.5}$ concentrations ranged from 7-30 µg/m^3 A 5-µg/m^3 increase in annual $PM_{2.5}$ exposure was associated with 19% non-significant increased risk of incident stroke (HR=1.19, 95% CI 0.88, 1.62). No other air pollution exposures significantly increased the risk of incident stroke.
Cohen et al. 2017 **International** **Global Burden of Diseases Study 2015**	NA	Individuals included in the Global Burden of Diseases Study (1990-2015)	The burden of disease attributable to the effects of long-term exposure to ambient fine particle air pollution including particulate matter of ≤ 2.5 µm in diameter ($PM_{2.5}$) and ozone from 1990 to 2015, were estimated	Mortality, Disability-adjusted life-years (DALYs), for ischaemic heart disease (IHD), cerebrovascular disease (ischaemic stroke and haemorrhagic stroke), lung cancer, chronic obstructive pulmonary disease (COPD) and lower respiratory infections (LRI), and the burden attributable to ozone for COPD	In 2015, Canada was among the countries with the lowest exposure to $PM_{2·5}$ with concentrations ≤8·0 µg/m³. In comparison, global population-weighted $PM_{2·5}$ ozone levels were 39·7 µg/m³ in 1990 and 44·2 µg/m³ in 2015 Long-term exposure to $PM_{2·5}$ contributed to 4·2 million (95% Uncertainty Interval [UI] 3·7- 4·8 million) deaths and to a loss of 103·1 million (90·8-115·1 million)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					DALYs in 2015, representing 7·6% of total global deaths and 4·2% of global DALYs, which represented an increase from 1990. In 2015, ambient $PM_{2·5}$ was the 5th-ranked risk factor for global deaths and 6th-ranked risk factor for DALYs. In Canada, <3% of deaths were attributable to exposure to $PM_{2·5}$.
Kim et al. 2017 **South Korea** **Retrospective study**	NA	136,094 participants included in the National Health Insurance database, aged ≥18 years who resided in Seoul between 2007 and 2013, with no previous history of cardiovascular disease. Mean age at baseline was 42 years, 49.1% were men.	The association between long-term exposure to multiple air pollutants and the incidence of the outcomes was assessed. Exposure included particulate matter ≤ 2.5 μm in diameter ($PM_{2.5}$), particles with a diameter 2.5-10 μm ($PM_{2.5-10}$), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3). Models were adjusted for age, sex, socioeconomic status, hypertension, diabetes, dyslipidemia, chronic renal failure, end-stage renal diseases, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, malignancy, BMI, fasting blood glucose total cholesterol and hemoglobin	Cardiovascular mortality, acute myocardial infarction, congestive heart failure, and stroke	The median duration of follow-up was 7.0 years. The daily mean concentration of $PM_{2.5}$ during the study period was 25.0 μg/m^3. The risk of cardiovascular death was increased significantly for each 1-μg/m^3 increase of $PM_{2.5}$ (HR=1.36, 95% CI 1.11–1.66, p =0.003), as were the risks of stroke (HR=1.39, 95% CI 1.27–1.52, p<0.001), and all other outcomes. The risks of all outcomes were increased significantly for each 1-μg/m^3 increase of $PM_{2.5-10}$, CO per IQR 0.25 ppm, SO_2 per IQR 2.54 ppb and NO_2, per IQR 18.4 ppb. Ozone was associated with a significantly reduced risk of all outcomes (per IQR 15.9 ppb). Long-term exposure to a $PM_{2.5}$ concentration >25 μg/m^3 was responsible for 30.8% of the population-attributable risks for composite cardiovascular events, which was higher than that of hypertension (27.2%), diabetes (12.1%), dyslipidemia (10.9%) or obesity (11.0%).
Crouse et al. 2012	NA	2,145,400 persons included in the 1991-2001 Canadian	The association between long-term exposure to fine	Cardiovascular mortality	There were ~ 21.7 million person years of follow-up

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **Prospective study**		mortality follow-up study, who were nonimmigrants, ≥25 years and were not a long-term resident of an institution such as a prison, hospital, or nursing home. Mean age at baseline was 45.3 years, 49% were men. The sample represented 20% of residents mandated to complete the census.	particulate matter [≤ 2.5 μm in aerodynamic diameter (PM2.5)], derived from satellite data and non-accidental causes of death were estimated, controlling for ecological covariates and mortality risk factors		The median $PM_{2.5}$ concentration was 7.4 μg/m3, the mean was 8.7 $\mu g/m^3$ The risk of all accidental death was increased significantly per 10 μg/m3 in $PM_{2.5}$ (HR=1.10, 95% CI 1.05, 1.15). Similarly, the risks of mortality associated with cardiovascular diseases, circulatory diseases, and ischemic heart disease were all significantly increased, while the risk of mortality-related cerebrovascular disease, was not significantly increased (HR=1.04, 95% CI 0.93, 1.16)

Behavoiral and Educational Interventions to Improve Modifiable Risk Factors

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ahmadi et al. 2020 **Germany** **RCT** ***INSPiRE-TMS***	CA: ☑ Blinding: Patient ☑ Assessor ☒ ITT: ☑	2,098 patients recruited from 8 centres with recent minor stroke or TIA within the previous 2 weeks and with at least one modifiable risk factor. Mean age was 67·4 years, 34% were women.	Participants were randomized (1:1) to a support programme + conventional care or to conventional care alone. The support programme used feedback and motivational interviewing strategies with 8 outpatient visits over 2 years, which aimed to improve adherence to secondary prevention targets including blood pressure, smoking, diabetes, cholesterol, physical activity, nutrition, and pharmacological therapy.	**Primary outcome:** Composite of major vascular events (stroke, acute coronary syndrome, and vascular death) **Secondary outcomes:** Single components of the primary outcome	Mean duration of follow-up was 3·6 years. The primary outcome occurred in 163 (15·8%) of patients in the support programme group compared with 75 (16·8%) of patients in the conventional care group (HR= 0·92, 95% CI 0·75–1·14). There were 122 strokes (11·8%) in the support programme group vs. 119 (11·4%) in the conventional group (HR= 1·02, 95% CI 0·79–1·32). There were no significant differences in the number of acute coronary syndrome events or vascular death between groups. At 3 years, significantly more participants in the support programme had achieved

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					blood pressure, LDL-cholesterol and physical activity targets.
Fukuoka et al. 2019 **Japan** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor ☒ ITT: ☑	321 persons aged 40- 80 years who experienced their last ischemic stroke event or TIA within the previous year. Persons with mRS scores ≥4 and those with dementia, were excluded. Mean age was 67.5 years, 48% were women.	Participants were randomized 1:1 to a nurse-led disease management program (DMP) or usual care. Participants in the DMP group received education through 4 interviews and 10 phone calls over the 6-month study period. The focus of the intervention was risk factor management using different educational booklets created by the researchers and a self-management journal in which the subjects recorded their daily blood pressure, body weight, and lifestyle improvement goals. Participants in the usual care group received a leaflet on risk factor management and a self-management journal.	**Primary outcome:** Change in the Framingham risk score (general cardiovascular disease 10-year risk) from baseline **Secondary outcome:** Stroke recurrence, onset of cardiovascular disease, all-cause mortality, and all vascular events Outcomes were evaluated at baseline, 6 months, 12 months, 18 months, 24 months, and 30 months after registration	The mean Framingham risk scores at baseline were 17.2 in the DMP intervention group and 17.2 in the usual care group. At no point at either the end of the intervention or during follow-up was the change in Framingham risk score significantly different between groups. Mean difference at 6 months was -0.68 (95% CI -1.49 to 0.14), mean difference at 30 months was -0.51 (95% CI -1.42 to 0.39). The risks of all vascular events, stroke recurrence, cardiovascular disease and all-cause mortality were not significantly lower in the DMP group
Bridgwood et al. 2018 **UK** **Cochrane review**	Assessed as moderate- or low-quality	42 RCTs including 33,840 participants ≥18 years, with confirmed stroke or TIA. The mean or median age of participants ranged from 60 years to 74.3 years.	Trials examined stroke service interventions designed to improve modifiable risk factor control. Most studies were set in primary care or community settings. Trial examined organizational approaches (n=26) behavioral and educational (n=16). Usual care was the comparator in 30 trials. The interventions were initiated during hospitalization for acute stroke through 18 months post stroke.	**Primary outcomes:** Mean systolic and diastolic blood pressure (SBP, DBP), achievement of target blood pressure, medication adherence, BMI, mean $HgA1_C$, mean LDL chol **Secondary outcome:** Recurrent cardiovascular events	**Educational or behavioral interventions** Mean SBP of participants in the control group at the end of treatment/follow-up was 135.59 mmHg. The mean SBP of those in the intervention group was 2.81 mm Hg lower (95% CI -7.02 to 1.39 mm Hg). Based on results from 11 RCTs. Mean DBP of participants in the control group at the end of treatment/follow-up was 78.3 mmHg. The mean SBP of those in the intervention group was 0.83 mm Hg lower (95% CI –2.8 to 1.13 mm Hg). Based on results from 11 RCTs.

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			Duration of the intervention ranged from 3-12 months in most trials.		The odds of achieving blood pressure target were not increased significantly among persons in the intervention groups (OR=1.34, 95% CI 0.70 to 2.59). Mean LDL chol level of participants in the control group at the end of treatment/follow-up was s 2.62 mmol/ L. The mean LDL-chol of those in the intervention group was 0.13 mol/L lower (95% CI-2.8 to 0.02 mmol/L). Based on results from 4 RCTs. Mean HbA1c was 5.98% for participants in the control group. The mean Hg A1c for those in the intervention group was 0.11% lower (95% CI -0.39% to 0.17%). Results from 1 RCT included. Mean BMI was 24.0 for participants in the control group. The mean BMI for those in the intervention group was 0.22 lower (95% CI -0.85 to 1.29). Results from 2 RCT included. **Organizational interventions** The pattern of results was similar as per behavioral interventions, although interventions were associated with significantly higher odds of achieving target BP (OR=1.44, 95% CI 1.09 to 1.90). Results from 13 trials included. The odds of recurrent stroke or TIA were not reduced significantly (OR= 0.66, 95% CI 0.23 to 1.86). Results from 4 trials included.
Deijle et al. 2017 **The Netherlands** **Systematic review**	Risk of bias was assessed as low (n=9), moderate (n=8) or high (n=5)	22 RCTs (n=2,574) including participants ≥18 years with a history of stroke or TIA.	Trials compared the effect of lifestyle interventions with usual care or no intervention, which aimed to improve cardiovascular risk profile, recurrence of	**Primary outcomes:** Cardiovascular events, mortality, blood pressure, cholesterol, cardiovascular fitness	The risk of future cardiovascular events and mortality were not reduced significantly with intervention (RR=0.79, 95% CI 0.30-2.06 and RR=1.16, 95% CI 0.82-1.63, respectively). Results from 4 trials included.

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			cardiovascular events and mortality. Trials evaluated a behavior change interventions (n=12), cardiovascular fitness (n=5) and a combined intervention (n=5). The timing of the intervention ranged from 2 weeks to >1 year after the index event.		Mean systolic blood pressure was significantly lower in the intervention group (MD=-3.63, 95% CI -5.63 to -1.63, p=0.0004). Results of 10 trials included. Interventions with a duration of > 4 months were more effective than those lasting ≤4 months, as were those that included ≥3 behavior change techniques compared with <3. Cardiovascular fitness interventions and combined interventions were both effective in reducing SBP, while behavior change interventions were not. There was no significant difference in mean chol levels associated with intervention (MD=0.09 mmol, 95% CI -0.03 to 0.48). Results from 3 trials included.

Abbreviations

ARR: absolute risk reduction	CA: concealed allocation	CI: confidence interval
HR: hazard ratio	ITT: intention-to-treat	NA: Not assessed
OR: odds ratio	RR: relative risk	RRR: relative risk reduction

Reference List

Ahmadi M, Laumeier I, Ihl T, et al. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (INSPiRE-TMS): an open-label, randomised controlled trial. *Lancet Neurol* 2020; 19: 49–60.

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.

Asscheman H, Giltay EJ, Megens JA, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol.* 2011 Apr 1;164(4):635-42.

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.

Boardman HMP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD002229. DOI: 10.1002/14651858.CD002229.pub4 **NEW**

Bridgwood B, Lager KE, Mistri AK, Khunti K, Wilson AD, Modi P. Interventions for improving modifiable risk factor control in the secondary prevention of stroke. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD009103. DOI: 10.1002/14651858.CD009103.pub3. **NEW**

Canonico M, Carcaillon L, Plu-Bureau G, Oger E, Singh-Manoux A, Tubert-Bitter P, Elbaz A, Pierre-Yves S. Postmenopausal hormone therapy and risk of stroke. *Stroke* 2016; 47(7): 1734-1741. **NEW**

Carrasquilla GD, Frumento P, Berglund A, et al. Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. *PLoS medicine*. 2017; 14: e1002445.

Chang C, Donaghy M, Poulter N, et al. Migraine and stroke in young women: case-control study. The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ.* 1999;318:13-18.

Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet.* 2017 May 13;389(10082):1907-18. **NEW**

Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Enviro Health Perspect*. 2012;120(5):708-14. **NEW**

Deijle IA, Van Schaik SM, Van Wegen EE, Weinstein HC, Kwakkel G and Van den Berg-Vos RM. Lifestyle Interventions to Prevent Cardiovascular Events After Stroke and Transient Ischemic Attack: Systematic Review and Meta-Analysis. *Stroke*. 2017; 48: 174-9. **NEW**

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.

Fukuoka Y, Hosomi N, Hyakuta T, Omori T, Ito Y, Uemura J, Yagita Y, Kimura K, Matsumoto M, Moriyama M, DMP Stroke Trial Investigators. Effects of a Disease Management

Program for Preventing Recurrent Ischemic Stroke: A Randomized Controlled Study. *Stroke*. 2019; 50:705-712. **NEW**

Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, Hunkeler E, Lash TL, Millman A, Quinn VP, Robinson B. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med* 2018 Aug 21;169(4):205-13. **NEW**

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.

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.

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.

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.

Kim H, Kim J, Kim S, Kang SH, Kim HJ, Kim H, et al. Cardiovascular Effects of Long-Term Exposure to Air Pollution: A Population-Based Study With 900 845 Person-Years of Follow-up. J Am Heart Assoc. 2017;6:e007170. **NEW**

Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet (London, England)*. 2017; 390: 2643-54.

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.

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

MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke*. 2007 Sep;38(9):2438-45.

Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. Sex steroids and cardiovascular outcomes in transgender individuals: a

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.

Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. The Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy: Results from a Large Cohort Study. *Circulation.* 2019; 139:1461–1462. **NEW**

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.

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.

Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD011054. DOI: 10.1002/14651858.CD011054.pub2.

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.

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

Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, Quesenberry CP Jr, Kelaghan J. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. *Stroke.* 1998 Nov;29(11):2277-84.

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

Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect* 2014;122(9):919-25. **NEW**

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.

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.

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.

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.

Yang H, Li S, Sun L, Zhang X, Cao Z, Xu C, Cao X, Cheng Y, Yan T, Liu T, Wang Y. Smog and risk of overall and type-specific cardiovascular diseases: A pooled analysis of 53 cohort studies with 21.09 million participants. *Environ Res.* 2019 May 1;172:375-83. **NEW**

* Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. *Neurol 2010*; 74 (7): 588-593. (not included in evidence tables, but cited in evidence summary).