CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Lifestyle & Risk Factor Management (Alcohol Consumption, Recreational Drug Use and Smoking Cessation)*

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Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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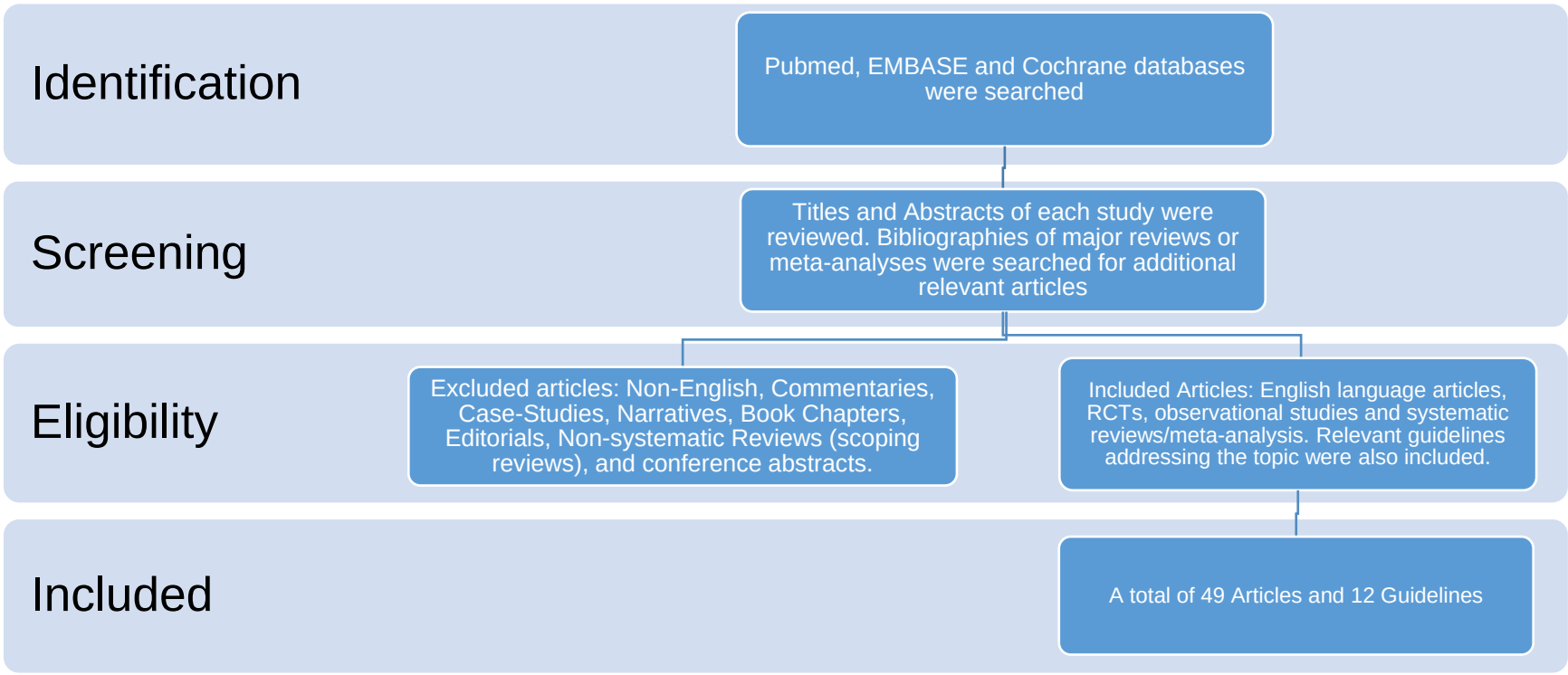
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“Stroke” and “lifestyle” or “alcohol” or “recreational drugs or illicit drugs” ”smoking” or electronic cigarettes”). 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
Page RL, Allen LA, Kloner RA, et al. **Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement from the American Heart Association.** ***Circulation* 2020 Sep 8;142(10):e131-e152.**	This statement reviews the pharmacology, pharmacokinetics, and pharmacodynamics of cannabinoids, its potential and known benefits, safety considerations including cardiac- and vascular-specific effects, smoking and vaping concerns, chronic side effects, addiction concerns, drug interactions, and concerns in specific populations (youth and pregnant women, geriatrics, and persons with cardiovascular disease or cardiovascular risk factors). This statement also addresses issues related to policy and public health, emphasizing the need for education (clinicians and the general public), research and specific legal action.
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.** **(selected)**	Healthcare staff should strongly recommend that all patients with AIS who have smoked in the past year quit smoking (class I, level of evidence C). Patients with AIS who smoke should consider starting intervention measures combined with drug therapy and behavioural support during hospitalisation (class IIb, level of evidence B). For alcohol drinkers, it may be reasonable for men to drink ≤2 units and non-pregnant women to drink ≤1unit per day (class IIb, level of evidence B). The relationship between drugs and stroke needs to be further studied. Drugs may be a risk factor for stroke and a factor for poor prognosis (class III, level of evidence C).
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 tobacco cessation should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits. Quality of evidence: low Strength of the recommendation: strong The Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia. Quality of evidence: moderate Strength of the recommendation: conditional

Guideline	Recommendations
	A healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet. Quality of evidence: low to high (for different dietary components) Strength of the recommendation: conditional Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia. Quality of evidence: moderate Strength of the recommendation: strong Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits. Quality of evidence: moderate (for observational evidence) 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)**	In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. COE I; LOE A
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**	I. Health behaviour management Guidelines C. Alcohol consumption To prevent hypertension and reduce BP in hypertensive adults, individuals should limit alcohol consumption to ≤ 2 drinks per day, and consumption should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women (Grade B). (Note: One standard drink is considered to be equivalent of 13.6 g or 17.2 mL of ethanol or approximately 44 mL [1.5 oz] of 80 proof [40%] spirits, 355 mL [12 oz] of 5% beer, or 148 mL [5 oz] of 12% wine.)

Guideline	Recommendations
Treatment of Hypertension in Adults and Children. ***Can J Cardiol* 2018 May 1;34(5):506-25.** **(selected)**	
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Smoking** Practice point People with stroke or TIA who smoke should be advised to stop and assisted to quit in line with existing guidelines, such as Supporting smoking cessation: a guide for health professionals. **Alcohol** Practice point People with stroke or TIA should be advised to avoid excessive alcohol consumption (>2 standard drinks per day) in line with the Australian Guidelines to Reduce Health Risks from Drinking Alcohol.
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)** C. Alcohol consumption: To prevent hypertension and reduce BP in hypertensive adults, individuals should limit alcohol consumption to ≤ 2 drinks per day, and consumption should not exceed 14 standard drinks per week for men and 9 standard drinks per week for women (Grade B). (Note: One standard drink is considered to be equivalent of 13.6 g or 17.2 mL of ethanol or approximately 44 mL [1.5 oz] of 80 proof [40%] spirits, 355 mL [12 oz] of 5% beer, or 148 mL [5 oz] of 12% wine.
Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, Rehm J, Room R. **Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations.** ***Am J Public Health*. 2017;107:e1–e12**	Recommendation 1: The most effective way to avoid any risks of cannabis use is to abstain from use.Those who decide to use need to recognize that they incur risks of a variety of—acute and long-term—adverse health and social outcomes. These risks will vary in their likelihood and severity with user characteristics, use patterns, and product qualities, and so may not be the same from user to user or use episode to another. [Evidence Grade: None required.] Recommendation 2: Early initiation of cannabis use (i.e., most clearly that which begins before age 16 years) is associated with multiple subsequent adverse health and social effects in young adult life. These effects are particularly pronounced in early-onset users who also engage in intensive and frequent use. This may be in part because frequent cannabis use affects the developing brain. Prevention messages should emphasize that, the later cannabis use is initiated, the lower the risks will be for adverse effects on the user's general health and welfare throughout later life. [Evidence Grade: Substantial.]

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	Recommendation 3: High THC-content products are generally associated with higher risks of various (acute and chronic) mental and behavioral problem outcomes. Users should know the nature and composition of the cannabis products that they use, and ideally use cannabis products with low THC content. Given the evidence of CBD's attenuating effects on some THC-related outcomes, it is advisable to use cannabis containing high CBD:THC ratios. [Evidence Grade: Substantial.] Recommendation 4: Recent reviews on synthetic cannabinoids indicate markedly more acute and severe adverse health effects from the use of these products (including instances of death). The use of these products should be avoided. [Evidence Grade: Limited.] Recommendation 5: Regular inhalation of combusted cannabis adversely affects respiratory health outcomes. While alternative delivery methods come with their own risks, it is generally preferable to avoid routes of administration that involve smoking combusted cannabis material (e.g., by using vaporizers or edibles). Use of edibles eliminates respiratory risks, but the delayed onset of psychoactive effect may result in the use of larger than intended doses and subsequently increased (mainly acute, e.g., from impairment) adverse effects. [Evidence Grade: Substantial.] Recommendation 6: Users should avoid practices such as "deep inhalation," breath-holding, or the Valsalva maneuver to increase psychoactive ingredient absorption when smoking cannabis, as these practices disproportionately increase the intake of toxic material into the pulmonary system. [Evidence Grade: Limited.] Recommendation 7: Frequent or intensive (e.g., daily or near-daily) cannabis use is strongly associated with higher risks of experiencing adverse health and social outcomes related to cannabis use. Users should be aware and vigilant to keep their own cannabis use—and that of friends, peers, or fellow users—occasional (e.g., use only on 1 day/week, weekend use only, etc.) at most. [Evidence Grade: Substantial.] Recommendation 8: Driving while impaired from cannabis is associated with an increased risk of involvement in motor-vehicle accidents. It is recommended that users categorically refrain from driving (or operating other machinery or mobility devices) for at least 6 hours after using cannabis. This wait time may need to be longer, depending on the user and the properties of the specific cannabis product used. Besides these behavioral recommendations, users are bound by locally applicable legal limits concerning cannabis impairment and driving. The use of both cannabis and alcohol results in multiply increased impairment and risks for driving, and categorically should be avoided. [Evidence Grade: Substantial.] Recommendation 9: There are some populations at probable higher risk for cannabis-related adverse effects who should refrain from using cannabis. These include individuals with predisposition for, or a first-degree family history of, psychosis and substance use disorders, as well as pregnant women (primarily to avoid adverse effects on the fetus or newborn). These recommendations, in part, are based on precautionary principles. [Evidence Grade: Substantial.]

Guideline	Recommendations
	Recommendation 10: While data are sparse, it is likely that the combination of some of the risk behaviors listed above will magnify the risk of adverse outcomes from cannabis use. For example, early-onset use involving frequent use of high-potency cannabis is likely to disproportionately increase the risks of experiencing acute or chronic problems. Preventing these combined high-risk patterns of use should be avoided by the user and a policy focus. [Evidence Grade: Limited.]
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	C- People with stroke or TIA who are overweight or obese should be offered advice and support to aid weight loss including adopting a healthy diet, limiting alcohol intake to 2 units a day or less and taking regular exercise. Targeting weight reduction in isolation is not recommended. E- People with stroke or TIA who drink alcohol should be advised to limit their intake to 14 units a week, spread over at least three days. **Smoking** People with stroke or TIA who smoke should be advised to stop immediately. Smoking cessation should be promoted in an individualised prevention plan using interventions which may include pharmacotherapy, psychosocial support and referral to NHS Stop Smoking Services.
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	**Cigarette smoking** • Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit (Class I; Level of Evidence C). • It is reasonable to avoid environmental (passive) tobacco smoke (Class IIa; Level of Evidence B). • Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers to quit (Class I; Level of Evidence A). **Alcohol consumption** • Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol (Class I; Level of Evidence C). • Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking (Class IIb; Level of Evidence B).
Bhatnagar A, Maziak W, Eissenberg T, Ward KD, Thurston G, King BA, Sutfin EL, Cobb CO, Griffiths M, Goldstein LB, Rezk-Hanna M. **Water Pipe (Hookah) Smoking and Cardiovascular Disease Risk: A Scientific**	To identify and treat water pipe tobacco smokers in clinical settings, healthcare providers are encouraged to do the following: 1. Ask users about water pipe use and frequency explicitly, using a variety of terms if necessary, as well as use of other tobacco products, as part of routine clinical examinations. 2. Advise users to quit water pipe and other tobacco product use. 3. Assist water pipe smokers to quit by providing cessation counseling, including setting a quit date and providing social support and coping assistance.

Guideline	Recommendations
Statement from the American Heart Association. ***Circulation.* 2019;139:e917–e936**	4. Refer water pipe smokers to credible sources for information on potential addictiveness and health consequences of water pipe use, including this statement.
CAN-ADAPTT. Canadian Smoking Cessation Clinical Practice Guideline. Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment, Centre for Addiction and Mental Health. Toronto, Canada. 2011. **(selected)**	Minimal interventions, of 1-3 minutes, are effective and should be offered to every tobacco user. However, there is a strong dose-response relationship between the session length and successful treatment, and so intensive interventions should be used whenever possible. GRADE: 1A. Counselling by a variety or combination of delivery formats (self-help, individual, group, helpline, web-based) is effective and should be used to assist patients/clients who express a willingness to quit. GRADE: 1A Because multiple counselling sessions increase the chances of prolonged abstinence, health care providers should provide four or more counselling sessions where possible. GRADE: 1A Combining counselling and smoking cessation medication is more effective than either alone, therefore both should be provided to patients/clients trying to stop smoking where feasible. GRADE: 1A Motivational interviewing is encouraged to support patients/clients willingness to engage in treatment now and in the future. GRADE 1B Two types of counselling and behavioural therapies yield significantly higher abstinence rates and should be included in smoking cessation treatment: 1) providing practical counselling on problem solving skills or skill training and 2) providing support as a part of treatment. GRADE: 1B

Evidence Tables

Alcohol Consumption and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Millwood et al. 2019 **UK** **China Kadoorie Biobank Prospective study**	NA	512,715 adults from 10 areas in China, aged 35-74 years, without known major disabilities, enrolled from 2004-2008. Mean age was 52 years, 41% were men.	The association between alcohol consumption and cardiovascular events was examined using conventional epidemiological analyses and from genetic analyses, which used Mendelian randomization to study the effects of the genetic variants (ALDH2-rs671 and ADH1B-rs1229984) among 161,498) persons who had been genotyped. In men, 6 categories of mean weekly alcohol intakes (grams) were created representing geographical and genotype information (with cut-points at 10, 25, 50, 100, and 150). Using conventional methods, past and current alcohol drinking patterns were self-reported, and classified as current drinkers (those drinking <140g; 140-279g; 280-419g; 420+ g/week (men), and <70 or; 70+ g/week (women),	**Primary outcomes:** ischaemic stroke, intracerebral hemorrhage (ICH), total stroke, acute myocardial infarction (MI), and total coronary heart disease (CHD) Models were adjusted for area, age, education, income and smoking, and exclude prior CVD	33.2% of men and 2.1% of women reported drinking alcohol most weeks. The mean weekly intake of alcohol intake across the genetic/geographical categories ranged from 4-256 g (men) and <2 to 8 g for women. Mean self-reported alcohol intake was 97.1 g (men) and 4.1 g (women). There was a total of 19,859 strokes. Median duration of follow-up was 10 years. In men, using conventional analysis, the risk of stroke was U-shaped, whereby the relative risk of total stroke was 1.23 (95% CI 1.19, 1.27) for non-drinkers, compared with 1.00 (95% CI 0.98-1.03) for occasional drinkers. Among current drinkers, the risks of ischemic stroke, ICH and total stroke were all significantly increased (when intake exceeded 100 g per week). Per each 280 g per week increase in alcohol intake, the risks of ischemic stroke ICH and total stroke were all significantly increased (RR= 1·28, 95% CI 1·19–1·38; HR= 1·59, 95% CI 1·37–1·85 and RR= 1·35, 95% CI 1·27–1·44, respectively) Using genetic analysis, there was no U-shaped pattern. The risk of ischemic stroke, ICH and total stroke increased across the whole range of genotype-predicted mean alcohol intake (RR= 1·27, 95% CI 1·13–1·43, RR= 1·58, 95% CI 1·36–1·84 and RR= 1·38, 95% CI 1·26–1·51, respectively). In men, mean systolic blood pressure was increased by 4.8 mm Hg per 280 g per week increase in alcohol intake among current drinkers, using conventional methods (4.3 mm Hg using genetic analysis).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			some alcohol use in most weeks in the past year), nondrinkers (no alcohol use in the past year and never drank in most weeks), occasional drinkers (occasional alcohol use in the past year but never drank in most weeks), or ex-drinkers (none or occasional alcohol use in the past year but previously drank in most weeks). Models using conventional analysis were adjusted for area, age, education, income, and smoking, while those using genetic analysis (done only in men) were adjusted for age and stratified by area.		In men, there was U-shaped curve for acute MI and alcohol consumption and CHD and alcohol consumption assessed using conventional analysis. Increasing alcohol intake was not associated with increasing risk of acute MI using conventional or genetic analysis. Using conventional analysis, increasing alcohol intake significantly increased the risk of CHD (RR per 280 g per week= 1·12, 95% CI 1·04–1·21), but not using genetic analysis (RR per 280 g per week= 1·05, 95% CI 0.94-1.17). In women, the risks of ischemic stroke, ICH, total stroke, acute MI and CHD were not increased with alcohol consumption in neither the conventional analysis, nor genetic analysis.
GBD 2016 Alcohol Collaborators **International** **Retrospective study**	NA	Men and women, aged ≥15 years.	Estimates of alcohol use and the associated health burden were obtained from 1990-2016 for 195 countries using 694 data sources of individual and population-level alcohol consumption. Alcohol use was expressed as daily standard drinks (10 g of pure ethyl alcohol).	Death, DALYs attributable to alcohol	In 2016, 32.5% (95% UI 30·0%-35·2%) of people globally were current drinkers. In 2016 in Canada, the prevalences of drinkers among women and men were 81% (95% UI 77%-84%) and 87% (95% UI 84%-89%), respectively. Globally, the mean amount of alcohol consumed daily was 0·73 (95% UI 0·68–0·78) standard drinks for women and 1·7 (UI 1·5–1·9) standard drinks for men. In Canada, women consumed an average of 2.7 standard drinks per day, and men 3.0. In 2016, age-standardized alcohol-related deaths for men and women were 2·2% (95% UI 1·5%-3·0%) and 6·8% (95% UI 5·8–8·0), respectively.

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					The percent of total attributable deaths due to alcohol in Canada in 2016 was 2.8% for women and 5.1% for men. Percent of total attributable DALYs due to alcohol in Canada in 2016 was 2.2% for women and 3.7% in men. Overall, the weighted relative risk curve demonstrated that consuming zero (95% UI 0·0–0·8) standard drinks daily minimized the overall risk of all health loss.
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. Alcohol use was classified as: never or former, low intake, moderate intake, and high (>14 drinks/week in women or >21 drinks/ week in men) or episodic heavy (>5 drinks in one episode at least once/month) intake	The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Low or moderate ETOH intake was associated with significantly higher odds of stroke compared with former/never drinkers. All stroke: OR=1.14, 99% CI 1.01-1.28, Ischemic stroke: OR=1.07, 99% CI 0.93-1.23 Hemorrhagic stroke: OR=1.43, 99% CI 1.17-1.74 High or heavy episodic drinking was associated with significantly higher odds of stroke compared with former/never drinkers . All stroke: OR=2.09, 99% CI 1.64-2.67, PAR 5.8%, 99% CI 3.49-9.7% Ischemic stroke: OR=2.14, 99% CI 1.62-2.82; PAR 4.6%, 99% CI 20.-10.0% Hemorrhagic stroke: OR=2.44, 99% CI 1.64-3.63; PAR 9.8%, 99% CI 6.4-14.8% PARs were higher for men vs. women (light/moderate drinking vs former/never: 1.20%, 99% CI 1.05-1.37% vs. 0.92%, 99% CI 0.70-1.21)
O'Donnell et al. 2010 **Canada (International)**	NA	Participants were recruited from 22 countries from 2007-2010.	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake,	The odds of all stroke, ischemic stroke and intracerebral hemorrhagic	Moderate alcohol consumption was associated with reduced risk of ischemic stroke and increased risk of hemorrhagic stroke compared with never/former drinkers.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
INTERSTROKE Phase 1 **Case-control study**		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)	psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples. Alcohol intake was classified as never/former drinker, moderate drinker (1-30 drinks/month), >30 drinks/month or binge drinker (>5 drinks/day at least once/month).	stroke (ICH) and population attributable risk (PAR) Results were adjusted for age, sex, and region	All stroke: OR=0.90, 99% CI 0.72-1.11, PAR 3.8%, 99% CI 0.9-14.4% Ischemic stroke: OR=0.79, 99% CI 0.63-1.00 Hemorrhagic stroke: OR=1.52, 99% CI 1.07-2.16 >30 drinks/month or binge drinking was associated with an increased risk of stroke compared with never/former drinkers. All stroke: OR=1.51, 99% CI 1.18-1.92 Ischemic stroke: OR=1.41, 99% CI 1.09-1.82 Hemorrhagic stroke: OR=2.01, 99% CI 1.35-2.99
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 any alcohol consumption) in high-income countries and low-income and middle-income countries	Stroke burden (expressed as DALYs)	Globally, 7.0% (95% uncertainty interval 5.6%-8.0%) of the stroke burden was attributed to alcohol use. In high income countries, 9.6% (95% uncertainty interval 8.1%-10.7%) of the stroke burden was attributed to alcohol use. **In Canada, 7.7% (95% uncertainty interval 4.8%-10.2%) of the stroke burden was attributed to alcohol use.** Globally, during the study period, there was an increase of 32.4% (95% UI 31.1%-35.1%) in the burden of stroke related to alcohol use.
Zheng et al. 2015 **China** **Systematic review & meta-analysis**	NA	23 prospective cohort studies (n=489,696). Mean baseline age varied widely among studies. Duration of follow-up ranged from 5-20 yrs	The risk of cardiovascular outcomes and ETOH consumption were explored.	Coronary disease, total mortality, cardiac death, stroke and ischemic stroke.	Compared with the lowest or no ETOH groups, the risk of stroke was not significantly increased in **men** as ETOH consumption increased. Low: RR=0.89, 95% CI 0.79-1.00 Moderate: RR=0.91, 95% CI 0.81-1.02 Heavy: RR=1.19, 95% CI 0.93-1.52 The risk of ischemic stroke was decreased among men who were light drinkers (RR=0.83, 95% CI 0.69-0.99).

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

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

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		case-control studies ranged from 89-677. Studies included men and women (n=21), women (n=2) and men (n=12). Age at baseline varied widely among studies.	12-23, 24-60 and >60, where 12 grams =1 drink. Self-administered questionnaires and in-person interviews were used to obtain consumption data.		Risk of total stroke among consumption groups, compared with abstainers: <12 g/day: RR=0.83, 95% CI 0.75-0.91 12-24 g/day: RR=0.91, 95% CI 0.78-1.06 24-60 g/d: RR=1.10, 95% CI 0.97-1.24 >60 g/d: RR=1.64, 95% CI 1.39-1.93 Results from 35 studies included. Risk of ischemic stroke among consumption groups, compared with abstainers: <12 g/day: RR=0.80, 95% CI 0.67-0.96 12-24 g/day: RR=0.72, 95% CI 0.57-0.91 24-60 g/d: RR=0.96, 95% CI 0.79-1.18 >60 g/d: RR=1.69, 95% CI 1.34-2.15 Results from 15 studies included. Risk of hemorrhagic stroke among consumption groups, compared with abstainers: <12 g/day: RR=0.79, 95% CI 0.60-1.05 12-24 g/day: RR=0.98, 95% CI 0.77-1.25 24-60 g/d: RR=1.19, 95% CI 0.80-1.79 >60 g/d: RR=2.18, 95% CI 1.48-3.20 Results from 12 studies included. Risk patterns were similar between men and women, with increasing intake associated with a j-shaped increase in stroke risk.

Recreational Drug Use and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Characteristics of illicit drug users who experience stroke					
Desbois & Cacoub 2013 **France**	NA	Studies that reported on cases of arterial complications associated with cannabis use.	Descriptive summaries of included studies.	Ischemic stroke, MI and arteritis	Among the included studies there were 71 cases of ischemic stroke. Of these, 86.2% were male. The average age was 35.5 years (range: 15-63 years).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review		23 case studies that examined stroke incidence, 17 studies that examined myocardial infarction and 23 studies examining arteritis, were identified			6 patients had known stroke factors (hypercholesterolemia, hypertension and factor V gene mutation). 55.3% of cases involved posterior cerebral circulation, 42.2% anterior, and 4.4%, both. 43% of patients presented with cerebral vasoconstriction syndrome. >85% of cases were heavy users (i.e >1x/week) There was a strong temporal relationship between cannabis use and stroke. 76.5% of patients were using cannabis at the time of symptom onset, or during the preceding 30 minutes. The remaining patients had used cannabis within the previous 24 hours of symptom onset. 18 patients had increased their cannabis use in the days preceding their stroke. 33.8% of patients had consumed other toxic substances including alcohol, cocaine and ecstasy.
De los Rios et al. 2012 **USA** **Retrospective Study**	NA	All patients aged 18-54 years who had experienced a stroke during three, one-year periods who resided in 5 counties of Kentucky and Ohio, were identified.	Use of illicit drugs, smoking and alcohol were examined in each of the 3 time periods. Exposure status for drug use (including cannabis, cocaine, crack and other) was based on patients' self-report or by results of urine or serum drug testing, when available.	Trends in drug and alcohol use of 3 time periods	The total number of persons aged 18-54 years who experienced a stroke increased over time, as did the proportion of young strokes. 1993-1994: Of the 2,735 strokes, 10.9% occurred in the young. 1999-2000: Of the 2,875 strokes, 13.1% occurred in the young. 1999-2000: Of the 2,697 strokes, 118.6% occurred in the young. The number of patients who reported using illicit drugs increased over time (3.8% vs. 9.8% vs. 19.8%). The number of patients who reported using drugs or alcohol within 24 hours of symptom onset increased (1.4% vs. 6.3% vs. 12.8%).

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cooperative Young Stroke Study		Man age was 36 years, 48.6% were male.	within 48 hours of stroke onset, convincing physical evidence of drug use (i.e., needle in vein when patient found), or a positive toxicology screen.		In patients with any drug use and recent drug use, hypertension and diabetes mellitus were significantly less common (p = 0.004) and smoking was significantly more common (p = 0.006). Of the patients with recent illicit drug use, drug use was identified as a probable cause in 4.7% of cases, and a probable cause in 7.3%. Among patients with drug use was identified as a possible stroke mechanism, more likely diagnoses included cardioembolic stroke (n=18), hematologic/collagen vascular (n=6), nonatherosclerotic vasculopathy (n=5) and atherosclerosis (n=3).
ii) Increased risk of stroke associated with illicit drug use					
Desai et al. 2019 **USA** **Retrospective study**	NA	3,307,310 young adults 18-49 years, who were hospitalized between 2007 and 2014 and who were current or previous cannabis users.	The associations between cannabis use and stroke risk, and in-hospital mortality, were examined. Models were adjusted for all baseline demographics characteristics, hospital-level characteristics and baseline comorbidities	**Primary outcomes:** Stroke, in-hospital mortality	34,857 (1.1%) hospitalizations were stroke related. The odds of any stroke and ischemic stroke were increased significantly among cannabis users compared with non-users (adj OR= 1.16, 95% CI 1.14–1.19, p<0.001 and adj OR= 1.41, 95% CI 1.31–1.51, p<0.001). In-hospital mortality increased from 3.7% to 4.3% among cannabis users over the study period whereas it decreased from 7.7% to 5.9% in nonusers (p trend < 0.001).
San Luis et al. 2020 **USA** **Retrospective study**	NA	9,350 patients ≥18 years admitted to a single institution from January 1, 2015 to December 31, 2017 who underwent urine toxicology testing on admission	A multivariate logistic regression model was used to determine if recent marijuana use was an independent predictor of acute ischemic stroke	**Primary outcome** Incident stroke	1,643 patients (18%) tested positive for cannabis. 1,337 patients suffered an ischemic stroke. A significantly lower percentage of patients who tested positive for cannabis had a stroke (7.9% vs.15.7%; RR=0.505; 95% CI 0.425 to 0.600). After adjustment for age, race, ethnicity, sickle cell disease, dyslipidemia, hypertension, obesity, diabetes, cigarette smoking, atrial fibrillation, and other cardiac conditions, the effect was no

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					longer significant (OR=1.038; 95% CI 0.773 to 1.394).
Parekh et al. 2019 **USA** **Retrospective study**	NA	43,860 participants aged 18-44 years, included in the Behavioral Risk Factor Surveillance System (2016-2017)	Regression models were used to examine the association between recent marijuana use (within the last 30 days), and frequent us (>10x/month) and stroke, adjusting for patient demographics, risk behavior, and relevant comorbidities	**Primary outcome:** Incident stroke	13.6% participants reported using marijuana in the previous month. The odds of stroke were significantly higher among recent marijuana users compared with nonusers (adj OR=1.82, 95% CI, 1.08–3.10) and among frequent users adj OR=2.45, 95% CI, 1.31–4.60). The odds of stroke were significantly higher in marijuana users who were concomitant cigarette and e-cigarette users.
Reis et al. 2017 **USA** **Retrospective study**	NA	5,113 adults aged 18 to 30 years at baseline (1985–1986) included in the Coronary Artery Risk Development in Young Adults study, who were followed for ≥ 25 years.	The cumulative lifetime exposure to marijuana was estimated, using data from assessments conducted every 2-5 years. Recent marijuana exposure was established based on the survey question: “During the last 30 days, on how many days did you use marijuana?” Lifetime exposure was also assessed at each examination using the question “About how many times in your lifetime have you used marijuana?” Marijuana use was categorized as: never,1 day to less than 0.5 marijuana-years, 0.5 to less than 2.0 marijuana-	**Primary outcome:** Incident cardiovascular disease (CVD) including coronary heart disease (CHD), myocardial infarction (MI), acute coronary syndrome, or CHD death, including fatal MI, stroke, transient ischemic attack (TIA), hospitalization for heart failure, intervention for peripheral arterial disease, or death from cardiovascular causes.	Median cumulative lifetime marijuana use was 0.51 marijuana years. During a median 26.9 years of follow-up, there were 215 total CVD events (1.63 per 1,000 person-years), including 62 strokes or TIAs (0.47 per 1,000 person-years), 104 cases of CHD (0.78 per 1,000 person-years), and 50 CVD deaths (0.38 per 1,000 person-years). Neither lifetime, nor recent marijuana exposure were associated with increased risk of any of the outcomes (no exposure vs. any level of exposure), after adjusting for age, gender, race, educational attainment, study center, family history of CVD and time-varying physical activity, body mass index, high blood pressure, diabetes, dyslipidemia, depression, smoking (pack-years), cumulative alcohol use, cumulative binge drinking episodes, and cumulative use of other illicit drugs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			years, 2.0 to less than 5.0 marijuana-years, and 5.0 or more marijuana-years, and none, 1 to 9 days, 10 to 19 days, and 20 or more days.		
Falkstedt et al. 2017 **Sweden** **Cohort study**	NA	49,321 Swedish men, conscripted into military service in 1969/70, when they were 18-20 years of age.	At conscription, all participants underwent a 2-day screening procedure, which included an extensive health examination (and stroke risk factors) and the completion of 2 questionnaires—one focusing on social and behavioral factors and the other on substance use. Participants were asked which drugs they had used, and the frequency of their use. They were also asked about tobacco and alcohol use. National databases were used to track the incidence of fatal and nonfatal stroke from 1971-2009, when participants were aged 20-59 years.	**Primary outcome:** Risk of any stroke and ischemic stroke, controlling for BMI, SBP/DBP, cardiorespiratory fitness, migraine, diabetes mellitus, early parental CVD, socioeconomic status until young adulthood, and tobacco smoking and alcohol consumption.	There were 1,037 first-time strokes over the study period. Among men <45 years, there was no significantly increased risk of stroke (n=192) associated with cannabis use, regardless of intensity of exposure (1-10 times, 11-50 or >50 times). Only cigarette smoking was associated with increased stroke risk among men <45 years, which was dose-dependent. Among all men, there was no significantly increased risk of any stroke or ischemic stroke associated with cannabis use, regardless of intensity of exposure (used 1-10 times, 11-50 or >50 times). Cigarette smoking was associated with a dose-dependent increased stroke risk in all participants.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cheng et al. 2016 **USA** **Case-control study**	NA	1,090 cases were those aged 15-49 years, with first-ever ischemic stroke identified from 59 acute care hospitals (1992-2008). Mean age was 41 years, 53.6% were male. 1,154 controls, matched by age, sex and region of residence. Mean age was 38.6 years, 46.6% were male.	Participants were asked to recall whether they had ever used cocaine before the reference date (date of stroke for cases, date of interview for controls). Timing of use was also noted (acute use-within 24 hours of reference date; current use-with the previous month). Data on traditional risk factors for stroke were also obtained through interview.	**Primary outcome:** Incidence of ischemic stroke Analysis was adjusted for age, sex, ethnicity, and other stroke risk factors	Cases were more likely to have a history of diabetes and hypertension, and were more likely to be smokers and current ETOH users. 28.1% of cases and 25.7% of controls reported to have ever used cocaine. (p=0.95) Cocaine use within 24 hours of the reference date was associated with a significantly increased risk of ischemic stroke (n=26 vs. 4; OR=6.4, 95% CI 2.2-18.6, p<0.001). Smoking as the route of administration of cocaine was associated with a significantly increased risk of ischemic stroke among acute users (n=16 vs. 2; OR=7.9, 95% CI 1.8-35.0, p=0.006) Frequent cocaine use (≥1/week) was also associated with significantly increased odds of ischemic stroke (n=65 vs. 23; OR=2.6, 95% CI 1.6-4.3, p<0.001).
Rumalla et al. 2016 **USA** **Case-control study**	NA	Patients aged 15-54 years from the Nationwide Inpatient Sample admitted from 2004 to 2011 with a primary diagnosis of ischemic stroke	The risk of ischemic stroke among cannabis users (identified through ICD-9 codes, n= 11,320) was compared to stroke risk among non-users (n= 467,329)	**Primary outcome:** Stroke risk	The incidence of ischemic stroke was significantly greater among marijuana users compared to non-users (RR=1.17, 95% CI: 1.15–1.20, p<0.0001), controlling for age, sex, race, payer status, Charlson's Comorbidity Index, substance abuse and cardiovascular risk factors. The greatest risk of stroke was among patients aged 25-34 years (RR=2.26, 95% CI: 2.13–2.38, p<0.0001). After adjusting for demographics, other forms of substance abuse, and medical risk factors, marijuana use was associated with significantly greater odds of vasospasm (OR= 2.18, 95% CI 1.77–2.67, p< 0.0001).
Barber et al. 2013	NA	Cases: 160 patients, aged 18-55 years,	Relationship between cannabis use and stroke	**Primary outcome:**	25 (15.6%) of stroke patients tested positive for cannabis. They were more likely to be male,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
New Zealand **Case-control study**		admitted to a single institution with a diagnosis of ischemic stroke/TIA during 2009-2012 and who had provided a urine sample within 72 hours of admission. Controls: 160 patients, matched for age, sex and ethnicity, who had been admitted to the Internal Medicine Service.	risk was explored using bivariate and logistic regression	Independent risk factors associated with stroke	Maori, tobacco users and to have worse outcomes at discharge (median mRS 3 vs. 1, p=0.036). 13 (8.1%) of control patients tested positive for cannabis. The odds of stroke were significantly higher in cannabis users, after adjusting for age, sex, and ethnicity (OR=2.3, 95% CI 1.08-5.08); however, the association was no longer significant after adjusting for current tobacco use (OR=1.59, 95% CI 0.71-3.70).
Westover et al. 2007 **USA** **Retrospective study**	NA	1,935 patients aged 18-44 years discharged from all hospitals across Texas with a diagnosis of stroke in 2003	The associations between illicit drug use and the risk of ischemic and hemorrhagic stroke were examined using logistic regression.	**Primary outcome:** Independent risk factors associated with stroke	There were 998 cases of ischemic stroke and 937 cases of hemorrhagic stroke. Amphetamine use was associated with an increase in the risk of hemorrhagic stroke (OR=4.95, 95% CI 3.24-7.55), but not ischemic stroke (OR=1.04, 95% CI 0.42-2.55). Amphetamine use was also associated with an increased risk of hemorrhagic stroke resulting in death (OR=2.63, 95% CI 1.07-6.50). Cocaine use was associated with an increase in the risk of hemorrhagic stroke (OR=2.33, 95% CI 1.74-3.11), and ischemic stroke (OR=2.03, 95% CI 1.48-2.79). Cannabis use was associated with an increased risk of ischemic stroke (OR=1.76, 95% CI 1.15-2.71) but not hemorrhagic stroke (OR=1.36, 95% CI 0.90-2.06). Across both stroke types, the increased risk of death associated with amphetamine use was higher than that of coagulation defects (OR=3.92, 95% CI 1.79-8.59 vs. 3.06 95% CI 1.89-4.95) and 3 times higher than that of hypertension.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Qureshi et al. 2001 **USA** **Retrospective study**	NA	10,085 individuals age 19-45 years who had been included in the Third National Health and Nutrition Examination Survey Mortality Follow-up Study (1988-1994). Mean age of the cohort was 30.9 years, 46.5% were male.	The relationship between cocaine use and MI and stroke were examined. The survey included a household interview, a medical examination in a mobile examination center, a brief household medical examination for those unable to travel to the center, and a phlebotomy to measure serum markers including glucose, cholesterol, high-density lipoproteins, triglycerides, and apolipoproteins A-1 and B. Lifetime cocaine use was classified as never, <10 times Infrequent users), 10-100 times (frequent users), or >100 times (regular users). Persons were considered to have had a stroke or MI if they reported that they had been told by a physician that they had suffered from either event	**Primary outcome:** Nonfatal MI and stroke Analysis was adjusted for age, sex, race/ethnicity, educational attainment, hypertension, hyperlipidemia, diabetes mellitus, BMI, cigarette smoking, and insurance status.	731 individuals (7.2%) reported infrequent use of cocaine, 532 (5.3%) reported frequent use. There were 33 nonfatal strokes. The odds of a nonfatal stroke associated with cocaine use were not increased significantly: Nonusers: Reference OR=1.0 Infrequent users: OR=0.48, 95% CI 0.01-7.66 Frequent users: RR=0.49, 95% CI 0.01-7.69 Regular users: OR not reported.
Kaku & Lowenstein 1990 **USA** **Case-control study**	NA	Cases: 214 patients aged 15-44 years, admitted to a single institution with a diagnosis of stroke from 1979-1988. Controls: 180 patients admitted emergently with asthma, appendicitis or cholecystitis, with documentation of drug	The association between recreational (illicit) drug use and the risk of stroke was examined using conditional logistic regression. The temporal relationship among drug users was also examined.	**Primary outcome:** Independent risk factors associated with stroke	The mean age of patients in both groups was 35 years. Stroke types were 34% ICH, 27% cerebral thrombosis, 25% SAH and 14% cerebral embolism. Drug abuse was documented more frequently in stroke patients 34% vs. 8%. Among patients with stroke, cocaine, heroin and amphetamine were the most commonly used drugs. Mortality

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		abuse (present or absent) matched for age, sex and year of discharge.	Exposure status for drug use was based on documentation provided in the medical chart.		associated with stroke was 26% during the acute admission period. The risk ratio for drug abuse was 6.5, 95% CI 3.1-13.6. The risk was highest during the first 6 hours after use and decreased over time. Among patients <35 years, drug abuse was a stronger predictor of stroke (RR=11.7, 95% CI 3.2-42.5) compared with those ≥35 years (RR=3.6, 95% CI 1.3-10.4)

Association between Smoking and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
O'Donnell et al. 2016 **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. Smoking status was classified as current or never/former	The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Smoking was associated with an increased risk of stroke. All stroke: OR=1.67, 99% CI 1.49-1.87; PAR 12.4%, 99% CI 10.2-214.9% Ischemic stroke: OR=1.93, 99% CI 1.69-2.21, PAR 15.1%, 99% CI 12.8-18.8% Hemorrhagic stroke: OR=1.14, 99% CI 0.95-1.36, PAR 3.6%, 99% CI 0.9-13.0%
O'Donnell et al. 2010 **Canada (International)**	NA	Participants were recruited from 22 countries from 2007-2010. Cases were 3,000 persons	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake,	The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk	Smoking was associated with an increased risk of stroke compared with never/former smokers. All stroke: OR=2.09, 99% CI 1.75-2.51,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
INTERSTROKE Phase 1 **Case-control study**		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).	psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples. Smoking status was classified as current or never/former.	(PAR) Results were adjusted for age, sex, and region	PAR 18.9%, 99% CI 15.3-23.1% Ischemic stroke: OR=2.32, 99% CI 1.91-2.81, PAR 21.4%, 99% CI 17.5-25.8% Hemorrhagic stroke: OR=1.45, 99% CI 1.07-1.96, PAR 9.5%, 99% CI 4.2-20.0%
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 tobacco use, defined as previous or current use) in high-income countries and low-income and middle-income countries.	Stroke burden (expressed as DALYs)	Globally, 20.7% (95% uncertainty interval 18.2%-22.7%) of the stroke burden was attributed to tobacco use. In high income countries, 18.1% (95% uncertainty interval 16.2%-19%) of the stroke burden was attributed to tobacco use. **In Canada, 13% (95% uncertainty interval 10.6%-15.4%) of the stroke burden was attributed to tobacco use** Globally, during the study period, there was an increase of 10.4% (95% UI 8.6%-13.7%) in the burden of stroke related to tobacco use.
Peters et al. 2013 **Australia & US** **Systematic review & meta-analysis**	NA	81 prospective cohort studies, published from 1966-2013, including the results from, 3,980,359 persons, reporting sex-specific risk of current smoker vs. nonsmokers.	Dose-response relationship (<10, 10-20, >20) and stroke subtype (ischemic vs. hemorrhagic) were also examined.	Combined fatal/nonfatal incident stroke, expressed as relative risk (RR) and a ratio of RR in women/men (RRR). Variables adjusted for in the individual studies included: age, race, education blood pressure, diabetes, serum cholesterol, alcohol intake, physical activity.	Duration of the included studies ranged from 6-40 years. There were 42,401 strokes. The prevalence of current smoking ranged from 8% to 59% in men and from 1% to 51% in women. Most studies reported higher smoking rates among men. The risk of stroke was higher in current

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					smokers compared with nonsmokers. Women: RR=1.83, 95% CI 1.58-2.12 Men: RR=1.67, 95% CI 1.49-1.88 The risk was not significantly different between the sexes (RRR=1.06, 95% CI 0.99-1.13, p=0.10). The risk of stroke was higher in former smokers compared with never smokers: Women: RR=1.17, 95% CI 1.12-1.22 Men: RR=1.08, 95% CI 1.03-1.13 The risk was not significantly different between the sexes (RRR=1.10, 95% CI 0.99-1.22) The risk of stroke was higher in women who smoked >20 cigarettes/day compared with men: <10 cigs: RRR=0.94, 95% CI 0.67-1.22 10-20 cigs: RRR=0.91, 95% CI 0.67-1.22 >20 cigs: RRR=1.31, 95% CI 1.00-1.72 The risk of ischemic stroke was elevated significantly in both men and women who smoked, compared with nonsmokers, but the risk was not significantly different between the sexes (RRR=0.97, 95% CI 0.79-1.18, p=0.73). The risk of hemorrhagic stroke was significantly increased in women who smoked compared with men who smoked (RRR=1.17, 95% CI 1.02-1.34, p=0.02).
Robbins et al. 1994 **US** **Observational study**	N/A	22,071 male physicians enrolled as part of the Physicians' Health Study. Participants were aged 40-84 and did not have histories of stroke, TIA, or myocardial infarction at the time of study entry.	Smoking status was defined as never smoked, formally smoked, currently smoking <20 cigarettes/day, and currently smoking ≥20 cigarettes/day.	Occurrence of stroke. **Timing of Assessment:** Baseline, 6-month follow-up, and every 12-months until diagnosis of stroke, fatal event, or the end of the 10-year study period.	During the study period, 312 non-fatal and 28 fatal strokes occurred. Compared with those who never smoked, the risk of non-fatal stroke occurrence was: Significantly higher for those currently smoking ≥20 cigarettes/day (RR=2.52, 95% CI 1.75 to 3.61),

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Significantly higher for those smoking <20 cigarettes/ day. (RR=2.02, 95% CI 1.23 to 3.31) Higher for former smokers (RR=1.20, 95% CI 0.94 to 1.53) Test for trend: p<0.001), adjusting for age and aspirin and beta-carotene use. The risk for fatal stroke was not significantly increased for former (RR= 0.96; 95% CI 0.42 to 2.19) or current smokers (RR= 1.46; 95% CI 0.32 to 6.76).

Interventions to Promote Smoking Cessation

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pharmacological Interventions +/- behavioural support					
Hartmann-Boyce et al. 2018 **UK** **Cochrane review**	12 trials were considered to have a low risk of bias across all domains	136 RCTs (n=64,640) including current smokers who were people motivated to quit. Trials typically recruited people who smoked at least 15 cigarettes a day. Participants were recruited from primary care, the community, the workplace and hospitals	Trials compared nicotine replacement therapy (NRT) including chewing gum (n=56), transdermal patches (n=51), nasal (n=4) or oral spray (n=5), inhalators and tablets or lozenges (n=8), and combinations of NRTs to placebo or no treatment.	**Primary outcome:** Sustained smoking abstinence at ≥6 months **Secondary outcomes**: Adverse events	Duration of follow-up ranged from 6 to 24 months). Overall, the use of all forms of NRT was associated with a significantly increased chance of successful smoking cessation (RR=1.55, 95% CI 1.49 to 1.61). Results from 133 trials included. There was little effect of type of NRT on cessation. Intensive behavioural support was not found to be essential for NRT to be effective. The odds of chest pain or palpitations were increased significantly with NRT (OR=1.88, 95% CI 1.37 to 2.57). Results from 15 trials included.
Halpern et al. 2018	CA: ☑ Blinding:	6,006 adult participants who were employees at 54 companies that used Vitality	Participants were randomized to one of 5 groups: a control group	**Primary outcome:** Sustained smoking abstinence (confirmed by urine sample) for	80 participants (1.3%) were abstinent 6 months after quitting. Usual care: 0.1% (95% CI 0 to 0.3),

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **RCT**	Patient ☒ Assessor☑ ITT: ☑	wellness programs, and who reported current smoking during the previous year. Median age was 44 years. Approx 50% were females. The median duration of smoking was 18 years.	(usual care) and 4 intervention groups. The control group received access to information resources and to a motivational text-messaging service. Interventions groups included: 1) free smoking cessation aids 2) free e-cigarettes; 3) $600 rewards plus free cessation aids; and 4) $600 redeemable deposit plus free cessation aids	6 months after the target quit date **Secondary outcomes**: Point prevalence for quitting at 1 month and sustained abstinence rates at 3 months and 12 months	Free cessation aids: 0.5% (95% CI 0.2-0.9) Free e-cig group: 1.0% (95% CI 0.4-1.6) Rewards group: 2.0% (95% CI 1.2-2.8) Redeemable deposit group: 2.9% (95% CI 2.0-3.8). Three between-group comparisons were statistically significant for the primary outcome: Redeemable deposits were superior to free cessation aids (OR=5.77, 95% CI 2.66 to 12.50, p<0.001); rewards were superior to free cessation aids (OR=3.95, 95% CI 1.77 to 8.84; p=0.006), and redeemable deposits were superior to free e-cigs (OR=2.95, 95% CI, 1.52 to 5.71; p=0.008). Free e-cigs were not superior to usual care or to free cessation aids. The pattern of results was similar among the engaged cohort of 1,191 participants who logged on to the trial website at least once; however, a much higher percentage of engaged participants had quit and were abstinent at 6 months. Usual care: 0.7% (95% CI 0 to 2.1) Free cessation aids: 2.9% (95% CI 0.9-4.9) Free e-cig group: 4.8% (95% CI 2.1-7.4) Rewards group: 9.5% (95% CI 5.9-13.1) Redeemable deposit group: 12.7% (95% CI 8.8-16.7).
Mullen et al. 2016 **Canada** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☒	1,367 patients admitted to one of 14 hospitals, >17 years of age who smoked ≥1 cigarette per day in the 6 months prior to their hospitalization. Mean age was 52 years, 48% of	Patients were randomized to participate in the 'Ottawa Model' for Smoking Cessation (OMSC), a systematic approach to tobacco dependence treatment delivered within	**Primary outcome:** All-cause mortality and all-cause hospital readmission **Secondary outcomes:** Smoking-related readmission; all-cause and smoking-related	**30-day outcomes:** The risk of death was not reduced significantly in the OMSC group (HR=0.66, 95% CI 0.29-1.48, p=0.38); however, the incidence of rehospitalization was reduced significantly (HR=0.50, 95% CI 0.34-0.72,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	ITT: ☑	patients were male, 32% of patients smoked >20 cigs/day.	healthcare settings that involves: identifying and documenting the smoking status of all patients; providing brief counselling and in hospital pharmacotherapy to smokers; and, offering follow-up support post hospitalization (n=726) or to a usual care group (n=641) that (most frequently) received self-help brochures	ED visits; and all-cause and smoking-related physician visits Analysis was adjusted for baseline covariates: age, sex, income, number of cigarettes smoked per day, community size, resource usage prior to index event, and history of: acute MI, asthma, COPD, heart failure, diabetes, hypertension, mental illness, stroke/TIA.	p<0.001). **One-year outcomes:** The cumulative incidences of death and all-cause rehospitalizations were significantly lower in the OMSC group (HR=0.55, 95% CI 0.36-0.82, p<0.001 and HR=0.72, 95% CI 0.61-0.86, p<0.001, respectively). **Two-year outcomes:** The cumulative incidences of death and all-cause rehospitalizations were significantly lower in the OMSC group (HR=0.60, 95% CI 0.42-0.85, p<0.001 and HR=0.79, 95% CI 0.68-0.92, p<0.001, respectively).
Stead et al. 2015 **UK** **Cochrane Review**	NA	47 RCTs (18,000+) examining the effectiveness of behavioural support as an adjunct to pharmacotherapy for smoking cessation as compared to a control condition that received pharmacotherapy and less intensive behavioural support. Trials recruited people who smoked, in all settings and populations except pregnant women and adolescents. All participants had access to one or more of the following pharmacological agents: nicotine replacement therapy (NRT), varenicline, bupropion, and nortriptyline.	Participants were provided NRT in the majority of included trials. The intensity of behavioural support varied greatly for both intervention and control groups and was typically only slightly greater for those in the intervention arm than those in the control arm.	Abstinence from smoking after at least six months of follow-up.	9 new trials have been added since the review was last updated (2012). More intensive behavioural support was associated with a better chance of long-term abstinence from smoking when combined with pharmacotherapy, as compared to pharmacotherapy combined with less intensive behavioural support (RR= 1.17, 95% CI 1.11 to 1.24) An increased number of sessions (≥4 vs. no sessions) was associated with a greater chance of successful low-term abstinence (RR=1.25; 95% CI 1.08 to 1.45; 6 trials).
Cahill et al. 2013	NA	12 Cochrane reviews (including the results from	The main treatments examined included: nicotine	Sustained (at least 6 months)	Pharmacotherapy was associated with increased odds of success (odds ratio,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
UK **Cochrane review of reviews**		267 RCTs, 101,804 participants) which examined the effectiveness of pharmacological treatments to promote smoking cessation in adults (excluding pregnant women).	replacement therapy (NRT), provided as gum (n=55), transdermal patch (n=43), oral nicotine tablet or lozenge (n=6), choice of product (n=5), intranasal nicotine spray (n=4), nicotine inhaler (n=4), one of oral spray (n=1), patch plus inhaler (n=1) and patch plus lozenge (n=1), bupropion, nortriptyline, and the nicotine receptor partial agonists, varenicline and cytosine. Additional treatments included: antidepressants, anxiolytics, and selective type 1 cannabinoid receptor antagonists. The control conditions included placebo, other pharmacological treatments, or combinations of treatments or usual care.	smoking cessation.	95% Credible interval). NRT vs. placebo: OR=1.84, 95% CI 1.71 to 1.99, based on 119 comparisons. Combination NRT outperformed single formulations. All forms of NRTs were superior to placebo. Bupropion vs. placebo: OR=1.82, 95% CredI 1.60 to 2.06. 36 comparisons. Varenicline vs. placebo: OR= 2.88, 95% CredI 2.40 to 3.47. 15 comparisons. Bupropion vs. NRT: OR= 0.99; 95% CredI 0.86 to 1.13. 9 comparisons. Varenicline was superior to single forms of NRT: OR= 1.57, 95% CredI 1.29 to 1.91. Varenicline vs. bupropion: OR= 1.59, 95% CredI 1.29 to 1.96. Odds of serious adverse events (chest pains and heart palpitations) associated with NRT was: OR= 1.88, 95% CI 1.37-2.57. The corresponding event rate was 2.5% in the NRT group and 1.4% in the control group, reported in 15 trials. Bupropion: the most common side effects were insomnia, occurring in 30% to 40% of patients, dry mouth (10%) and nausea. Typical drop-out rates due to adverse events ranged from 7% to 12%. The main serious adverse event was seizures, which may occur at a rate of around 1:1000 users. Varenicline: the main adverse event was

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					mild-moderate nausea, subsiding over time. The event rates for serious adverse events 2.1% in the varenicline arms and 2.0% in the placebo arms, reported in 14 trials.
Edjoc et al. 2012 **Canada** **Systematic Review**	NA	4 RCTs (n=354) including participants with cerebrovascular disease, a portion of whom were smokers (28%-54%). Trials were not excluded based on age or ethnicity of participants.	Trials evaluated the effectiveness of a smoking cessation intervention (medications +/- counselling) vs. usual care	Smoking Cessation (follow-ups ranged from 26 weeks to 42 months).	The overall smoking cessation rate was 23.9% (42/176) for participants randomized to receive an active smoking cessation intervention and 20.8% (37/178) for participants randomized to a control group,
Non-pharmacological Interventions					
Lindson-Hawley et al. 2015 **UK** **Cochrane Review**	NA	28 RCTs (n=16,803) examining the use of motivational interviewing (MI) for smoking cessation. Trials included participants who were tobacco users, recruited from any setting. Pregnant women and adolescents were excluded.	Included trials based the active intervention on the principles and practice of MI. MI was provided in 1-4 sessions, with duration of 15-45 minutes per session. Control groups received brief advice, a low-intensity intervention, or routine care.	Abstinence from smoking after at least six months of follow-up.	Compared to brief advice or usual care, motivational interviewing was associated with a significantly greater likelihood of long-term smoking cessation (RR=1.26, 95% CI 1.16 to 1.36; 28 trials). MI was associated with a significant treatment effect whether delivered in single (RR=1.26, 95% CI 1.15 to 1.40) or multiple sessions (RR=1.20, 95% CI 1.02 to 1.42). Sessions of <20 and >20 minutes' duration were both associated with an increased likelihood of cessation (RR= 1.69, 95% CI 1.34-2.12 and RR= 1.20, 95% CI 1.08- 1.32, respectively).
Rice et al. 2013 **USA** **Cochrane Review**	NA	49 RCTs (17,000+) that recruited adult participants from any type of healthcare, or other setting. Trials that exclusively recruited pregnant participants were excluded. In 20 trials the intervention was provided while patients were in hospital, while in 24 trials	Trials evaluated smoking cessation interventions delivered by nurses, including provision of advice, counselling, and strategies to help participants stop smoking vs. usual care or control	Abstinence from smoking after at least six months of follow-up.	Participants who were randomized to receive the nurse-delivered active intervention were significantly more likely to be abstinent from smoking at the longest point of follow-up (RR= 1.29; 95% CI 1.20 to 1.39; 35 trials, n=17,629). High Intensity interventions: RR=1.26; 95% CI 1.17 to 1.36 (28 trials, n=13,613).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		participants were recruited from primary care or outpatient clinics.			Low intensity interventions: RR= 1.27; 95% CI 0.99 to 1.62 (7 trials, n=4,016).
Stead et al. 2013 **UK & Bogota** **Cochrane Review**	NA	42 RCTs (n=31,000+) that recruited participants from any setting. Trials that exclusively recruited pregnant participants were excluded.	Trials evaluated smoking cessation advice delivered by a physician vs. usual care or no advice.	Abstinence from smoking after at least six months of follow-up.	Participants who received smoking cessation advice from a medical practitioner were significantly more likely to be abstinent from smoking at the longest point of follow-up (RR= 1.76; 95% CI 1.58-1.96, 26 trials, n=22,239) Smoking cessation was associated with an increased likelihood of smoking cessation among sub groups including more vs. less intensive treatment, high-risk vs. unselected participants, and the use of aids as adjuncts to advice vs. no aids.

Smoking Cessation Pharmacotherapy and Risk of Adverse Cardiovascular Events

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mills et al. 2014 **USA** **Systematic Review & Meta-analysis**	N/A	63 RCTs (n=30,508) including current smokers who were treated with NRT at any marketed dose or combination, bupropion at licensed doses, for any duration and which reported cardiovascular outcomes.	Trials examined smoking cessation therapy with nicotine replacement therapy (NRT; 21 trials), bupropion (27 trials), or varenicline (18 trials) vs. placebo or no treatment	All cardiovascular events and all major adverse cardiovascular events (defined as cardiovascular death or non-fatal stroke or myocardial infarction.	**All cardiovascular events:** NRT: RR= 1.81, 95% CI 1.35 to 2.43. Bupropion: RR= 1.03, 95% CI 0.71 to 1.50. Varenicline: RR= 1.24, 95% CI 0.85 to 1.81. **Major cardiovascular events:** NRT: RR= 1.38, 95% CI 0.58 to 3.26. Bupropion: RR= 0.57, 95% CI 0.31 to 1.04. Varenicline: RR= 1.44, 95% CI 0.73 to 2.83. The authors concluded that smoking cessation therapies did not appear to be associated with a significant increase in the risk of major cardiovascular events,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					but were associated with a significant increase in risk of less serious CV events.
Prochaska & Hilton, 2012 **USA** **Systematic Review & Meta-analysis**	N/A	22 RCTs (n=9232) including current smokers aged 18 years or older using varenicline and reporting cardiovascular outcomes.	Trials compared varenicline smoking cessation therapy vs. placebo control	Occurrence of ischemic or arrhythmic adverse cardiovascular events during treatment or within 30-days of treatment discontinuation.	The rate of treatment emergent cardiovascular events was 0.63% (n=34) for participants randomized to receive varenicline and 0.47% (n=18) for those randomized to a control group: risk difference = 0.27%, 95% CI -10% to 63%, p=0.15. In a secondary analysis that only included the 14 trials in which at least one outcome event occurred, the risk of adverse cardiovascular events was not significantly increased among those receiving an active intervention (RR=1.40 (95%, CI 0.82 to 2.39, p=0.22),

Electronic Cigarettes

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

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

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

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) RCTS examining effectiveness of the use of e-cigarettes to reduce/quit smoking					
Eisenberg et al. 2020 **Canada** **RCT** ***Evaluating the Efficacy of e-Cigarette Use for Smoking Cessation (E3 Trial)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	376 persons (486 planned) adults who smoked a mean of ≥10 cigarettes per day, who had a moderate or strong desire and intention to attempt to quit, recruited from 17 centres. Mean age was 52 years, 47% were women. Participants had smoked a mean of 21 cigarettes/d at baseline for a mean of 35 years.	Participants were randomized to nicotine e-cigarettes (15 mg nicotine/mL, n=128), nonnicotine e-cigarettes (n= 127), or no e-cigarettes (n=121) for 12 weeks. All participants received counselling (a (minimum 30 minutes at baseline, 10 minutes during telephone follow-ups, and 15-20 minutes at clinic visits). Follow-up was conducted by telephone at weeks 1, 2, 8, and 18, and at clinic visits at weeks 4, 12, 24, and 52. Self-reported smoking (7-day recall), adherence, and adverse events (AEs) were assessed during follow-up contacts.	**Primary outcome:** Abstinence at 12 weeks **Secondary outcomes:** Abstinence at other follow-ups, continuous abstinence, daily cigarette consumption change from baseline at all follow-ups (1, 2, 4, 8, 12, 18, 24, and 52 weeks)	Compared with counselling alone, significantly more participants in the nicotine e-cigarette group were abstinent at 12 weeks (21.9% vs 9.1%; risk difference [RD]= 12.8 95% CI, 4.0 to 21.6), but not at 24 weeks (17.2% vs 9.9%; RD= 7.3 95% CI, –1.2 to 15.7). Compared with counselling alone, there was no significant difference in 12-week abstinence with nonnicotine e-cigarettes, (17.3% vs 9.1%; RD= 8.2 95% CI, –0.1 to 16.6), but there was at 24 weeks, favouring nonnicotine e-cigarettes (20.5% vs 9.9%; RD=10.6, 95% CI, 1.8 to 19.4). Cough and dry mouth were the most common adverse events.
Hajek et al. 2019 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	886 adult smokers recruited from 3 National Health Service stop-smoking service sites. Median age was 41 years, 48% were women.	Participants were randomized 1:1 to either nicotine-replacement products (NRP) of their choice, provided for up to 3 months, or an e-cigarette starter pack, with a recommendation to purchase further e-liquids of the flavor and strength of their choice. Persons in both groups participated in a weekly behavioral support for at least 4 weeks.	**Primary outcome:** Sustained abstinence for 1 year, validated biochemically **Secondary outcomes:** Sustained abstinence from 26 to 52 weeks, at 4 weeks, and at 26 weeks, participant-reported treatment usage and respiratory symptoms	The 1-year abstinence rate was significantly higher in the e-cigarette group (18.0% vs. 9.9%; RR=1.83; 95% CI, 1.30 to 2.58; p<0.001). Abstinence rates were higher in the e-cigarette group at all other time points, as was the reduction in smoking of ≥50% in participants without abstinence between weeks 26 and 52 (12.8% vs. 8.4%; RR=1.73, 95% CI 1.11–2.69). There were no significant differences between groups in the frequency of any respiratory symptoms (shortness of breath, wheezing, coughing, phlegm).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					There were 27 serious adverse events in the e-cigarette group and 22 in the nicotine-replacement group. There were 83 dropouts in the e-cigarette group and 105 in the NRP group
Halpern et al. 2018 **USA** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	6,006 employees at 54 companies and their spouses who were ≥18 years and current smokers. Mean age of participants was 45 years, Median duration of smoking was 18-20 years. Median number of cigarettes smoked/day was 10.	Participants were randomized to one of 4 intervention groups or a control group, which consisted of access to information regarding the benefits of smoking cessation and to a motivational text-messaging service (n=813). In addition to usual care, intervention groups received: i) free cessation aids (nicotine-replacement therapy or pharmacotherapy, with e-cigarettes if standard therapies failed, n=1,588); ii) free e-cigarettes, without a requirement that standard therapies had been tried (n=1,199); iii) free cessation aids plus $600 in rewards for sustained abstinence (n=1,198) or iv) free cessation aids plus $600 in redeemable funds, deposited in a separate account (n=1,208)	**Primary outcomes:** Sustained (laboratory confirmed) smoking abstinence for 6 months after the target quit date.	Overall, sustained smoking abstinence through 6 months after the target quit date was confirmed in 80 (1.3%) participants (0.1% in the usual-care group, 0.5% in the free cessation aids group, 1.0% in the free e-cigarettes group 2.0% in the rewards group (and 2.9% in the redeemable deposit group. Significant differences in abstinence between groups were noted for: Redeemable deposit vs. free cessation aids (p<0.001) Rewards vs. free cessation aids (p=0.006) Redeemable deposit vs. free e-cigarettes (p=0.008) Among participants in the engaged cohort i.e. those who actively participated, n=1,191), sustained smoking abstinence through 6 months after the target quit date was confirmed in 0.7% in the usual-care group, 2.9% in the free cessation aids group, 4.8% in the free e-cigarettes group, 9.5% in the rewards group and 12.7% in the redeemable deposit group.
Hartmann-Boyce et al. 2016 **UK** **Cochrane Review**	NA	2 RCTs and 11 cohort studies including participants who were current smokers who may/may not have been motivated to quit.	Studies included electronic cigarettes (EC) vs. placebo ECs, ECs vs. alternative smoking cessation aids, including nicotine replacement therapy (NRT or no intervention, and	**Primary outcome:** Smoking cessation at longest follow-up (≥6 months following initiation of treatment) **Secondary outcome:** >50% reduction in cigarette use	Participants using nicotine EC were more likely to quit smoking compared with those using placebo ECs (RR=2.29, 95% CI 1.05-4.96, p= 0.037). Results from 2 RCTs included. Participants using EC were no more

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					RR=1.46, 95% CI 1.04-2.04). There was no significant difference in abstinence at 1 month between nicotine e-cig users and placebo e-cig users (23.2% vs. 16.4%, p=0.21). There were no significant differences in abstinence at 3 months (nicotine e-cigs vs. patch 13.1% vs. 9.2%, p=0.12 &nicotine e-cig vs. placebo e-cigs 13.1% vs. 6.8%, p=0.14. At 6 months, nicotine e-cig users had reduced their mean daily tobacco use significantly more compared with the other 2 groups (9.7 vs. 7.7. vs. 1.9 cigs/day, p=0.002). There were no significant differences in the total number of adverse events among groups (event rate: 0.8 events/person month in both nicotine e-cig and patch group & 0.9 events/person month in placebo e-cig group). Losses to follow-up: nicotine e-cig: 17%, patches: 27%, placebo e-cig: 22%.
Caponnetto et al. 2013 **Italy** **RCT** ***EffiCiency and Safety of an eLectronic cigareTte (ECLAT)***	CA: ☒ Blinding: Patient ☑ Assessor ☑ ITT: ☑	300 participants aged 18-70 yrs who smoked ≥10 cigs/day for at least the previous 5 yrs, in good health and **not intending to quit smoking** (or wishing to do so) for the next 30 days. Mean age was 44 yrs, 63% male. On average, participants had smoked for 25 yrs. Exclusions included pregnancy or breastfeeding, symptomatic CVD, ETOH	All participants used e-cigs, but were randomized to different doses units in the nicotine cartridges: 7.2 mg/cartridge x 12 weeks, (Group A, n=100); 7.2 mg for 6 weeks then 5.4 mg/cartridge for 6 weeks (n=100) or 0 mg nicotine x 12 weeks (n=100). Participants used the cartridges *ad libitum* up to 4/day.	**Primary outcome:** Decline in tobacco use at 1 yr. **Secondary outcomes:** Self-reported abstinence (verified by exhaled CO ≤7 ppm) Assessment were conducted at baseline, weeks 2, 4, 6, 8, 10, 12, 24 & 52	The numbers (%) of patients who reported a reduction of ≤50% tobacco use since baseline were: **6 weeks** Group A: 24%, Group B: 26%, Group C: 25% **24 weeks** Group A: 17%, Group B: 19%, Group C: 15% **52 weeks** Group A: 10%, Group B: 9%, Group C: 12%. Quit rates **6 weeks**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		abuse and nicotine replacement therapy			Group A: 11%, Group B: 15%, Group C: 25% **24 weeks** Group A: 12%, Group B: 10%, Group C: 5% **52 weeks** Group A: 13%, Group B: 9%, Group C: 4%. (no p values reported) At baseline, the mean number of cigs/day was 20. It had decreased to 13.9 cigs/day at week 52 (p<0.0001). There were significant reductions in the median number of cigs/day among groups at weeks 2, 6 & 8 (favouring groups A&B over group C). There were no significant differences in adverse events at any time point, among groups (dry cough, mouth irritation, SOB, throat irritation, headache) Losses to follow-up: Group A 35%, Group B 37%, Group C 45%
Bullen et al. 2010 **UK/NZ** **Crossover RCT**	CA: ☒ Blinding: Patient ☒ Assessor ☑ ITT: ☑	40 participants aged 18-70 yrs who smoked ≥10 cigs for the previous year, who smoked their first cig of the day within 30 minutes of waking and who were **not attempting to quit** nor intending to do so within the next 30 days. Mean age was 48 yrs. 47% male, average cig use was 20 /day Exclusions: women who were pregnant or breast feeding, history of serious medical conditions or	Participants were randomized to use 4 different products for 1 day, in random order: e-cigs (0 and 16 mg nicotine), nicotine inhaler and their own brand of cigs. They were instructed to only to use their assigned product for the day, but it could be used *ad libitum*. There was a 3-day washout period between treatments. Participants were instructed to abstain from smoking on study days	**Primary outcome:** Withdrawal symptoms, desire to smoke Assessments were conducted 5, 10, 15, 20, 25, 30, 40, 50- & 60-minutes counting from first puff of product.	Over the 60- minute assessment period, participants using the 16 mg nicotine e-cig reported significantly lower mean desire to smoke scores compared with those using 0 mg cartridges (-2.6 vs. -1.8 units on Likert scale, mean difference=-0.82 units, p=0.006. There were no significant differences in scores related to irritability, restlessness or difficulty concentrating. There was no significant difference in mean desire to smoke score between 16 mg e-cig group and nicotine inhaler group (Mean difference: -0.10, 95% CI -1.16-0.95, p=0.99).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		current use of any other smoking cessation product.			As an alternative to regular cigs, 58% preferred e-cigs, 25% preferred the inhaler and 13% liked neither. 16 mg e-cigs were associated in shorter interval to peak serum nicotine levels (19.6 min vs. 32 min for inhaler). There were no serious adverse events. The most common adverse events were mouth/throat irritation (highest in nicotine inhaler group-88%), headache and nausea (≥18% in e-cig and inhaler groups) Losses to follow-up: n=4
ii) Observational studies examining the use of e-cigarettes to reduce/quit smoking					
Polosa et al. 2011 **Italy** **Uncontrolled study**	NA	40 healthy smokers aged 18-60 yrs who had smoked ≥15 cigs/day for at least the previous 10 yrs., who were **not attempting to quit** and had no desire to quit within the next 30 days. Mean age was 43 yrs, 65% male. Mean of 27 yrs smoking history. Exclusions included recent MI, severe angina, high BP, symptomatic, DM and poorly controlled asthma	Participants were provided with e-cigs and cartridges (7.4 mg nicotine/cartridge) and instructed to use a maximum of 4 cartridges/day for the duration of the study period (12 weeks).	**Primary outcome:** Smoking reduction (50%) **Secondary outcomes:** Smoking reduction (80%), quitters (sustained abstinence at 24 weeks, verified by exhaled CO ≤10 ppm). There were 5 study visits at baseline, weeks 4, 8, 12 &24	27 participants attended the final follow-up visit. Of these, 13 had reduced cig use by ≤50%, reducing their daily cig use significantly from a median of 25 to 6 ($p<0.001$). 5 participants had reduced their cig use by ≥80%, reducing their daily cig use significantly from a median of 30 to 3 ($p=0.043$). There were 9 quitters. Of these, 6 had continued their use of e-cigs during the follow-up period (weeks 12-24). There were 5 smoking failures (those unable to quit/reduced tobacco use). Mean cartridge use was 2/day. Mouth/throat irritation, sore throat, dry cough, headache, nausea and dizziness were reported in >10% of participants at week 4, but declined throughout the study period. Only mouth and throat

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					irritation were reported in >10% of participants.
Etter & Bullen 2014 **Switzerland/NZ** **Observational study**	NA	Subjects who had participated in an online survey posted on a smoking cessation website and who agreed to follow-up at one month (n=477) and one year (n=367)	The use of e-cigarette and tobacco usage was examined in follow-up surveys	Changes in e-cig and tobacco usage among smokers and ex-smokers.	1,329 people completed the baseline survey. The one month and one-year response rates were 62% and 47%, respectively. **1-month respondents**: Median age was 42 yrs. 72% were former smokers. 92% were using e-cigs to prevent relapse. 76% used e-cigs daily. Of the persons still smoking, the mean number of cigs/day was 18.2. 61.6% indicated that they were currently trying to quit smoking. **1-year respondents**: Median age was 43 yrs. 76% were former smokers. 90% were using e-cigs to prevent relapse. 79% used e-cigs daily. Of the persons still smoking, the mean number of cigs/day was 16.3. 60.7% indicated that they were currently trying to quit smoking. **Changes between baseline and follow-up**: 98% of vapors at baseline were still vaping at 1 month, 89% at 1 year. Among daily smokers who were vaping at baseline, 91% and 72% were still vaping at 1 month and 1 year, respectively. Among ex-smokers who were vaping daily at baseline, 99% and 92% were still vaping at 1 month and 1 year, respectively. Among ex-smokers who were vaping daily at baseline, 6% relapsed to smoking

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					daily or occasionally at 1 month and 1 year. Among dual users, smoking cessation rates were 22% at 1 month and 46% at 1 year. Mean daily cigarette usage declined significantly from 11.3-6.0 cig/day from baseline to 1 month (p=0.006), but there was no significant change at 1 year.
iii) E-cigarettes to facilitate behavioral change					
Wagener et al. 2013 **USA** **Uncontrolled study**	NA	20 participants aged 18-55 yrs. who had not previously tried e-cigs, who had smoked ≥15 cigs/day for the previous year, **not currently trying to quit**, nor intending to quit within the next 30 days. Mean age was 40 yrs, 35% male, smoking an average of 18.6 cigs/day. Mean duration of smoking was 13 yrs. Exclusions: women who were pregnant or breast feeding, history of cardiovascular distress, major psychiatric impairment	There were 3 phases of the study **Baseline phase**: baseline visit and data collection, Exhaled CO measured to confirm smoking (≥10 ppm) **Experimental phase:** consisted of 4 separate sessions, separated by 60 minutes in which participants sampled 3 different brands of e-cigs for 2-10 minutes in addition to their own brand of cigs (OBC), presented in random order. Nicotine levels of e-cigs were titrated to meet participants' preferences. Pre/post questionnaires related to product satisfaction, and readiness & confidence to quit were administered after each session. **Ad libitum phase:** Participants were invited to take home a one-week's	**Primary outcome:** Product preferences, readiness and confidence to quit, product satisfaction	Participants preferred OBC to e-cigs. Mean scores: 8.6 vs 6.6 vs. 4.7 vs. 5.2 (p<0.0001) There were no differences among groups in the mean scores associated with effectiveness to reduce urges/cravings (7.3 vs. 7.2 vs. 6.2 vs. 6.1, p=0.335). Participants reported OBC more satisfying than e-cigs (mean scores: 8.7 vs. 6.6 vs. 5.2 vs. 5.0, p<0.0001) From baseline to end of ad libitum phase, participants reported a significant increase in mean readiness to quit score (p=0.006) and a trend towards increased confidence to quit smoking (p=0.053). While there was a 44% reduction in the use of OBC over the study period, there was no change in total tobacco use (e-cigs + OBC) Losses to follow-up: n=4

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			supply of the e-cig (+ nicotine cartridges) that they liked the most and to use as they wished, to be followed by a 10-minute survey (conducted by telephone)		
iv) Increased risk of initiation of combustible tobacco cigarettes among youth					
Berry et al. 2019 **USA** **Prospective Cohort Study** ***Population Assessment of Tobacco and Health (PATH) Study***	NA	6,123 adolescents aged 12-15 years, who had never used any tobacco product at study entry (wave 1). Mean age was 13.4 years, 49.5% female.	Data from 3 waves of the PATH Study (2013-2016) were used to evaluate the associations of prior e-cigarette and other noncigarette tobacco product use (cigar, cigarillo, filtered cigar, pipe, hookah, smokeless tobacco, snus, dissolvable tobacco, bidi, or kretek) with subsequent cigarette initiation. Tobacco product use was established through self-report. Models were developed to evaluate the odds of ever and current cigarette use at wave 3 given prior tobacco product use (prior use of e-cigarettes, prior use of other products, or no prior tobacco use)	**Primary outcomes:** Ever cigarette use and current cigarette use	By wave 3, 8.6% of the sample reported e-cigarettes and 5.0% reported another noncigarette product as their first tobacco product, whereas 3.3% reported using cigarettes first. Ever cigarette use at wave 3 (6.1% overall) was higher among prior users of e-cigarettes (20.5%) and prior users of other products (21.1%) compared with youths with no prior tobacco use (3.8%). At wave 3, compared with those who did not smoke, the odds of ever cigarette use (defined as having ever tried cigarette smoking) were higher in those who reported prior e-cigarette use (OR=4.09, 95% CI 2.97-5.63), and in those who reported prior use of other products (OR=3.84, 95% CI 2.63-5.63). At wave 3, compared with those who did not smoke, the odds of current cigarette use (defined as having used cigarettes in the past 30 days) were higher in those who reported prior e-cigarette use (OR=2.75, 95% CI 1.60-4.73), and in those who reported prior use of other products (OR=3.34, 95% CI 1.88-6.26). The fraction of ever cigarette use attributable to prior e-cigarette use was estimated at 21.8%. The authors estimated there might have been

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					178,850 fewer cigarette initiators without the uptake of e-cigarettes. Corresponding figures for current cigarette use were 15.3% and 43,446.
Soneji et al. 2017 **USA** **Systematic review & meta-analysis**	The overall risk of bias was moderate for all studies based on the ROBINS-I tool.	9 studies including 17,389 adolescents and young adults, 14-30 years who were never cigarette smokers at baseline (n=7) or during the past 30-days (n=2). Mean ages ranged from 14.1 to 23.5 years. 56% of participants were female.	The association between e-cigarette use among never cigarette smokers at baseline and cigarette smoking initiation between baseline and follow-up, was examined, adjusting for demographic, psychosocial, and behavioral risk factors.	**Primary outcome:** Cigarette smoking initiation	Mean duration of follow-up ranged from 6-18 months. The odds of initiating tobacco cigarette at follow-up smoking were significantly higher among ever e-cigarette users compared with no e-cigarette use (OR= 3.50, 95% CI 2.38-5.16, n=7 studies). The odds of initiating tobacco cigarette smoking at follow-up were significantly higher among those used e-cigarettes in the past 30 days at baseline compared with those who had not used e-cigarettes in the past 30 days at baseline (OR= 4.28, 95% CI 2.52-7.27, n=2 studies).

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

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