

**Smoking and Cerebrovascular Disease: A three-phase research
program**

Rojiemiahd Edjoc MSc.

Thesis Supervisor:

Dr. Robert D. Reid

Committee Members:

Dr.'s Louise Balfour and Mukul Sharma

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements
for the Doctorate in Philosophy degree in Population Health

Population Health
Faculty of Graduate and Post-Doctoral Studies
University of Ottawa

© Rojiemiahd Edjoc, Ottawa, Canada, 2013

Author's Declaration

I hereby declare that I am the sole author of this dissertation. I am aware that my dissertation may be made publicly available.

Acknowledgements

I have had the great privilege to learn from great mentors during my dissertation. My committee members Dr. 's Sharma and Balfour: your guidance through this endeavour has been invaluable to me in completing this work. I thank you for your time and patience. I look forward to future collaborations. To Dr. Reid who saw the potential in me and provided not only support but his expertise during this work, I thank you. I have learned so much from your tutelage. For that, I am truly grateful.

To my colleagues at the University of Ottawa Heart Institute Prevention and Rehabilitation Centre and the University of Ottawa, I thank you for your continued support.

To my parents and family, thank you for your on-going support in anything that I do. Your confidence in my ability to be successful in anything I do is my inspiration.

Finally to Natalie, I want to thank you for your love, patience and incredible support through this work – without you nothing would be possible.

Dedication

I dedicate this work to Natalie and Reegan. You both have made my life complete.

Table of Contents

<i>Author's Declaration</i>	ii
<i>Acknowledgements</i>	iii
<i>Dedication</i>	iv
<i>Abstract</i>	1
<i>The causative role of smoking in cerebrovascular disease</i>	7
<i>Smoking and ischemic stroke</i>	7
<i>Smoking and haemorrhagic stroke</i>	11
<i>Smoking cessation as a secondary preventative measure in cerebrovascular disease</i>	13
<i>Phase I: Rationale</i>	15
<i>Smoking and cerebrovascular disease: The effect of smoking cessation interventions in smokers with incident and recurrent stroke.</i>	17
<i>Manuscript One</i>	18
Abstract	18
Introduction	20
Methods I	20
<i>Data extraction and analyses for 1st systematic review</i>	22
Methods II	24
<i>Eligibility criteria for 2nd systematic review</i>	24
<i>Type of studies for 2nd systematic review</i>	25
<i>Outcomes for 2nd systematic review</i>	25
<i>Risk of bias and quality assessment for 2nd systematic review</i>	26
<i>Summary and synthesis of study results for 2nd systematic review</i>	26
Information sources and search strategy for 2 nd systematic review	26
Presentation of Findings	27
Results	27
<i>Effect of SCI on long-term quit rates</i>	27
<i>Effect of smoking cessation on stroke recurrence</i>	31
<i>The prognostic effect of smoking status on stroke severity, disability, length of stay and mortality in smokers and non-smokers with cerebrovascular disease.</i>	40
<i>Manuscript two</i>	41
Abstract	41
Introduction	43
Methods	44
Model selection	45
<i>Univariate analyses</i>	46

<i>The association between stroke severity and smoking status</i>	46
<i>The association between length of stay and smoking status</i>	47
<i>The association between disability and smoking status</i>	47
<i>The association between mortality at 30, 90, days, 1 year and smoking status</i>	47
<i>Results</i>	48
<i>Univariate analyses</i>	48
<i>Multivariate analyses</i>	49
<i>Stroke severity analyses</i>	49
<i>Disability analyses</i>	49
<i>LOS analyses</i>	49
<i>Mortality analyses</i>	50
<i>Discussion</i>	50
<i>Conclusion</i>	54
<i>Interpersonal level</i>	58
<i>Rationale</i>	61
<i>Correlates of smoking cessation in smokers with cerebrovascular disease</i>	63
<i>Introduction</i>	66
<i>Methods</i>	67
<i>Statistical Analysis</i>	68
<i>Results</i>	69
<i>Discussion</i>	70
<i>Conclusion</i>	75
<i>Appendix A: Systematic review search strategy</i>	96
<i>Appendix B: Tables</i>	98
Table 1: Characteristics of included studies for 1 st systematic review	99
Table 1: Characteristics of included studies for 1 st systematic review continued.....	100
Table 2: Characteristics of included studies for 2 nd systematic review.....	101
Table 3: Characteristics of smoking and non-smoking patients	102
Table 4: Univariate analyses by smoking status and outcomes of interest (Stroke severity, disability, mortality, LOS)	103
Table 4a: Univariate analyses by smoking status and outcome of interest (LOS)	104
Table 5a: Multivariate analyses on smoking and outcome of interest (LOS).....	106
Table 6: Phase 3 study cohort characteristics	107
Table 6a: Phase 3 study cohort contd.	108

<i>Appendix C: Canadian Community Health Survey: stroke symptoms variable operationalization</i>	111
<i>Appendix D: Canadian Community Health Survey: depression variable operationalization</i>	113
<i>Appendix E: Figures</i>	115
Figure 1: Effects of nicotine on microcirculation	116
Figure 2: Exclusion criteria and paper selection procedure for the 1 st systematic review	117
Figure 3: The effect of SCIs on long term quit rates	119
Figure 4: The effect of smoking cessation on stroke recurrence	120
Figure 5: Socio-ecological model for multi-level correlates of smoking cessation in smokers with cerebrovascular disease	121

Abstract

Purpose: The purpose of this research program was three-fold. First it aimed to determine the effectiveness of smoking cessation interventions in increasing cessation rates in smokers with cerebrovascular disease and whether smoking cessation reduces stroke recurrence. Second it aimed to determine the prognostic influence of smoking and its association with stroke severity, disability, length of stay in hospital and mortality. Third it aimed to identify multi-level correlates of smoking cessation in Canadians who reported stroke symptoms in a large population based survey.

Methods: Two systematic reviews and meta-analyses were performed to achieve the first objective. For the second objective, a retrospective cohort study was undertaken using variables from the Registry of the Canadian Stroke Network. Finally, the third objective was achieved by analyzing respondents from the Canadian Community Health Survey.

Results: There is a paucity of intervention studies examining the effectiveness of smoking cessation in smokers with cerebrovascular disease. Most intervention studies that were found, failed to employ evidence-based approaches to smoking cessation. No evidence was found in regards to the effect of smoking cessation on stroke recurrence. We found smokers had strokes at a younger age compared to non-smokers. We found that in transient ischemic attacks and intracerebral haemorrhage, smoking was a significant predictor of stroke severity, disability, length of stay in hospital and 1 year mortality.

Correlates of smoking cessation among Canadians who have experienced symptoms of a stroke included: higher education and income, implementation of household and vehicle smoking restrictions, access to a general practitioner and the use of smoking cessation

pharmacotherapies and counselling support. Co-morbidities such as depression and alcohol consumption reduced the likelihood of successful cessation.

Conclusions: This three-phase research program elucidated the gaps in intervention research for this population along with co-morbidities that hinder success in cessation. Smoking negatively impacted outcomes such as disability, hospital length of stay and mortality in patients with transient ischemic attacks and intracerebral haemorrhage strokes. Future interventions should take into account modifiable smoking cessation correlates in order to increase cessation rates in smokers with cerebrovascular disease.

Smoking and Cerebrovascular disease: A Three-Phase Research Program

Introduction

Population health is an approach to health that aims to improve the health of the entire population and to reduce health inequities among population groups (Kindig and Stoddart 2003). It examines current interventions, the distribution of specific outcomes and ways to ameliorate the health of a population or sub-population (Kindig and Stoddart 2003).

Stroke is the 3rd leading cause of death in Canada (Heart and Stroke 2011). Approximately 14 000 Canadians die of this disease every year (Heart and Stroke 2011). One quarter of those who experienced a stroke were also cigarette smokers (Hankey 1999). Smoking has a large impact on patients with cerebrovascular disease (Hankey 1999) and it is important to study this problem using a Population Health approach. The aim of this three-phase research program is to better understand the process and benefits of smoking cessation in smokers with cerebrovascular disease.

Phase one of the research program included two systematic reviews that summarized the current evidence of the effect of smoking cessation for secondary prevention of cerebrovascular disease. Phase two of the research program was a retrospective cohort study. Using variables obtained from the Registry of the Canadian Stroke Network (RCSN) database, phase two compared clinical and demographic characteristics of smokers and non-smokers with cerebrovascular disease. It described the association between smoking status and important outcome of interests such as stroke severity, length of stay (LOS) in hospital, disability and mortality. Phase three of the research program used data from the 2007-2008 Canadian Community Health Survey

(CCHS) to determine significant correlates of smoking cessation in smokers with reported stroke symptoms.

Literature Review

What is a stroke?

A stroke occurs when there is an interruption in the blood supply to any part of the brain. According to Hickey (2003), cerebrovascular insults are classified into two main categories. An ischemic stroke is a result of blockage of blood vessels that supply the brain by a blood clot and accounts for an estimated 85% of cases (2003). A haemorrhagic stroke is a result of a blood vessel that has ruptured allowing blood to leak into the brain and accounts for 15% of cases (2003). Another related phenomenon is a transient ischemic attack (TIA). TIAs are most commonly caused by a blood clot (2003). The blockage is usually temporary; however the event serves as a warning sign for potential future events (Yeh and Waters 2008). According to Yeh and Waters (2008), ischemic and TIA patients are recognized as high risk for subsequent cerebrovascular recurrence.

An interruption in the blood supply from either an ischemic stroke or TIA results in brain cells being deprived of vital glucose and oxygen needed to function. According to Hickey (2003), sources of these occlusions are multi-faceted and may arise from small or large artery thrombi (45%) or are embolic in nature (20%).

Thrombosis results from endothelial injury allowing for the aggregation and adherence of platelets. At the site of the plaque formation, a thrombus forms and coagulation is activated thus decreasing extra-cranial and intra-cranial circulation, leaving the collateral circulation alone to maintain the status quo (Hickey 2003; Stoll, Leinschnitz, Newsandt 2008; Yeh and Waters 2008). The collateral circulation

eventually fails resulting in compromised perfusion and eventual cell death (Stoll et al. 2008).

An embolic stroke occurs when cerebral vessels become occluded from a distant migration of clot formations. These embolic formations may arise from sclerotic plaque from thrombi formations (Stein and Soble 1995), exogenous sources such as from surgical procedures (Hyman, Karalis and Ross 2006) or endogenous sources such as fat tissues that escape into the blood circulatory system (Shaikh, Parchani, Bhat, Kattren 2008).

As an embolism or thrombosis cause further decrease in blood supply to brain tissues, an ischemic cascade occurs on a cellular level. The ischemic cascade is a series of predictable events resulting in imbalances in the normal functioning of neurons and cells (Hinkle and Bowman 2003; Hinkle and Guanci 2007). It is marked by a failure in energy production in the cell allowing production of lactic acid through anaerobic metabolism (Hinkle and Bowman 2003; Hinkle and Guanci 2007). This leads to cell depolarization causing an influx of Ca^{++} ions. High intracellular Ca^{++} lead to the generation of the excitatory amino acid glutamate (Hinkle and Bowman 2003; Hinkle and Guanci 2007). This generation of glutamate allows more calcium to enter the cell creating harmful radicals, oxygen reactive species and calcium dependent agents such as: calpain, endonucleases, ATPases, and phospholipases (Hinkle and Bowman 2003; Hinkle and Guanci 2007). These harmful agents, mainly phospholipases, break down the cell membrane increasing its permeability allowing for more obtrusive ions and chemicals in the cell (Hinkle and Bowman 2003; Hinkle and Guanci 2007). These events lead to mitochondria breakdown and the release of apoptotic chemicals causing cell suicide

(Hinkle and Bowman 2003; Hinkle and Guanci 2007). If the cell dies it releases harmful toxins and glutamate that restarts these sequences of events. The end result is damage to the blood brain barrier and eventual cerebral edema (Hinkle and Bowman 2003; Hinkle and Guanci 2007).

The causative role of smoking in cerebrovascular disease

The causative role of smoking in stroke pathogenesis involves two mechanisms. First, smoking causes changes in the architecture and function of vascular endothelium (Hawkins, Brown, Davis 2002; Hinkle and Bowman 2007; Hinkle and Guanci 2007). Second, smoking causes perturbation to hemodynamic factors in circulation (Hawkins et al. 2002; Hinkle and Bowman 2003; Hinkle and Guanci 2007). To better demonstrate these alterations in function and hemodynamic circulation, they will be discussed in the context of ischemic and haemorrhagic stroke.

Smoking and ischemic stroke

Smoking is a major factor in the development of atherosclerosis (Baldassarre, Castelnuovo, Frigerio, Amato, Werba, De Jong, Ravani, Tremoli, Sirtori 2009; Blann, Kirkpatrick, Devine, Naser, 1998; Hankey 1999; Howard, Wagenkencht, Burke, Diez-Rouz, Evans, McGovern, Nieto, Tell 1998; Hinkle and Bowman 2003; Stoll et al. 2008). Atherosclerosis is known to result in the occlusion of cerebral vessels and carotid arteries via emboli or thrombi (Baldassarre et al. 2009; Blann et al. 1998; Hankey 1999; Howard et al. 1998; Stoll et al. 2008).

Howard and colleagues found that current cigarette smoking was associated with a 50% increase in the progression of atherosclerosis (mean progression rate over 3 years, 43.0 μm) relative to never smokers (mean progression rate over 3 years, 28.7 μm) after

adjustment for demographic characteristics and cardiovascular risk factors (Howard et al. 1998). Furthermore, individuals exposed to environmental tobacco smoke (ETS) have been shown to have a 20% increase in the rate of atherosclerosis progression compared to individuals not exposed to ETS (Howard et al. 1998).

In another study, Baldsarre et al. (2009) found that smoking exhibited atherogenic effects in that it was associated with an increase of carotid intima-media thickness (C-IMT). Furthermore these authors observed a positive relationship between C-IMT and the number of cigarette packs-year.

Smoking induces the development of atherosclerosis through endothelial injury. Investigations have shown that acute cigarette smoke exposure leads to the release of leukocytes causing endothelial damage through a pro-coagulant, von Willebrand Factor (vWF) (Blann et al. 1998).

Endothelial dysfunction and a reduction in dilatory ability have been confirmed in human smokers. Poredos and colleagues have found that the intima-media thickness (IMT) of smokers compared with non-smokers were significantly greater (Poredos, Orehek, and Tratnik 1999). Also, Celermajer and associates (1993) have found that smoker's arteries have diminished or absent flow mediated dilation (Celermajer, Georgakopoulous, Bull, Thomas, Robinson, Deanfield 1993).

The results of these alterations place smokers at a higher risk of cerebral ischemia due to a reduced ability to respond to changes in perfusion pressure and to the lack of distensibility of arterial walls (Blann et al. 1998; Hankey 2003; Hawkins 2002; Kool, Hoeks, Struijker Boudier, Reneman, Van Bortel 1993; Tebor, Bramer, Weiller, Rother 2002).

In addition to atherosclerotic changes induced by smoking on the vessel walls, smokers have an impaired coagulant/anti-coagulant balance throughout their vascular system. Smokers therefore have a higher susceptibility to cerebral ischemia due to this imbalance. Hoiki and colleagues found that thrombin, which is a pre-cursor to fibrinogen and then to fibrin as part of the coagulant cascade, was significantly elevated in smokers (Hoiki, Aoki, Kawano, Homori, Hasumura, Yasumura et al. 2001). Furthermore, smokers have been found to have higher levels of fibrinogen and white blood cell counts when compared to non-smokers (Hoiki et al. 2001). These accounts further support the idea that smokers are more prone to coagulation and thrombosis (Hoiki et al. 2001).

A review by Hawkins (2002) found that nicotine has an effect on haemostatic functions. Nicotine appears to propagate the production of plasminogen activator inhibitor 1 (PAI-1) that depletes free tissue plasminogen (t-PA). This results in a reduction in fibrinolysis and therefore thrombus formation. Nicotine appears to increase leukocyte migration through its effects on mediators such as P-selectin and CD-18 both of which are inhibited by mecamylamine, a nicotinic acetylcholine receptor (nAChR) antagonist (Hawkins 2002).

Nicotine affects cerebral blood flow (CBF) (Hawkins 2002). Advances in non-invasive ultrasonic Doppler velocimetry have demonstrated that one acute effect of nicotine is an increase in blood distribution in several areas of the brain such as the middle cerebral artery (Hawkins 2002; Boyajian and Otis 2000), internal carotid artery and vertebral artery (Hawkins 2002). However a more complex pattern was observed using positron emission topography during intranasal nicotine administration (Domino, Minoshima, Guthrie, Ohl, Ni, Koeppe, Zubieta 2000; Hawkins 2002). This study found

that though increased blood distribution occurred in several areas in the brain, a marked decrease CBF was observed in the left parahippocampal regions suggesting that certain areas of cerebral vasculature are more sensitive to nicotine (Domino et al. 2000; Hawkins 2002).

Studies looking at inhalation of Xe to compare baseline CBF in smokers versus non-smokers found that cerebral perfusion improved after smoking cessation (Hawkins 2002; Rogers, Meyer, Judd, Mortel 1985). A suggested mechanism these authors propose lie in the role of atherosclerosis and its effects on CBF over time. Yamashita and colleagues provided an alternate mechanism. They suggest that the role of smoking may be related to changes in CBF with the decrease concentrations of CO₂ in the blood or hypocapnia. These authors suggest that a decrease in CBF can be attributed to an impaired pulmonary function as a result of less cerebral vascular reactivity to changes in pCO₂ (Hawkins 2002; Yamashita, Kobayashi, Yamaguchi, Kitani, Tsunematsu, 1988).

An important role of the blood brain barrier (BBB) is to prevent non-lipophilic molecules from entering the brain and it is susceptible to perturbations under ischemic conditions (Hawkins 2002). In rat models, the continuous injection of subcutaneous nicotine revealed the increased permeability of the blood brain barrier to sucrose, which indicates a loss of tight-junction integrity and a decrease in the expression of the tight junction protein zonula occludens (ZO-1) along with a decrease in global CBF (Vesnik 2000). Hawkins and colleagues confirmed these results more recently. They used a similar method and found that basal permeability of the BBB to sucrose can be induced by nicotine at a pharmacological level in vivo (Hawkins, Abbruscato, Egleton, Brown, Huber, Campos, Davis 2004). These results suggest that tight junction integrity can in

fact be perturbed by nicotine administration resulting in an expression of altered cellular distribution of ZO-1 and diminished junctional immunoreactivity of claudin-3 (Hawkins et al. 2004). These changes in CBF and BBB according to these authors are prime candidates in accentuating the effects of post-ischemic brain edema. Overall these multi-level perturbations as the result of nicotine include: increased mediators of thrombus formation; decreased overall CBF; reduced BBB function and integrity contributing to the exacerbation of the ischemic cascade (Hawkins et al. 2004). As summarized by Figure 1, nicotine has numerous detrimental effects on blood vessels in the brain. Endothelial components affected by nicotine include mediators of thrombosis [e.g. plasminogen activator inhibitor 1 (PAI-1) and tissue plasminogen activator (t-PA)] and leukocyte migration (e.g. P-selectin and CD18). Nicotine might also have adverse effects on the integrity and function of the blood–brain barrier and interferes with the regulation of blood flow (Hawkins et al. 2002).

These investigations provide evidence of the role of smoking in inducing short- and long-term changes to hemodynamic functions and arterial wall architecture resulting in atherosclerosis. These alterations may lead to the occlusion of cerebral vessels and carotid arteries resulting in an ischemic stroke.

Smoking and haemorrhagic stroke

The role of smoking in haemorrhagic stroke is less investigated. As with ischemic stroke, structural damage to the arterial wall due to smoking leads to an increased risk of haemorrhage (Ives, Heuschmann, Wolfe, Redfern 2008; Quresh, Suarez, Parekh, Sung, Geocadin, Bhardwaj et al. 1994). These structural damages weaken the vessel walls and may be due to the depletion of elastin within the blood vessel (Quresh et al. 1994).

Quresh and associates (1994) hypothesized that the depletion of elastin is due to the reduction of the activity of protease inhibitors, specifically α_1 antitrypsin. Smoking was found to inactivate α_1 antitrypsin from peroxynitrates and OH compounds (Evans and Pryor 1994). Also upon examination of the urine of smokers, high levels of elastase degradation products and an overall decrease of α_1 antitrypsin were found (Stone, Gottlieb, O'Connor, Ciccolella, Breuer, Bryan-Rhadi et al. 1995). The defect in α_1 antitrypsin appears to result in an imbalance between proteolytic enzymes and systematic inhibitory capacity (Tartara, Gaetani, Tancioni, Guagliano, Klersy et al. 1996). This imbalance increases collagen production resulting in arterial wall weakening.

The structural changes of the arterial wall increase the risk of haemorrhage due to the alterations in blood pressure after smoking. Data have shown that blood pressure rises sharply after smoking and may contribute to the rupture of aneurysms (Hankey 1999). According to a study by Feigin and associates of 26 cohorts involving 306 620 participants, smoking and elevated blood pressure are the most important risk factor in subarachnoid hemorrhage (Feigin, Parag, Lawes, Rodger, Suh et al. 2005). They found that during the median follow-up period of 8.2 years, a total of 236 incident cases of subarachnoid haemorrhage (SAH) were observed. Current smoking (HR 2.4; 95% CI: 1.8 to 3.4) and SBP >140 mm Hg (HR 2.0; 95% CI: 1.5 to 2.7) were significant and independent risk factors for SAH. Attributable risks of SAH associated with current smoking and elevated SBP (≥ 140 mm Hg) were 29% and 19%, respectively (Feignin et al. 2003). The evidence of structural changes in arterial walls and smoking-related changes in blood pressure provide a potential mechanism in the relationship between smoking and haemorrhagic stroke.

Smoking cessation as a secondary preventative measure in cerebrovascular disease

The association between cigarette smoking and stroke occurrence has been widely studied. Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for strokes (Kawachi, Colditz, Stapfer, Willett, Manson, Rosner 1993; Shinton and Beevers 1989; Wolf, D'Agostino, Kannel, Bonita, Belanger 1989).

The Framingham Heart Study was among the first to observe the relationship between smoking, number of cigarettes smoked, the type of stroke and smoking cessation. The authors found that heavy smokers (>40 cigarettes/day) compared to light smokers (< 10 cigarettes/day) were twice as likely to have a stroke (Wolf et al. 1989). Even after adjusting for hypertension and age, the relative risks for stroke were significantly increased in smokers (Wolf et al. 1989). The relative risks of stroke in men and women smokers compared to non-smokers were 2.2 and 2.5 respectively. Finally, they observed that the risk of having a stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting (Wolf et al. 1989).

An extensive meta-analysis by Shinton and Beevers (1989) found that cigarette smoking increased the relative risk of strokes by 50% (95% confidence interval (CI) 1.4 to 1.6). Participants who smoked at an earlier age nearly tripled their risk of having a stroke compared to non-smokers (Shinton and Beevers 1989). A gender effect was also observed. The risk of stroke was higher in women who smoked compared to men who smoked (Shinton and Beevers 1989). They concluded that smoking cigarettes posed an

excess risk of strokes, and should be added to diseases related to smoking (Shinton and Beevers 1989).

Growing evidence has demonstrated that smoking is also a risk factor for recurrent strokes (Burn, Dennis, Bamford, Sandercock, Wade, Warlow 1994; Hankey and Warlow 1999; Xu, Liu, Wu, Zhang, Yin 2007). Hankey and Warlow (1999) found that smoking was related to a 66% increase in the odds of stroke recurrence (OR 1.66 CI 1.10 to 2.51) while Xu and associates (2007) found that smoking cessation lead to a decrease of the hazard ratio of recurrence from 1.71 to 1.39 ($p < 0.05$).

These studies support the potential benefits of smoking cessation in the stroke population. Another study to explore these benefits was Kawachi and colleagues (1993). These authors explored the relationship of time since stopping smoking with risk of stroke in middle-aged women (Kawachi et al. 1993). They found excess risk of stroke among former women smokers largely disappeared from two to four years after cessation (Kawachi et al. 1993). They concluded that the risk of recurring stroke declines soon after cessation among smokers regardless of age (Kawachi et al. 1993).

Gaps in the literature

The evidence from these studies suggests that stroke and TIA patients would benefit in reducing the risk of strokes and stroke recurrence by quitting smoking (Burn et al. 1994; Kawachi et al. 1993; Shinton and Beevers 1989; Wolf et al. 1989; Xu et al. 2007). Given the effects that smoking has on patients with cerebrovascular disease, it is important to study this problem in a comprehensive manner.

A health care setting such as a stroke prevention clinic provides an excellent environment where smoking cessation services could be implemented to target this

particular high-risk population. Despite growing evidence of the effectiveness of smoking cessation as a secondary stroke prevention strategy, there is a well-documented practice gap in the general population. It is estimated that the rates patients are advised to quit are about 50-70% while the actual rates at which patients are assisted are only at <20% (CTUMS 2006).

These data are consistent with data from the stroke population as well. Smokers with cerebrovascular disease appear to have difficulty in quitting smoking; 80-90% of stroke and TIA patients identified as smokers at the time of their event were still smoking 6-12 months after (Papadakis, Aitken, Gocan, Riley, Laplante, Bhatnagar-Bost 2011). The question as to why smokers with cerebrovascular disease continue to smoke is a fundamental Population Health question of great importance and it needs to be addressed.

Phase 1: Rationale

The association between smoking and cerebrovascular disease has been unequivocally confirmed through large epidemiological studies (Kawachi et al. 1993; Shinton and Beavers 1989). It is clear from this evidence that smoking cessation has an important role in preventing cerebrovascular disease. However, a common thread of these large epidemiological studies is that previous investigations in this area have only been explored using cohort or observational designs. Data from intervention studies are currently lacking. Little evidence is available concerning the effectiveness of smoking cessation interventions in helping smokers quit with cerebrovascular disease. Further, there is little to no evidence on the effect of smoking cessation on stroke recurrence. Therefore the benefits and process of smoking cessation in patients with cerebrovascular disease are not clear.

The purpose of this phase of the research program was to summarize the effectiveness of smoking cessation interventions in increasing cessation rates in this population. It also aimed to summarize the effect of smoking cessation for reducing stroke recurrence in smokers with cerebrovascular disease. Two separate systematic reviews were conducted to better understand the current evidence relating to these issues. The first review explored the following research question. *Are smoking cessation interventions effective in increasing cessation rates among smokers with cerebrovascular disease?* The research question for the second systematic review was as follows. *How effective is smoking cessation in preventing stroke recurrence among smokers with cerebrovascular disease?*

Smoking and cerebrovascular disease: The effect of smoking cessation interventions in smokers with incident and recurrent stroke.

Rojiemiahd K. Edjoc, MSc.
Robert D. Reid, PhD., MBA
Mukul Sharma, MD MSc FRCPC

Manuscript One

Abstract

Purpose: Data from observational studies has led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a paucity of interventional studies and what is less established is the relative benefit of smoking cessation interventions (SCIs) in this population. Furthermore, the extent of the benefit of cessation in regards to stroke recurrence is relatively unclear. The purpose of these systematic reviews was two-fold. The first review aimed to determine the effectiveness of SCI's for increasing cessation rates in this population. The second review examined the effects of smoking cessation on stroke recurrence in smokers with cerebrovascular disease.

Methods: We followed the PRISMA and MOOSE statement approach to identify relevant randomized control studies and observational studies for the first and second systematic reviews, respectively. We used a mixed effects Mantel-Haenszel approach meta-analysis to pool estimate effects for randomized control trials for the first systematic review. A generic inverse variance random effects meta-analyses was conducted to assess the effects of smoking cessation on stroke recurrence in observational studies in the second systematic review.

Results: Of 852 relevant articles, 4 articles fit the inclusion criteria and were included for the first review. Of 900 relevant articles 2 articles were included for the second review. The first meta-analysis revealed a non-significant effect of SCI on quitting (relative risk [RR] 1.08; 95% CI: 0.74 to 1.58; $p=0.68$, $I^2=0.00$). A non-significant effect of smoking cessation on stroke recurrence was found in the second review (RR 0.5; 95% CI: 0.24 to 1.16; $p=0.1$, $I^2=37.8\%$).

Conclusion: This paper provided results from two systematic reviews that explored the effectiveness of SCIs for increasing cessation rates in patients with cerebrovascular disease and the effect of smoking cessation on stroke recurrence. Few studies have examined SCIs in smokers with cerebrovascular disease. Of the 4 intervention studies identified only 2 used evidence-based intervention components. A non-significant effect of smoking cessation on stroke recurrence was found. More studies using contemporary “best-practices” are needed to determine how effective SCIs are for increasing cessation rates in this population and whether smoking cessation decreases stroke recurrence in smokers with established cerebrovascular disease.

Introduction

Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke (Kawachi et al. 1993; Shinton and Beevers 1989; Wolf et al. 1989).

Data from observational studies has led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is however relatively little information from interventional studies that show the relative benefits of smoking cessation interventions (SCIs) in this population. Furthermore, the effect of smoking cessation on stroke recurrence is also less established. The purpose of these systematic reviews is two-fold. The first systematic review determined the effectiveness of SCIs for increasing cessation rates in smokers with an incident stroke. The second systematic review determined the effect of smoking cessation on stroke recurrence in patients with established cerebrovascular disease.

Methods I

Eligibility criteria for 1st systematic review

The eligibility criteria were formulated using the PICO (population, intervention, comparator and outcome) approach to identify relevant studies for the first systematic review (Pai, McCulloch, Gorman, Pai, Enanoria, Kennedy 2008). In the first systematic review, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for randomized control trials (Liberati, Altman, Tetzlaff, Mulrow, Gøtzsche, Ioannidis et al. 2009).

Type of studies for 1st systematic review

Randomized control trials (RCTs) published from prior to the 22nd of May 2012 were included to determine the effectiveness of SCIs in increasing cessation rates in smokers with cerebrovascular disease.

Time frame for 1st systematic review

The time frame (1980-present) was determined through a preliminary search implemented by an information specialist at our facility. Through this preliminary search, it was identified that the earliest study was from the year 1980, verifying that this was a reasonable cut-off point.

Type of participants for 1st systematic review

The proposed patient population was as follows: males and females with confirmed cerebrovascular disease (ischemic, TIA, haemorrhagic) diagnosed by a physician at a hospital. No ethnicity or age limitations were applied in order to be as inclusive as possible.

Types of interventions for 1st systematic review

Studies of interventions that examined behavioural, pharmacotherapy and combination therapy were included. Behavioural interventions included: counselling support from a health care professional (e.g. nurse, physician, therapist, and or psychologist), telephone counselling or the use of national phone quit-lines.

Pharmacotherapy interventions included: nicotine replacement therapy, bupropion and varenicline. Combination therapy involved items from behavioural and pharmacotherapy that were used in conjunction with one another.

Outcome measures for 1st systematic review

The main outcome was quit rates using either an intervention or not. Cessation rates were used from follow-up data from each study. Lost to follow-up patients were included in the denominators and were considered as smokers.

Information Sources for 1st systematic review

We searched MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012). Similar terms were used for EMBASE and CENTRAL databases.

Search strategy for 1st systematic review

The following search terms were used to search the MEDLINE database: smoking cessation; stop or quit or cease or cessation; cerebrovascular disorders; brain ischemia; transient ischemic attack; brain or cerebral; brain hemorrhage; brain or intracranial; cerebrum or cerebral; stroke; brain embolism; occlusive cerebrovascular disease; mortality; morbidity; sudden death; diabetes; carotid stenosis; depression; dementia; revascularization; high blood pressure; hypertension; hyperlipidemia; emergency service; hospital; patient readmission. The search strategy can be found in Appendix A. A similar strategy was implemented while using CENTRAL and EMBASE.

Data extraction and analyses for 1st systematic review

We conducted a preliminary screening of selected abstracts that met the inclusion criteria for the first review. Abstracts were selected if a smoking cessation intervention was reported along with cessation rates for smokers with cerebrovascular disease. From

selected abstracts, full articles were gathered and reviewed independently to determine they met the inclusion criteria. A joint consensus from both reviewers determined the final number of selected articles for full review. We used a standardized form completed by two reviewers independently and extracted data from selected articles. The study name (along with the name of first author, and the year of publication), follow-up period, number of patients in the intervention versus control, number of smokers in the intervention versus control, and patient demographics of interest (mean age, gender, type of stroke diagnosis) were extracted from selected articles. Other pertinent data included: the content of intervention conditions (behavioural, pharmacotherapy, combination therapy), and outcome of interest such as bio-chemically or self-reported quit rates.

Risk of bias and quality assessment for 1st systematic review

We appraised selected articles for their methodological quality and bias using the Jadad scale (Jadad, Moore, Carroll, Jenkinson, Reynolds, Gavaghan et al. 1996). The Jadad scale is a 5-point quality scale that includes points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, additional 1 point), use of double-blinding (described as double-blind, 1 point; use of masking such as identical placebo, additional 1 point), and follow-up (the numbers and reasons for withdrawal in each group are stated; 1 point) in the report of an RCT (Jadad et al. 1996). In general, scores of 2 or less are considered as low quality, and scores of 3 to 5 are considered as high quality (Jadad et al. 1996).

Summary and synthesis of study results for 1st systematic review

A meta-analysis was performed for the outcome of interest. Statistical results from studies that were reviewed were pooled together using Comprehensive Meta-

analysis (CMA). Relative risks (RR) with 95% confidence intervals (CIs) were calculated from the numbers of the 4 cells of the 2 x 2 tables of each of the studies. The direction and size of effect was considered, and whether they were consistent across studies. The Mantel-Haenszel method was used to calculate weighted summary estimates of the pooled data. The Mantel-Haenszel method have been shown to be more robust when data are sparse and assumes a fixed effect when combining studies to determine the weight given to each study (Eggers, Davey Smith and Altman 2001). Heterogeneity test was run using the I^2 statistic. The I^2 statistic describes the percentage of variation across studies that are due to heterogeneity rather than chance (Higgins and Thompson 2002). It is derived by the formula:

$$I^2 = 100\% \times (Q-df)/Q \text{ (Higgins and Thompson 2002).}$$

Presentation of findings for 1st systematic review

Findings were presented as per the PRISMA statement. A flow diagram of the number of identified studies, the reasons for their inclusion and exclusion was captured and reported at all levels of the screening process. Where appropriate, forest plots representing study-level outcome data and estimated associations with 95% confidence intervals, the pooled estimate of effect with corresponding 95% confidence interval, related measures and tests for the presence of heterogeneity (I^2 measure) were presented.

Methods II

Eligibility criteria for 2nd systematic review

In the second systematic review, we followed the MOOSE (Meta-analyses of Observational Studies in Epidemiology) statement for observational studies (Stroup, Berlin, Morton, Olkin, Williamson, Rennie et al. 2009).

Type of studies for 2nd systematic review

Observational and cohort studies published from 1980 to the present were included to determine the effects of smoking cessation on stroke recurrence. The rationale for including observational and cohort studies to explore stroke recurrence was based on the short follow-up periods for RCTs. The durations of the RCTs were too short to determine if smoking cessation reduces stroke recurrence for this population of interest.

Time frame for 2nd systematic review

The time frame suggested (1980-present) was determined through a preliminary search implemented by an information specialist at our facility. Through this preliminary search, it was identified that the earliest study was reported in 1980 thus providing a reasonable cut-off point.

Type of participants for 2nd systematic review

The patient population was as follows: males and females with a confirmed diagnosis of recurrent stroke by a physician at a hospital. No ethnicity or age limitations were applied in order to be as inclusive as possible.

Outcomes for 2nd systematic review

Outcomes examined in this review included: recurrent stroke, TIA or haemorrhagic stroke confirmed by a physician. Lost to follow-up patients were included in the denominators and were considered as smokers.

Risk of bias and quality assessment for 2nd systematic review

We appraised selected articles for their methodological quality using the Downs and Black scale. The Downs and Black checklist consists of 27 questions assessing the quality of: reporting, external validity, bias, and confounding (Downs and Black 1998). We modified the scale by eliminating questions that were irrelevant to our review. The maximum Downs and Black checklist score for our review is 19. We resolved discrepancies between reviewers by consensus.

Summary and synthesis of study results for 2nd systematic review

As per the MOOSE statement, the calculation of a single summary estimate of effect of exposure may be potentially misleading due to the extreme diversity of study designs in observational studies (Pai 2012; Stroup et al. 2000). An inverse variance (IV) method was used to calculate study weights where the variance of the summary estimates is inversely proportional to importance (i.e. larger weight is given to larger studies with lower standard errors) thereby minimizing the variability of the pooled treatment (Pai 2012; Eggers et al. 2001).

Information sources and search strategy for 2nd systematic review

Similar information sources and search strategy were used for the second systematic review. Please refer to Methods I for further details.

Data extraction for 2nd systematic review

We conducted a preliminary screening of selected abstracts that met the inclusion criteria for the second review. Abstracts were selected if smoking cessation rates for smokers with a recurrent stroke were reported. From selected abstracts, full articles were

gathered and reviewed independently to determine they met the inclusion criteria. A joint consensus from both reviewers determined the final number of selected articles for full review. We used a standardized form completed by two reviewers independently and extracted data from selected articles. The following were extracted for the second systematic review: the study name (along with the name of first author, the year of publication), stroke diagnoses, patient demographics (mean age (SD), sex), smoking status and time of follow-up, and outcome of measure of interest such as the number of stroke recurrence in those who quit and did not quit smoking.

Presentation of Findings

The second review was presented as per the MOOSE statement. A flow diagram of the number of identified studies, the reasons for their inclusion and exclusion was captured and reported at all levels of the screening process. Where appropriate, forest plots representing study-level outcome data and estimated associations with 95% confidence intervals, the pooled estimate of effect with corresponding 95% confidence interval, related measures and tests for the presence of heterogeneity (I^2 measure) were presented.

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 2 respectively. An overall Jadad score of the selected papers was 3.75 (+/- 0.56) out of a possible score of 5. With an intervention, 42 out of 176 smokers quit versus 37 out of

178 in the control group. This results in an overall cessation rate of 23.9% for interventions versus 20.8% for controls. The meta-analysis revealed a non-significant effect of using a SCI on quitting (RR 1.08; 95% CI: 0.74 to 1.58; $p=0.68$, $I^2=0.00$) (Figure 3).

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke (Wolfe, Redern, George, Rudd et al. 2010). The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers at baseline. They were then randomized into the control ($n=78$) and intervention group ($n=76$). The intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers at 10 weeks, 5 months, and 8 months post-stroke regarding treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to NRT use. (Wolfe et al. 2010). The primary outcome was management of key modifiable risk factors for stroke at 1 year and 18 months post-stroke. The authors found that at 1 year, 21 out of 76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. No NRT was provided. The control group received usual care. In the control group at 1 year, 22 out of 78 (28.2%) patients successfully quit smoking (Wolfe et al. 2010).

The second study explored the impact of a stroke nurse specialist's input on risk factor modification (McManus, Craig, McAlpine et al. 2009). The population was selected from a clinic of patients with a diagnosis of stroke or TIA who were attending on-going rehabilitation in a UK teaching hospital. Patients in the intervention group

received advice on smoking cessation medications. Patients in the control group received usual care. At 42 months, there was 1 out of 36 (2.8%). None had quit in the control group (0 out of 42%, 0.0%).

The third study was a pilot randomized trial of standardized counselling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention (Papadakis, Aitken, Gocan, Riley, Bhatnagar-Bost et al. 2011). Patients who had recently experienced a TIA or stroke or who had been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention or prescription (P) control group. Patients randomized to the CF group received cost-free medications along with counselling with a smoking cessation nurse for 26 weeks. Patients randomized into the control group received usual care and prescriptions to smoking cessation medications. There were 255 smokers identified and 28 participants were enrolled based on readiness to quit. Cessation rates at 26 weeks for the intervention and control group was 4 out of 15 (26.6%) and 2 out of 13 (15.4%) respectively (Papadakis et al. 2011).

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention for increasing cessation rates in recruited patients with a recent stroke or TIA (Frandsen, Sørensen, Hyldahl, Henriksen, Bak 2012). There were 94 smoking patients with a recent stroke or TIA that were recruited for this study. For the purpose of this review and meta-analyses, the minimal smoking cessation intervention was considered as the control group while the intensive smoking cessation intervention was regarded as the intervention group. The control group consisted of a 30 minute counselling session with the study nurse advising patients to quit smoking. A total of 45

patients were randomized into the control group. The intervention group received five sessions of smoking cessation counselling with the study nurse while receiving free NRT such as gum, tablets, patches and nasal spray. Furthermore, patients were followed-up via telephone visit for six weeks at two days, 1 week, 3 weeks, 3 and 4 months. A total of 49 patients were randomized into the intervention group. Cessation rates at 6 months for the intervention and control group was 16 out of 49 (32.7%) and 13 out of 45 (28.9%), respectively.

There were some limitations to each study that will be discussed here. Sample size was an issue in all of the included studies. For example the small number of participants (n =28) in Papadakis et al.'s study meant that the study was relatively underpowered. Similarly, only 94 patients were recruited in the Frandsen et al.'s (2012). This study saw little effect of the intensive smoking cessation intervention. Larger trials with adequate power would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counselling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and stroke patients. A similar under-powered result due to a small sample size was observed in the study by McManus et al. (2009). They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. Finally, all included studies recruited patients from fairly homogenous sources such as a single stroke clinic (Papadakis et al. 2011), hospitals (McManus et al. 2009; Frandsen et al. 2012) and 2 GP clinics (Wolfe et al. 2010) and may not be generalizable to a broader stroke population in other settings.

Effect of smoking cessation on stroke recurrence

Of 900 potential articles, 2 studies met the inclusion criteria. Characteristics and the flow of included studies can be found in Table 2 and Figure 2a respectively. The average modified Downs and Black score was 15.2 (+/-2.12) out of a possible score of 19.

Effect of smoking cessation on stroke recurrence

Two studies were identified to explore the effects of smoking cessation and stroke recurrence (Eguchi, Kario, Hoshide, Hoshide, Ishikawa, Morinari et al. 2004; Xu et al. 2007). From these studies, there was 263/437 reported stroke recurrences in smokers compared to only 174/437 reported stroke recurrences in former smokers. It was found that quitting lead to a non-significant reduction in stroke recurrence (RR 0.5; 95% CI: 0.22 to 1.34; $p=0.12$, $I^2=67.2\%$) (Figure 4).

The first study examined recurrence of ischemic stroke in Chinese patients (Xu et al. 2007). The selected population for this study were those with recurrent ischemic and haemorrhagic stroke captured by Nanjing Stroke Registry Program (NSRP). There were 369 patients identified with recurrent ischemic stroke and a history of smoking of whom 211 (25.3%) were current smokers. There were 158 (18.9%) former smokers. This study found that recurrence in smokers was more common (211 out of 369) compared to former smokers (158 out of 369). Furthermore, they found that quitting smoking reduced the hazard ratio from 1.71 to 1.39 ($p<0.05$).

The second study sought to determine the relationship between smoking and silent cerebrovascular damage in a Japanese community. There were 170 patients with silent cerebrovascular damage recruited for this study of which 28 (16.5%) were identified as

smokers. There were 15/28 recurrent silent cerebrovascular events in smokers compared to only 3/20 cerebrovascular events in former smokers (Eguchi et al. 2004).

The methodological quality of each study was relatively good as they collectively scored a 15.2 out of 19 on the modified Down's and Black scale. Limitations of each study will be discussed here. Xu et al. (2007) and Eguchi et al. (2004) included exclusively Chinese and Japanese participants in their studies. It has been found that eastern countries such as China and Japan tend to have different epidemiological features for incident ischemic and haemorrhagic stroke (Jiang, Wang, Chen, Hong, Yang, Wu, Du, Bao 2006). In fact observed rates of ischemic and haemorrhagic stroke are higher in eastern countries compared to rates in western countries (Jiang et al. 2006).

Homogeneity of the sample along with higher epidemiological rates of stroke associated with eastern countries may make these results un-generalizable to stroke patients in western countries. Along the same vein, Eguchi et al. (2004) only recruited from a single community further limiting the generalizability of their results.

Discussion

The purpose of these systematic reviews was two-fold. The first review examined the effectiveness of SCIs for increasing cessation rates in patients with established cerebrovascular disease. The second review examined the effects of smoking cessation on stroke recurrence in this population.

Our results demonstrate that few SCI studies have been reported. Furthermore, not all interventions that have been tested have used proven smoking cessation intervention components (i.e. concurrent smoking cessation pharmacotherapy, counselling and follow-up). Only 2 of the 4 intervention studies (Papadakis et al. 2011; Frandsen et al. 2012)

implemented evidence-based smoking cessation intervention. The approach taken by these studies fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update* (Fiore, Jaen, Baker, Bailey, Benowitz, Curry et al. 2008).

Fiore and associates (2008) suggested that effective smoking interventions consist of pharmacotherapy coupled with counselling and follow-up. First line pharmacotherapy such as NRT, bupropion and varenicline can double or even triple the likelihood of long-term smoking abstinence for heavy smokers that consume > 10 cigarettes per day when coupled with behavioural counselling and follow-up (Cahill, Stead and Lancaster 2007; Eisenberg, Filion, Yavin, Belisle, Mottillo, Joseph et al. 2008; Stead, Perera, Bullen et al. 2008).

Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD) receiving an intervention. A 44% increase in cessation rates can be observed in CHD patients (Reid, Pipe and Quinlan 2006). A decrease in mortality risk and non-fatal myocardial infarction by 32% and 36% respectively (Critchley and Capewell 2004) can be observed in CHD patients using this approach. Larger clinical studies need to employ evidence-based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

Stroke recurrence is a consistent and independent predictor of disability, institutionalisation and death, often resulting in a stepwise decline into dependency in stroke survivors (Joubert, Reid, Barton et al. 2008). We were unable to quantify the effects of smoking cessation on stroke recurrence.

There are several limitations to the present study that should be considered in any interpretation of the findings. There was a high degree of heterogeneity among pooled data for the meta-analyses in regards to the population, intervention and outcome. There was significant variability in the population of the included studies for both meta-analyses. For example, an array of stroke diagnoses was found in the first systematic review ranging from incident stroke and TIA. This was similarly observed in the second systematic review where both studies included an array of stroke diagnoses such as incident ischemic and haemorrhagic stroke and silent cerebral infarcts. Pooled interventions also varied between studies ranging from non-specific advice on quitting and pharmacotherapy use to more specific interventions that involved the use of medications, counselling and follow-up. Furthermore, the duration of follow-up was also different amongst the included studies ranging from 3 to 42 months follow-up. Finally, cessation was only quantified biochemically by Papadakis et al. (2011) and Frandsen et al. (2012). Wolfe et al. (2010) used both biochemical assays along with self-reported smoking status to quantify cessation. However, these authors only used the biochemical assays to determine the amount of misreporting in self-reported data and did not correct misreported smoking status (Wolfe et al. 2010). McManus et al. (2009) did not report how cessation was quantified. Larger homogenous studies with cerebrovascular disease are needed to assess the efficacy of SCI's and the effect smoking cessation on incident and recurrent stroke respectively.

Conclusion

This paper provided results from two systematic reviews that explored the effectiveness of SCI's for increasing cessation rates and the effect of smoking cessation

on stroke recurrence in smokers with cerebrovascular disease. There were few reported intervention studies in this area of secondary stroke prevention. Furthermore, of those intervention studies, only 2 studies implemented evidence-based approaches in smoking cessation. Finally a non-significant effect of smoking cessation on incidence stroke recurrence was found. Larger studies using evidence-based interventions in homogenous cerebrovascular disease populations are required to understand the efficacy of SCI's and whether smoking cessation decreases stroke recurrence in smokers with cerebrovascular disease.

Phase 2: Theoretical models and rationale

The causative role of smoking in cerebrovascular disease was described in the literature review. In brief, smoking causes hemodynamic and structural changes in the vascular system leading to a higher susceptibility of smokers to strokes and transient ischemic attacks. The following discussion will outline the role of socio-demographic factors and allostatic loads (ALs) that provided the rationale for the research question for this phase of the research program.

Socio-demographic factors such as age and gender are important risk factors in cerebrovascular disease. What sets them apart from modifiable behavioural risk factors such as smoking or exercise is that they underlie the basis of susceptibility to cerebrovascular disease and strokes from birth. A report by the Public Health Agency of Canada (PHAC 2010): *Tracking Heart Disease and Stroke in Canada* indicated that men were hospitalized more than women for cerebrovascular disease (PHAC 2010). This report found that men had an age-standardized hospitalization rate of 144.0 (per 100 000 population) compared to women that had an age-standardized hospitalization rate of 102.3 (per 100 000 population) (PHAC 2010). Longer length of stay in hospital was reported for men at 16.8 days compared to women at 14.3 days (PHAC 2010). In 2005/2006 after adjustment for age and sex, rates for men for hospitalization due to acute stroke, were consistently higher than women at all ages (PHAC 2010). For Canadians age 65-74 years, the rate of hospitalization for men was 441.0 (per 100 000 population) compared to women at 296.0 (per 100 000 population) (PHAC 2010). A similar trend can be observed at age group 75-84 years and 85 and up. These rates of hospitalization were

953.1 for men and 796.1 for women at ages 75-84 years (per 100 000 population) and 1513.9 for men and 1457.9 for women at ages 85 and up (per 100 000) (PHAC 2010).

Stroke severity is associated with disability according to Strum and associates (Strum, Donnan, Dewey, Macdonell, Gilligan, Thrift 2004). These authors found that initial stroke severity was a significant predictor of 2-year post-stroke disability along with age, female sex, socioeconomic status, alcohol intake, stroke subtype, recurrent stroke, anxiety, 2-year physical impairment, disability, depression, anxiety scores and institutionalization (Strum et al. 2004). Not surprisingly, stroke severity has been shown to be associated with longer length of stay. Chang and associates found that those who scored the highest on the National Institute of Health Stroke Scale (NIHSS) measuring severity of stroke had a longer length of stay in hospital by 13 days (Chang, Tseng, Weng, Lin, Liou, Tan 2002). Similarly, stroke severity is a predictor of mortality risk (Adams, Davis, Leira, Chang, Bendixen, Clarke, Woolson, Hansen 1999; Johnston, Connors, Wagner, Knaus, Wang, Haley 2000). The link between smoking and stroke severity is less defined. The following discussion will describe the potential role of smoking in stroke severity as explained through the allostatic load model.

Allostatic load model

McEwen and colleagues developed the concept of allostatic loads (ALs) and their relationship to allostasis (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993). Allostasis was first introduced by Sterling and Eyer (1988) and refers to the ability of the human body to achieve stability through change. Adaption leads to the chronic over-or-under activity of allostasis systems that in turn produce ALs (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993). The allostatic load model

(ALM) describes that chronic stress is influenced by one's experiences, genetics and behaviour. The brain is the integrative center for coordinating behavioural and neuroendocrine responses (whether they are hormonal or autonomic) to challenges in the environment (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993).

The effect of chronic stress on the body has been extensively studied. When the brain is exposed to excess glucocorticoids such as cortisol, it results in atrophy of the hippocampus leading to the deterioration of neurons in the hippocampus (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993). The loss of hippocampus neurons affects the regulation of the stress response thus inhibiting the role of the hypothalamic pituitary axis (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993). Chronic stress causes a decrease in sensitivity response of lymphocytes and macrophages of the immune system leading to the susceptibility to pathogens that make people sick (McEwen 1998; McEwen and Seeman 1999; McEwen and Stellar 1993).

At the population level, a study that demonstrates the concept of ALs and the cumulative effect on health was the MacArthur studies of successful aging (Seeman, Crimmin, Huan, Singer, Burton, Bucur, Guenaewald, Berkman 2004). The purpose of their study was to examine the concept of ALs as a measure of cumulative biological burden. They used a multi-system summary of ALs (e.g. BMI, SBP/DBP, HbA1c/Cholesterol levels) that includes physiological activity across a range of regulatory systems pertinent to disease risks (Seeman et al. 2004). Their results showed that higher allostatic load measures were associated with a greater risk of 7-year mortality, declines in physical function and cognitive function and a marginally

significant increase in the incidence of cardiovascular disease (Seeman et al. 2004). They conclude that the concept of ALs offers an insight into the cumulative risks to health from biological dysregulation across multiple regulatory systems (Seeman et al. 2004).

Rationale

The converging lines of evidence point to the role of smoking status and socio-demographic factors in predicting stroke severity in patients with cerebrovascular disease. Smoking, due to its hemodynamic and structural effects on the cardiovascular system, is a stressor based on the ALM that would create further cumulative biological dysregulation in smokers with cerebrovascular disease. As a result, smokers should have more severe strokes and in turn have greater disability, length of stay in hospital and greater mortality risk after the acute event. The question of whether smoking status has a prognostic effect on stroke severity, disability, length of stay in hospital and mortality in smokers with cerebrovascular disease is not well understood. The evidence for this is clearly lacking and was therefore the focus of phase 2 of the research program.

The purpose of phase two of the research program was to determine if smoking status has a prognostic effect on stroke severity, disability, length of stay in hospital and mortality. Phase 2 of the research program compared clinical and demographic characteristics of smoking and non-smoking cerebrovascular patients. This study used prospectively collected data from the Registry of the Canadian Stroke Network (RCSN) database. The research question for this study was as follows. *Is smoking status associated with an increase of stroke severity, disability, length of stay in hospital and mortality in patients with cerebrovascular disease?*

The prognostic effect of smoking status on stroke severity, disability, length of stay and mortality in smokers and non-smokers with cerebrovascular disease.

Rojiemiahd K. Edjoc, MSc
Robert D. Reid, PhD., MBA
Mukul Sharma, MD MSc FRCPC
Jiming Fang, PhD

Manuscript two

Abstract

Background and Purpose: Smoking is a well-established risk factor for initial and recurrent stroke. Multiple mechanisms including hypercoagulability and progression of atherosclerosis are felt to be responsible. However the prognostic influence of smoking on outcomes such as stroke severity, length of stay (LOS) in hospital, disability and mortality in different stroke subtypes remains unclear.

Methods: Data from the Registry of the Canadian Stroke Network (RCSN) were analyzed using logistic regression to determine the association between smoking status, stroke severity, LOS in hospital, disability and mortality while controlling for socio-demographics and clinical characteristics.

Results: There were 20523 patients that were included for this study. A total of 3629 (17.7%) patients with a recent diagnosis of stroke, transient ischemic attack (TIA) and or intracerebral haemorrhage (ICH) were reported smokers. Smokers had a mean age at initial stroke at 61.8 (+/- 13.2) while non-smokers had a reported mean age of 73.2 (+/- 13.5). These patients were largely male (64.4%) and had predominantly ischemic strokes (66.2%) compared to TIA's (23.2%) and ICH's (10.6%). Multi-variate analyses revealed that smoking was not a significant predictor of stroke severity. Smoking increased the odds of disability in ischemic stroke (OR 1.1; 95% CI: 1.01 to 1.20) patients. Smoking resulted in an incremental increase of LOS in hospital in TIA by 5.7 days (95% CI: 0.30 to 0.40) and ICH by 21.4 days (95% CI: 0.005 to 0.70) but not so in ischemic stroke patients. Smoking was not a significant predictor of short-term mortality but was a

significant predictor of long-term mortality in TIA (OR 1.5; 95% CI: 1.10 to 2.08) and ICH (OR 1.3; 95% CI: 1.00 to 1.76) patients.

Conclusions: Smoking did not positively predict stroke severity. Smoking lead to an increase in disability; LOS in hospital and mortality but the magnitude of the effect varied by stroke sub-types. Our results provide empirical evidence in regards to the prognostic influence of smoking status on disability, LOS and mortality.

Introduction

Smoking is a well-established risk factor for initial and recurrent stroke (Burn et al. 1994; Kawachi et al. 1993; Shinton and Beevers 1989; Wolf et al. 1989; Xu et al. 2007). Multiple mechanisms including hypercoagulability and progression of atherosclerosis are felt to be responsible (Baldassarre et al. 2009; Blann et al. 1998; Hankey 1999; Howard et al. 1998; Stoll et al. 2008).

Several studies have suggested clinical and demographic characteristics may differ between non-smoking and smoking patients with a recent cerebrovascular event (PHAC 2010). Furthermore, the prognostic influence of smoking status on important cerebrovascular outcomes is still unclear.

Outcomes such as stroke severity, disability, length of stay (LOS) in hospital and mortality have been separately examined in past studies yielding variable results (Ives, Heuschmann, Wolfe, Redfern 2008; Mynt, Welch, Bingham, Luben, Wareham, Day et al. 2006; Weng et al. 2011). In general these studies have demonstrated that smoking negatively impacts each of these outcomes (Ives et al. 2008; Mynt et al. 2006; Weng et al. 2011). However these studies have only examined stroke severity, disability, LOS in hospital and mortality separately in relation to smoking status and only in specific stroke sub-types. Therefore the impact of smoking on these outcomes and in different stroke sub-types is still poorly understood (Andersen, Olsen, Dehlendorff, Kammersgaard 2009; Steiner, Gotkine and Wirguin 2008; Weng et al. 2011).

The aim of this study was to determine the prognostic influence of smoking status on stroke severity, disability, LOS in hospital and mortality in different stroke sub-types.

A secondary aim was to describe the demographic and clinical characteristics of smoking and non-smoking patients with cerebrovascular disease.

Methods

The Registry of the Canadian Stroke Network (RCSN) contains data for over 50000 strokes in Canada (Kapral, Hall, Silver, Richards, Robertson, Fang 2009; RCSN 2010). Participating sites include all Ontario acute care institutions, excluding children's and mental health care hospitals and those with fewer than 10 stroke or TIA separations per year. The inclusion factors include: all patients seen in emergency departments or admitted to hospital with a most responsible diagnosis of stroke or TIA (Kapral et al. 2009; RCSN 2010). Diagnoses are identified from the discharge abstract database (DAD) and the National Ambulatory Care Reporting System (NACRS) databases that are maintained by the Canadian Institute for Health Information (CIHI). The collected data focuses on time intervals between stroke onset and the delivery of care including thrombolysis, and include information on patient demographics, stroke type, stroke risk factors, premorbid conditions, brain imaging, treatments (including medications), and the utilization of stroke protocols/units (Kapral et al. 2009; RCSN 2010).

We analysed a distinct cohort of patients grouped by their smoking status (current smoker or not a current smoker: within the last six months). Covariates of interest included: age (12-39, 40-59, 60-79, 80+) sex (male or female), type of stroke (ischemic stroke, transient ischemic attack and or intracerebral haemorrhage), and medical history (depression, diabetes, dyslipidemia, hypertension, atrial fibrillation, family history of stroke, dementia, alcohol consumption). Outcomes of interest included: mortality (30, 90,

and 360 days), LOS in hospital, Modified Rankin score (MRs) that measured disability, and the Canadian Neurological Scale (CNS) that measured stroke severity.

For the purposes of calibrating the CNS scale, logical clinical categories of stroke severity were created. Specifically, scores were categorized as “mild” (scores 8.5 to 11.5), “moderate” (scores 6.0 to 8.0), and “severe” (scores 0.0 to 5.5). Mild was defined as non-motor deficits or mild hemi-paresis with or without dysarthria and without alteration in sensorium. A moderate score referred to moderate/severe hemi-paresis with or without dysarthria and with or without disorientation or isolated receptive aphasia. Finally, a severe score referred to comatose, hemiplegic, or globally aphasic patients.

Statistical analysis

Characteristics of smoking and non-smoking patients were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. Sub-group analyses for each stroke sub-type: ischemic, TIA and ICH were performed. The association between smoking status and three of the four outcomes of interest (CNS, MRs, and mortality) was examined using univariate and multivariate logistic regression analyses. Univariate and multivariate poisson linear regression analyses were used to determine the association between smoking status and LOS in hospital.

Model selection

Four outcomes of interest were examined for their association with smoking status. These outcomes included: stroke severity, LOS in hospital, mortality and modified Rankin score for disability. For each outcome, separate regression analyses were performed based on the nature of the dependent variable (categorical or count variable). The method of model building for logistic regression analyses was forward-

stepwise selection. The Wald statistic was used for variable selection. If the Wald statistic was less than 0.05, the independent variable was considered to be significant and was entered into the overall model. For linear and multiple regression analyses, the method of model building was forward variable selection. This method determined which variable was included in the model based on the increases of the R^2 statistic.

Univariate analyses

Univariate analyses were performed for each dependent variable (stroke severity, LOS in hospital, mortality, disability) and predictor of interest (smoking status) with each independent variable. Significant covariates were included in the regression models if they reached a 95% significance level.

The association between stroke severity and smoking status

An unadjusted logistic regression analysis was performed with the dependent variable as stroke severity and the predictor variable as smoking status. Stroke severity was dichotomized into mild vs. severe categories. Reference category for the predictor variable was non-smoker. Adjusted logistic regression analysis was performed on the association between stroke severity and smoking status. Independent variables included all significant covariates from the univariate analyses ($p < 0.05$). Stratified analyses of this association (stroke severity and smoking status) were performed while considering stroke type (ischemic vs. TIA vs. ICH stroke). Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

The association between length of stay and smoking status

An unadjusted poisson regression was used to describe the association between length of stay and smoking status. Three adjusted multiple poisson regression models were used to describe the same association while controlling for covariates of interest stratified by stroke type (ischemic vs. TIA vs. ICH stroke). Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

The association between disability and smoking status

An unadjusted logistic regression analysis was performed with the dependent variable as the modified Rankin score and the predictor variable smoking status. The Rankin score was dichotomized into no disability versus severe disability. Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

Stratified analyses of this association (disability scores and smoking status) were performed considering stroke type (ischemic vs. TIA vs. ICH). Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

The association between mortality at 30, 90, days, 1 year and smoking status

Unadjusted logistic regression analyses were performed with the dependent variable as mortality at 30 days, 90 days and 1 year and the predictor variable smoking status. Adjusted logistic regression analyses were performed on the association between mortality at 30 days, 90 days and 1 year and smoking status. Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

Stratified analyses of this association (mortality at 30 and 90 days and 1 year and smoking status) were performed considering stroke type (ischemic vs. TIA vs. ICH

stroke). Independent variables included all significant covariates from the univariate analyses ($p < 0.05$).

Results

A cohort of 20523 patients was selected for this study from the RCSN. Patients were included if they: 1) had a confirmed diagnosis for stroke/TIA/ICH; 2) had a confirmed stroke severity (CNS) and disability (MRS) score; 3) had a LOS and mortality report. Characteristics of this cohort can be found in Table 3. Of this sample, 17.7% were reported smokers and had a reported mean age of initial stroke at 61.8 (+/- 13.17). Smokers were largely male (64.4%) and had predominantly ischemic strokes (66.2%) compared to TIA's (23.2%) and ICH's (10.6%). Co-morbidities such as depression (7.2% vs. 4.9%) and alcohol consumption (> 2 drinks/day: 16.1% vs. 3.1%) were more common in smokers compared to non-smokers. Diabetes (23.6%), hypertension (67.0%), atrial fibrillation (16.5%), family history of stroke (19.8%) and dementia (9.1%) were more common in non-smokers (Table 3).

Univariate analyses

Univariate logistic regression analyses can be found in Table 4. The univariate analyses revealed that smoking was a negative predictor of stroke severity (OR 0.8; 95% CI: 0.73 to 0.85; $p < 0.001$), disability (OR 0.9; 95% CI: 0.82 to 0.93; $p < 0.001$), mortality at 30 days (OR 0.6; 95% CI: 0.50 to 0.64; $p < 0.001$), at 90 days (OR 0.6; 95% CI: 0.5 to 0.63; $p < 0.001$) and at 1 yr. (OR 0.6; 95% CI: 0.56 to 0.68; $p < 0.001$). The poisson univariate linear regression revealed that smoking was associated with an increased length of stay in hospital of 9.67 days (95% CI: -0.02 to 0.002; $p = 0.09$).

Multivariate analyses

Stroke severity analyses

Multivariate logistic regression analyses for the association between smoking and stroke severity can be found in Table 5. After adjusting for socio-demographics, co-morbidities and stroke sub-type, smoking was not a predictor of stroke severity in ischemic strokes (OR 0.99; 95% CI: 0.90 to 1.10), TIA's (OR 1.20; 95% CI: 0.81 to 1.77) or for ICH (OR 0.7; 95% CI: 0.51 to 0.91).

Disability analyses

Multivariate logistic regression analyses for the association between smoking and disability can be found in Table 5. After adjusting for socio-demographics, co-morbidities stroke sub-type and stroke severity, smoking independently led to an increase in disability in patients with ischemic strokes (OR 1.1; 95% CI: 1.01 to 1.20) and TIA (OR 1.3; 95% 1.09 to 1.54) but not with patients who had ICH (OR 1.0; 95% CI: 0.79 to 1.21).

LOS analyses

Results of the multivariate poisson linear regression analyses for the association between smoking and LOS in hospital can be found in Table 5a. After adjusting for socio-demographics, co-morbidities, stroke severity and stroke subtype, smoking increased the length of stay in hospital for TIA by 5.7 days (95% CI: 0.30 to 0.40) and ICH by 21.4 days (95% CI: 0.005 to 0.70). Smoking was not a predictor of LOS in hospital for ischemic patients.

Mortality analyses

Results of the multivariate logistic regression analyses for the association between smoking and mortality can be found in Table 5. After adjustment of socio-demographics, stroke severity, and co-morbidities, smoking was not a significant predictor of mortality at 30 or 90 days for any stroke sub-type. However, smoking was a predictor of 1 yr. mortality in patients with TIA (OR 1.5; 95% CI: 1.10 to 2.08) and in patients with ICH (OR 1.3; 95% CI: 1.00 to 1.76).

Discussion

Our primary aim for this study was to determine the association between smoking status, stroke severity, disability, LOS in hospital and mortality. A secondary aim was to elucidate the clinical and demographic characteristics of smoking and non-smoking patients with a recent cerebrovascular event.

Univariate analyses revealed that smoking seems to offer a protective effect on stroke severity, disability, LOS in hospital, and mortality (Table 4). However, we found that when we adjusted for age and other confounders (sex, stroke severity and co-morbidities), smoking no longer had protective effects on disability, LOS in hospital or mortality. We believe that univariate analyses significantly differed from multivariate analyses due to the effect of age. There is evidence that the severity of disease is related to age. Asplund and associates found that with increasing age, the risk of stroke increases by 10% and 9% in men and women respectively (Asplund, Karvanen, Giampaoli, Jouhsilahti, Niemela 2009). This is supported by the difference in mean ages of non-smokers of 73.2 years (+/- 13.5) and smokers of 61.8 years (+/- 13.17) and how non-smokers had more severe strokes than smokers (Table 3).

Multivariate analyses of smoking and stroke severity revealed that smoking was not a predictor of stroke severity for ischemic strokes and TIA's. This was a surprising finding as several studies have demonstrated the effect of smoking on stroke severity in cerebrovascular events. Weng and associates found that smoking was associated with higher scores on NIHSS for smoking patients with small-vessel occlusions than non-smoking patients (Weng et al. 2011). Similarly, Anderson and colleagues found that smoking was associated with more severe haemorrhagic strokes (Andersen et al. 2009).

We offer two explanations to why we found a non-significant effect of smoking on ischemic and TIA patients in regards to stroke severity. We believe that there were compensating mechanisms that lead to a non-significant association between smoking and stroke severity in ischemic and TIA patients. Steiner and associates suggest that due to an enhancement of atherosclerosis by hyperlipidemia in smoking patients, a progressive interference in oxygenation and blood supply to tissues may reduce stroke severity by preparing organs for acute ischemic conditions to a point (Steiner et al. 2008). These changes may offer protective effects to ischemic conditions. According to Fujita and associates, there is an increase in tissue threshold damage and increased flow through collateral channels (Fujita, Nakae, Kihara, Hasegawa, Nohara, Ueda et al. 1999; Granger 2000). However, when full vessel occlusion occurs, these compensatory mechanisms fail and as a result of prolonged ischemic conditions may result in more severe strokes in the long-term (Steiner et al. 2008). Our results may be indicative of local metabolic and circulatory compensatory mechanisms that have contributed to a non-significant effect of smoking on stroke severity in ischemic/TIA patients. Alternatively, there was an

imbalance of co-morbidities in particular atrial fibrillation (a-fib) in non-smokers. Non-smokers had a significantly higher rate of atrial fibrillation (16.5% vs. 6.3%) compared to smokers. A-fib is considered a predictor to stroke severity (Weng et al. 2011) and with a higher rate of a known predictor in non-smoking patients may have lead to the non-significant effect of smoking on stroke severity.

Overall smoking led to an increase in the odds of severe disability in ischemic stroke patients. Under the CNS categorization, these are patients who were comatose, hemiplegic, or globally aphasic patients. Compared to other studies, there have been varied results when smoking and disability was examined. According to Strum and colleagues (2004) determinants of disability did not include current smoking and was non-significant in multivariate analyses (Strum et al. 2004). Redfern and associates (2000) found that there were more moderately disabled smokers than severely disabled smokers using the Barthel index to measure disability (Redern, McKevitt, Dundas, Rudd, Wolfe 2000). To our knowledge, we are first to document a positive association between smoking and disability in different stroke sub-types.

In LOS analyses, we found that smoking was a significant predictor of increased LOS in hospital. In particular for ICH patients, smoking resulted in a longer LOS in hospital at 21.4 days. An attenuated but significant effect of smoking in TIA patients was also observed with an increased LOS in hospital of 5.7 days. Previous studies have identified socio-demographics such as age and sex and co-morbidities such as hypertension, claudication, diabetes, ischemic heart disease or life-style behaviours such as smoking, alcohol consumption and stroke sub-type had no influence on LOS in hospital (Jorgensen, Nakayama, Raaschou, Olsen 1997). However, Chang and colleagues

found predictors of LOS in hospital included socio-demographics as stated above, the Barthel index at admission, small-vessel occlusion stroke and smoking (Chang, Tseng, Weng, Lin, Liou, Tan 2002). This previous study found that smoking reduced the LOS in hospital by 1.2 days (Chang et al. 2002). It was unknown why such variations exist between these studies in regards to the effect of smoking in LOS in hospital. Perhaps the studied population, different stroke type mechanisms and hospital management policies regarding who are discharged may explain the variations between our studies.

Our results demonstrated that smoking was associated with increased mortality at 1 yr. but not so at 30 or 90 days. The association between smoking and increased mortality is well documented in the stroke literature. The Epic Norfolk population study found a 130% (OR 2.3; 95% CI: 1.12 to 4.57) increased in risk of mortality in current smokers after 7.5 years. Similarly, the Renfrew/Paisley study found that after 20 yrs. stroke mortality in men and female smokers increased by 50% (OR1.5; 95% CI: 1.08 to 2.00) and 64% (OR 1.64; 95% CI: 1.10 to 2.45) respectively (Redfern et al. 2000). Our data supported the long-term detrimental effect of smoking and its association with increased risk of mortality in smokers with cerebrovascular disease.

Our results revealed significant differences between smoking and non-smoking patients with a recent cerebrovascular event in all clinical and demographic characteristics except for hyperlipdemia. Smokers were younger, suffered more ischemic strokes, were more depressed and consumed more alcohol than their non-smoking counterparts. These characteristics were in line with previous investigations (Bang, Park, Lee, Kim, Chung, Lee 2007; Ballard, Kreiter, Claasen, Kowalski, Connolly, Mayer 2003; Longstreth, Nelson, Koepsell, van Belle 2002; Nidhinandana, Sithinamsuwan,

Chinvarun, Wongmek, Supakasem, Suwantamee, 2010; Ovbiagele, Weir, Saver, Muir, Lees 2006). Although non-smokers exhibited higher rates of hypertension, smokers tended to present with a cerebrovascular event at an earlier age and less severe strokes. On average, smoking patients presented with a cerebrovascular event at the age of 61.8 (+/- 13.2) compared to non-smokers at the age of 73.2 (+/- 13.5). This may have clinical implications in secondary stroke prevention. Smokers are at risk for a cerebrovascular event at a younger age than non-smokers. We suggest further study to ascertain the cause of this earlier presentation in smokers but speculate the role of multiple mechanisms such as hypercoagulability and progression of atherosclerosis due to smoking (Baldassarre et al. 2009; Blann et al. 1998; Hankey 1999; Howard et al. 1998; Stoll et al. 2008).

In light of these results we propose several limitations to our study. Our data was obtained from a registry from similar hospital settings with homogenous operating procedures. Therefore whether these results are generalizable to other hospital settings with different operating procedures, different time periods and other stroke sub-types needs to be considered. Furthermore, self-report was relied upon for patient's smoking status and should be interpreted with caution. Whilst there are recognized biochemical-validation techniques, self-report for use in observational studies such as ours have been found to be valid (Ives et al. 2008).

Conclusion

Our study found that there was a significant prognostic influence of smoking in several stroke sub-types on disability, LOS in hospital and mortality. Smoking was not a significant predictor of stroke severity except for ICH in our cohort. Furthermore, patients who smoke were more likely to be disabled and have a longer stay in hospital

regardless of stroke sub-type. Finally, smoking was not a significant predictor of short-term mortality but was a significant predictor of long-term mortality except in ischemic stroke patients. Significant differences in clinical and demographics were found between smokers and non-smokers with cerebrovascular disease. On average, smokers had an earlier initial stroke presentation in all three-stroke sub-types (stroke/TIA/ICH).

The significant age difference in smokers and non-smokers with cerebrovascular disease emphasizes the need for intensive public health and secondary prevention measures aimed at preventing smoking initiation and support for smoking cessation.

Phase 3: Theoretical model and rationale

The socio-ecological model proposed by and associates (2004) explains factors that influence different groups to use or not use tobacco (Sorensen, Barbeau, Hunt, Emmons, Karen 2004) (Figure 5). These factors include population characteristics, socio-economic status (SES), individual, interpersonal, community and organizational factors (Sorensen et al. 2004). The purpose of this phase of the research program was to examine multi-level correlates of smoking cessation in smokers with symptoms of cerebrovascular disease.

Population and socio-economic level

At this level of the socio-ecological model, factors that would influence one to smoke or quit smoking include population characteristics such as age, gender, and SES characteristics such as education and income. Butler-Jones (2008; 2011) described an inverse relationship between population characteristics and socio-economic status with the proportion of daily cigarettes smoked (Butler-Jones 2008; 2011). For example, those in the upper levels of society, in particular those with higher education and higher annual incomes, on average smoke less compared to those at lower levels. He reported that though the overall smoking prevalence has declined, sub-populations such as young male adults from age 20 to 29 years old continue to smoke at rates that are significantly higher than the population as a whole (24% vs. 17%).

A recent review by Hiscock and associates (2011) suggested that the smoking prevalence in lower SES groups might be a result of the clustering of disadvantages (Hiscock, Bauld, Amos, Fidler, Munafo 2011). These disadvantages include: a reduced social support for quitting, low motivation to quit, increased addiction to tobacco,

increased likelihood of not completing courses of pharmacotherapy or behavioural support sessions, psychological differences such as lack of self-efficacy, and tobacco industry marketing. As a result, quit attempts in this population are significantly less likely to be successful.

Individual level

At the individual level, the effect of addiction would influence the ability to quit smoking. The addictive properties of nicotine are well documented in the literature. Tobacco smoke and in particular nicotine is thought to trigger the mesocorticolimbic dopamine reward system (Domino 1997; Henningfield 1995; Henningfield and Fant 1999; Ortells and Areis 2010). This system is an integral part of the brain reward system resulting in a pleasurable experience during smoking (Domino 1997; Henningfield 1995; Henningfield and Fant 1999; Ortells and Areis 2010). Thus, addictive behaviour is developed through the need to repeat the pleasurable stimuli and avert withdrawal symptoms as nicotine concentration levels decrease (Domino 1997; Henningfield 1995; Henningfield and Fant 1999; Ortells and Areis 2010; Ortells and Barrantess 2010).

An excellent measurement tool for smoking addiction is the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, Fagerström 1991). FTND is a non-invasive self-report tool that conceptualizes dependence through physiological and behavioural symptoms (Heatherton et al. 1991). It queries frequency of cigarette use, number of cigarettes per day and difficulty in abstaining in certain circumstances (Heatherton et al. 1991). A score of 8-10 is considered to be high dependence and lower scores of 5 and 0-2 reflect moderate and low dependence to nicotine, respectively (Heatherton et al. 1991). Other important individual factors may

include co-morbidities such as depression. Among adults, the rate of major depressive episodes is highest in nicotine-dependent individuals, lower in nondependent current smokers, and lowest in those who quit or never started smoking (Bak et al. 2002; Quattrocki, Baird, Yurgelun-Todd 2000). Furthermore, there is evidence demonstrating that smoking cessation may lead to a new depressive episode in those who suffer from frequent depressive episodes (Keuthen, Niaura, Borrelli, Godstein, Depue, Murphy et al. 2000). Adult tobacco use also increases risk for the later development of anxiety disorders, which may be associated with an increased severity of withdrawal symptoms during smoking cessation therapy (Keuthen et al. 2000). Other co-morbidities such as diabetes, hypertension, cognitive function and alcohol consumption should also be considered, as they are associated with smoking and cerebrovascular disease (Keuthen et al. 2000).

Interpersonal level

Interpersonal factors may include social ties as they relate to exposure to environmental tobacco smoke (ETS) at home and in a vehicle. A smoker's social network often includes other smokers that provide little opportunity for behavioral change (Sorensen et al. 2004). Consequently, smokers who live with other smokers (i.e. a spouse) are less likely to be successful in smoking cessation than those who do not (Bader, Travis and Skinner 2006; Edjoc 2011; Shields 2007). A similar observation can be found in smokers who share a vehicle with other smokers (Evans and Chen 2005). Smokers who share the same social network, a home or vehicle with other smokers, are less likely to quit smoking (Bader et al. 2006; Edjoc 2011; Evans and Chen 2005; Shields 2007).

Another interpersonal factor that may be relevant to successful quitting is social support from health care professionals. It has been found that the lack of access to a family physician may also indicate a lack of social support (Heaney and Israel 2008). Health care settings such as a family physician's office provide an excellent environment where smoking cessation services could be implemented. For example, a review paper by Zwar and Richmond reported that general practitioners (GP) were contributors to improving the efficacy of smoking cessation interventions due to their constant contact with their patients (Zwar and Richmond 2006). It is clear that those without general practitioners may not have access to smoking cessation interventions that may otherwise be available to those who regularly see their GP.

Community level

At this level, the community correlate was comprised of reported exposure to public smoking restrictions such as in bars and restaurants. As of May 31st, 2006 under the Smoke Free Ontario Act (SFOA), it was prohibited to smoke in all enclosed workplaces and enclosed public places in Ontario in order to protect the health of all Ontarians (Smoker Free Ontario Act (SFOA), 2009). This act amended the 1994 Tobacco Control Act and demonstrated a clear emphasis on smoke-free work and public places province-wide (White 2006). The act also added restrictions on smoking promotions and an increase in the minimum age of purchase for youth (White 2006). Smoke-free public places include casinos, bingo halls, bowling and billiard establishments, restaurants and bars (SFOA, 2009a). Under this provision, there were also smoking restrictions on patios having a roof and in smoking shelters with particular characteristics (SFOA, 2009b) and in designated smoking rooms (SFOA, 2009a). There

were similar legislative smoking restrictions in public and workplaces implemented by other provinces in Canada. The overall effect of these interventions was a reduction in smoking prevalence Canada-wide.

Shields (2007) found that in the past decade, smokers working at places that have regulated smoking bans are more likely to quit within the next two years compared to those working in non-regulated places. Bauer and associates found a similar result (Bauer, Hyland, Li, Steger, Cummings 2005). These authors found that smoke-free policies tended to impact tobacco use. More specifically, they found that in workplaces that implemented smoke free restrictions from 1993 to 2001, smokers were twice as likely to have quit smoking by 2011 compared to workplaces that did not. Furthermore, restrictive smoking policies also impacted on the smoking behaviours of continued smokers by decreasing their average cigarette use by 2.57 cigarettes per day. The authors concluded that workplace smoking restrictions have beneficial effects for smokers and non-smokers alike. Policies that restrict smoking in workplaces help protect non-smokers from ETS exposure, decrease the amount of daily cigarette consumption, and aid in smoking cessation.

Restrictions in public and work places have been found to reduce a multitude of smoking-related diseases such as asthma, chronic obstructive pulmonary disease (Bader et al. 2006; CTUMS 2006; Edjoc 2011; Evans and Chen 2005; Shields 2007) as well as reducing atherosclerosis accumulation leading to coronary heart disease and stroke (Baldassarre et al. 2009; Blann et al. 1998; Hankey 1999; Howard et al. 1998; Stoll et al. 2008).

For example, in a longitudinal study by Cronin and associates, they found that a national smoking ban significantly reduced hospital admissions for acute coronary syndromes (Cronin, Kearney, Kearney, Sullivan, Perry 2012). They found that there was a significant 12% reduction in ACS admissions (177.9 vs. 205.9/100,000; 95% CI: 164.0 to 185.1, P = 0.002) upon the implementation of a national smoking ban in Ireland (Cronin et al. 2012).

Organization level

An important organizational factor may include the use of smoking cessation pharmacotherapies. There is strong clinical evidence that pharmacotherapy in combination with counselling can double or even triple the likelihood of long-term smoking abstinence for heavy smokers that consume > 10 cigarettes per day (Cahill et al. 2007; Eisenberg et al. 2008; Stead et al. 2008). They conclude that providing pharmacotherapy and counselling may further increase cessation rates to smokers to reduce withdrawal symptoms during the cessation attempt.

Rationale

These converging lines of evidence highlight the role of possible multi-level correlates of smoking cessation within the population. These correlates were examined in the stroke population, as these have not been previously reported. These levels include: population characteristics, SES, individual, interpersonal, community and organizational correlates of smoking cessation. Population and socio-economic level correlates included: age, gender, and mean annual income and education level. At the individual level, correlates included: co-morbidities and Fagerström score. At the interpersonal level, correlates included: home and vehicle smoking restrictions and access to a GP. At the

community level correlates included: exposure to workplace and public smoking restrictions. Finally at the organizational level, correlates include the use of smoking cessation medications such as bupropion or NRT gum or patch and physician counselling. Significant correlates of smoking cessation in this population at multiple levels have not been previously addressed. If significant correlates of smoking cessation in this vulnerable population of smokers can be identified, they can be used in the development of future interventions designed to decrease the overall health burden of smoking on health care. The focus of this phase of the research program was to identify significant correlates of smoking cessation from which an intervention can be created for this high-risk group of smokers with cerebrovascular disease.

Correlates of smoking cessation in smokers with cerebrovascular disease

Rojiemiahd K. Edjoc, MSc
Robert D. Reid, PhD., MBA
Mukul Sharma, MD MSc FRCPC
Louise Balfour, PhD

Manuscript three

Abstract

Purpose: Smoking continues to be a leading cause of preventable morbidity and premature mortality. The objective of the present study was to identify multi-level correlates of smoking cessation in smokers with cerebrovascular disease.

Methods: We used data from the 2007-2008 Canadian Community Health Survey (CCHS). Smoking status (quit smoking completely vs. smoker vs. non-smoker) was described by population characteristics (sex and age), socio-economic status (education and income), individual correlates (Fagerström Test of Nicotine Dependence (FTND), alcohol drinking, depression, diabetes mellitus (DM), hypertension), interpersonal correlates (household and vehicle smoking restrictions, access to a general practitioner), community correlates (exposure to public and workplace smoking restrictions) and organizational correlates (use of nicotine replacement therapy such as the patch and gum and other pharmacotherapy such as bupropion). The study sample was selected from those respondents of the CCHS that reported they suffered from stroke symptoms. Logistic regression was used to describe the association between quitting smoking and stroke while controlling for multi-level correlates of smoking cessation. Proportions were weighted to reflect the Canadian population.

Results: There were 383904 respondents who reported to suffer from stroke. From this sample, 211549 respondents (55.1%) reported they were non-smokers and 62960 (16.4%) respondents reported they were smokers. There were 109395 (28.5%) individuals who indicated they had quit smoking. Reported quitters were largely male (62.9%), older (70-80+ yrs: 46.1%) and had mostly post-secondary education (55.3%). Individuals who quit

compared to smokers drank less (> than 2 drinks per day; 45.9% vs. 49.1%; $p < 0.0001$) and reported fewer cases of depressive episodes (35.6% vs. 41.7%; $p < 0.0001$). At the population characteristics and socio-economic level, female sex (OR 0.4; 95% CI: 0.41 to 0.42) reduced the likelihood of quitting. The age groups 55-69 (OR 1.1; 95% CI: 1.10 to 1.19) and 70-80 (OR 1.6; 95% CI: 1.61 to 1.67) were positively related to smoking cessation. At the individual level, co-morbidities such as alcohol consumption (OR 0.70; 95% CI: 0.69 to 0.71) and depression (OR 0.89; 95% CI: 0.88 to 0.91) reduced the likelihood of quitting. At the interpersonal level, household (OR 1.1; 95% CI: 1.05 to 1.08) and vehicle (OR 2.9; 95% CI: 2.79 to 2.93) smoking restrictions significantly predicted smoking cessation. However at the community level, exposure to workplace and public place smoking restrictions did not significantly predict smoking cessation. The use of pharmacotherapy such as bupropion significantly predicted smoking cessation (OR 15.4; 95% of CI: 13.9 to 17.0) while the use of NRT patch did not. Counselling advice from a physician was also a correlate of smoking cessation (OR 3.7; 95% CI: 3.37 to 4.03).

Conclusions: Our results reveal that there are multi-level correlates of smoking cessation in smokers with reported stroke symptoms. Future interventions should be tailored with these correlates in mind to increase the likelihood of cessation.

Introduction

Smoking is an independent risk factor for incident and recurring stroke (Beevers and Shinton 1990; Kawachi et al. 1993; Wolf et al. 1989). It has been found that smoking cessation can reduce the relative risk of stroke and TIA by 50% (Wannamethee, Shaper, Whincup, Walker, 1995) and stroke related hospitalizations (Naidoo, Stevens, McPherson 2000). Despite the supporting evidence regarding the benefits of smoking cessation for smokers with cerebrovascular disease, there is evidence that 89% of these smokers were still smoking 12 months after their event (Mouradian, Majumdar, Senthilselvan, Khan, Shuaib 2002).

Stroke prevention guidelines recommend that healthcare providers strongly advise every smoker who is at high risk for a stroke or TIA to quit, and provide specific assistance with quitting, including counselling and pharmacotherapy (Furie, Kasner, Adams et al. 2011).

There are very few published smoking cessation intervention (SCI) studies in stroke and TIA patients. A recent systematic review found a non-significant effect of SCI's on quitting in stroke and TIA patients (Edjoc, Reid, Sharma in preparation). The authors found that with the available studies, there was a sub-optimal use of evidence - based approaches to smoking cessation comprised of counselling, pharmacotherapy and follow-up (Edjoc, Reid, Sharma 2012).

More interventions need to be developed by identifying significant correlates of smoking cessation among these high-risk smokers. The socio-ecological model proposed by Sorensen and associates (2004) explicates factors that influence different groups to use or not use tobacco. These factors include population characteristics and

SES, individual, interpersonal, community and organizational factors. Based on this socio-ecological model, the present study elucidated multi-level correlates of smoking cessation using data from the Canadian Community Health Survey.

Methods

Data from the 2007-2008 Canadian Community Health Survey (CCHS) were used for the present study. The CCHS is a cross-sectional survey that collects information related to the factors that contribute to health, social and economic determinants of Canadians (Statistics Canada 2008). The CCHS utilizes a complex sampling strategy with stratification and multiple stages of selection yielding a sample that is representative of 98% of the Canadian population (Statistics Canada 2008).

Only individuals who reported the effects of stroke were included in the present analysis. From this sample, smoking status (quit vs. not quit) was selected as the dependent variable. Important correlates were grouped by population characteristics and socio-economic status, individual, interpersonal, community and organizational level. Population characteristics included: sex and age. Socio-economic status included: income and education. Individual level correlates included: co-morbidities such as depression, diabetes mellitus, hypertension, alcohol consumption, and nicotine addiction (as measured by the Fagerström Test of Nicotine Dependence). Interpersonal level correlates included: having household and vehicle smoking restrictions and access to a GP. Community level correlates included: exposure to public and workplace smoking restrictions. Organizational level correlates were defined as the use of smoking cessation resources such as pharmacotherapy (nicotine replacement therapy and bupropion) and counselling support provided by a physician or referral to a smoking cessation group.

Ideally, varenicline would be included in the list of pharmacotherapy. Unfortunately, at the time of this survey, varenicline was not yet approved for use in Canada and was not collected by the CCHS. Age was re-coded into five categories (ages 12-19; 20-34; 35-54; 55-69 and 70-80+). Due to the complex survey design of the CCHS, adjusted weight was calculated for each respondent taking into account national average design effects and the relative sampling weights.

Statistical Analysis

All statistical analyses were performed using Statistical Analysis Software (SAS). Cross-tabulations between the dependent variable (reported stroke) and smoking status (smoking, former smoking and non-smoking) were performed while controlling for correlates of interest. A chi-square test of significance was used to determine significant differences between cross-tabulated proportions. Significance was reported at 95% confidence or having a value of $P < 0.05$.

A logistic regression model was ‘fitted’ using the dependent variable of reported smoking cessation while controlling for each correlate level (population characteristics, socio-economic position, individual, interpersonal, community and organizational level). Significant correlates of smoking cessation were expressed by odds ratio (OR) point estimates at a 95% confidence level (CI). The method of model building for logistic regression analyses was forward-stepwise selection. The Wald statistic was used for variable selection. Independent variables were identified as significant correlates if the p-value was less than 0.05 ($p < 0.05$).

Results

A summary of the characteristics of the study cohort can be found in Table 6. The following table is divided by smoking status (i.e. Non-smoker, Smoking and Quit smoking). The overall weighted sample was 383904 individuals who reported to suffer from stroke symptoms. From this sample 211549 individuals (55.1%) reported to be non-smokers and 62960 (16.4%) individuals reported to be smokers. There were 109395 (28.5%) individuals who reported to have quit smoking

There were more males who reported they had quit smoking than females (62.9% vs. 37.1%; $p < 0.0001$). In the smoking cohort, more males were continued smokers than females (56.4% vs. 43.6%; $p < 0.0001$). There were more males than females (50.7% vs. 49.3%; $p < 0.0001$) in the non-smoking cohort. Individuals who quit smoking as well as non-smoking individuals were older than smoking individuals. In general, all cohorts had post-secondary education and were earning an annual income of \$ 20 000 - 39 000.

Individuals who quit smoking reported to have higher proportions of household (74% vs. 35.5%; $p < 0.0001$) and vehicle smoking restrictions (93.7% vs. 0.0%; $p < 0.0001$) compared to smoking individuals. Exposure to public smoking restrictions (93.3 % vs. 0.6%) was higher in smokers compared to quitters.

Respondents who quit smoking compared to current smokers reported they used NRT (0.1% vs. 0.0%) more frequently as well as bupropion (0.4% vs. 0.0%). Smokers reported more physician counseling (4.5% vs. 0.5%) than quitters. Smoking individuals reported higher proportions of alcohol consumption (< 2 drinks per day; 49.1% vs. 7.9%), and more depression (41.7% vs. 35.6%) and diabetes (20.7% vs. 89%) than respondents who quit smoking. Similar trends were found when we compared smoking individuals

and non-smokers for alcohol consumption (< 2 drinks per day; 49.1% vs.39.1%), depression (41.7% vs. 32.8%) and diabetes (20.7% vs. 8.6%).

Logistic regression odds ratios and 95% CIs of significant correlates of smoking cessation can be found in Table 7 and 7a. At the population characteristic and socio-economic level, female sex (OR 0.4; 95% CI: 0.41 to 0.42) reduced the likelihood of quitting. Age 55-69 (OR 1.1; 95% CI: 1.10 to 1.19) and age 70-80 (OR 1.6; 95% CI: 1.61 to 1.67) were significant correlates of smoking cessation. At the individual level, co-morbidities such as alcohol consumption (OR 0.70; 95% CI: 0.69 to 0.71) and depression (OR 0.89; 95% CI: 0.88 to 0.91) reduced the likelihood of quitting. At the interpersonal level, household (OR 1.1; 95% CI: 1.05 to 1.08) and vehicle (OR 2.9; 95% CI: 2.79 to 2.93) smoking restrictions significantly predicted smoking cessation. However at the community level, exposure to workplace and public place smoking restrictions did not significantly predict smoking cessation. The use of pharmacotherapy such as bupropion significantly predicted smoking cessation (OR 15.4; 95% of CI: 13.9 to 17.0) while the use of NRT did not. Counselling advice from a physician was also a correlate of smoking cessation (OR 3.7; 95% CI: 3.37 to 4.03).

Discussion

The aim of this study was to identify the correlates of smoking cessation in smokers with reported stroke symptoms at multi-levels. Income and older age were predictive of smoking cessation while education at all levels predicted smoking cessation in this cohort. These results are in line with previous investigations of gender effects (Butler-Jones 2008; 2011; Reynoso, Susabda, Cepeda-Benito 2005), older age (Butler-Jones 2008; 2011) and level of income (Butler-Jones 2008; 2011) vis a vis smoking and

cessation. Koning and associates (2010) found that each additional year of education reduced the risk of continued smoking (Koning, Webbink and Martin 2010). Their data suggested that people with higher education may be able to better understand the consequences of long-term smoking and may have more resources available for them to quit smoking (Koning et al. 2010).

Our findings suggest that co-morbid conditions at the individual level such as alcohol consumption and depression significantly decreased the likelihood of smoking cessation. These findings are supported by evidence suggesting that cerebrovascular patients experience higher rates of co-morbidity particularly depression (Almeida, Alfonso, Flicker, Hankey, Norman, 2011; Luijendijk, Hofman, Breteler, Tiemeier 2011). Compared to cardiac patients, patients with a recent stroke suffered a three to five-fold increased risk of depressive disorders (Almeida et al. 2011; Luijendijk et al. 2011) as well as higher proportions of alcohol consumption (Li 2010) and hypertension (Jatoi, Jerrard-Dunne, Feely, Mahmud, 2007).

These findings may have clinical implications particularly for this population, as co-morbid conditions such as depression and increased alcohol consumption are significantly more common in patients who smoke. Considering their association with increased smoking behaviour, co-morbidities may be hindering the success of smoking cessation. The hindering effect of co-morbidity on smoking cessation is especially problematic as smoking increases blood coagulability, platelet aggregation, thrombus formation and endothelial damage (Benowitz 2009), increasing the chance of a stroke two-fold (Burn 2003) and stroke recurrence by 66% (Burn 1994). It is imperative that smoking cessation be incorporated in secondary prevention practice while taking these

significant co-morbidities into account. Depression and excessive alcohol consumption might impede cessation in people with cerebrovascular disease. However due to the limitation of cross-sectional studies, we do not know if these co-morbidities existed before or after the reported stroke. Further study regarding the effects of these co-morbidities on cessation using other study designs might be warranted.

Population based interventions such as household, workplace, vehicle and public smoking restrictions have all been found to predict smoking abstinence (Bauer et al. 2005; Bader et al. 2006; Edjoc 2011; Evans and Chen 2005; Shields 2007). They have also been found to reduce cigarette consumption, and initiation and increase smoking cessation rates (Bauer et al. 2005; Bader et al. 2006; Edjoc 2011; Evans and Chen 2005; Shields 2007). These authors suggest that population based interventions are anti-tobacco socialization tools that may promote the internalisation of behavioural norms against the initiation or continuation of smoking. Our results are partially in line with this evidence. We found that household and vehicle smoking restrictions predicted smoking cessation but not so with workplace or public smoking restrictions. It is not known to why workplace and public smoking restrictions did not predict smoking cessation especially since their implementation under the Smoke Free Ontario Act (SFOA 2003) in Ontario and similar legislations across Canada. Since their implementation, smoking prevalence in Canada has been dramatically decreased. Perhaps the insignificant effect of public and workplace smoking restrictions may be explained in the decrease of funding in the SFOA in 2007-2008 of 60 million, down 2.5 million from the year before of 62.5 million in 2006-2007 (OTRU 2009; OTRU 2011). Similar reductions in tobacco control funding can be observed in other provinces (OTRU 2009; OTRU 2011). There is a documented

association between population interventions effectiveness and sustained funding (Pierce, Gilpin, Emery, White, Rosbrook, Berry 1998a).

A similar situation was observed with the California Model in the state of California. The California Model is similar to the SFOA and is a population intervention that used workplace and public place smoking restrictions to de-normalize tobacco use (Pierce et al. 1998). Pierce and associates (1998a) found that the initial effect of the California Model to decrease smoking prevalence in the state dissipated as their funding was reduced.

In light of this conundrum, there is evidence that suggests that household and vehicle-smoking restrictions are more effective because they are less regulated (Pierce, Evans, and Farkas 1998b; Shelley Yerneni, Hung, Das, Fahs 2007). These authors suggest that smoking restrictions such as at home or in a vehicle are effective because those who implement them do so by choice and not through forced legislation (Pierce et al. 1998; Shelley et al. 2007) thereby increasing the odds of smoking cessation.

At the organizational level, we found that the use of pharmacotherapy such as bupropion and physician counselling increased the odds of smoking cessation but NRT use did not. According to Fiore and associates, pharmacotherapy along with counselling and follow-up increases the odds of smoking cessation (Fiore et al. 2008). NRT and bupropion have each been found to be more efficacious than placebo for increasing the odds of smoking cessation (Eisenberg et al. 2008).

The lack of effect of NRT may be indicative of the well-documented practice gap in health care in regards to smoking cessation. Young and Ward (2001) found that only 32% of physicians provided written materials for their patients and only 28% of

physicians set a “quit date” with their patients. Likewise Shaohua and colleagues (2003) found that many family physicians feel lack of time was their biggest barrier in terms of implementing smoking cessation practices. Their study found that less than half were willing or able to assist their patients to quit with the use of counselling, pharmacotherapy or arrange a follow-up visit to reinforce the benefits of smoking cessation (Shaohua et al. 2003). This is consistent with the stroke population as documented by Mouradian and associates (2002). Perhaps another explanation may be the lack of information regarding the effectiveness of smoking cessation medications and similar interventions in stroke and TIA patients. Furthermore, physicians may be reluctant to prescribe NRT’s due to their availability over the counter. Further research is required to determine if the latter explanations are supported by evidence.

Cross-sectional studies such as the CCHS are useful for initial exploratory studies. They are far reaching and reflect “a snapshot” of the population. However there are limitations to our study and they will be explored here. Since both exposure and outcome were measured at the same time, one cannot be certain which is the exposure or the outcome. In other words, the rules for contributory cause cannot be fulfilled. Another limitation is the mode of collection of the data. Social desirability and recall bias for example could play an important role and a source of biases within this study (Holbrook, Green and Krosnick 2003). For example, since smoking status, the presence of stroke symptoms and co-morbidities such as depression were self-reported, special care should be taken when interpreting our results. An example of social desirability effect would be respondents not accurately reporting their smoking status. Since smoking would be an undesirable image for some depending on age, gender or socio-economic status, data

obtained might not be representative of the real picture found in the population. Ideally all smoking related measures should be validated bio-chemically with breath samples measuring carbon monoxide levels or cotinine levels measuring the amount of nicotine in the blood. Furthermore, without an expert assessment from a health care professional of stroke symptoms or depression would also limit the generalizability of the results.

Conclusion

We found significant correlates of smoking cessation at multiple levels in smokers with reported stroke symptoms. Age and education level were significant correlates of smoking cessation at the population and socio-economic level. At the individual level, depression and alcohol consumption reduced the likelihood of cessation while at the interpersonal level, household and vehicle smoking restrictions and access to a GP were found to be significant correlates of smoking cessation. Public and workplace smoking restrictions were not correlates of smoking cessation at the community level. Finally, at the organization level the use of bupropion along with physician counselling predicted smoking cessation.

General Discussion

This dissertation outlines the results of a three-phase research program that examined the association between smoking and cerebrovascular disease. According to the smoking literature, patients with cerebrovascular disease have lower rates of success in regards to cessation (Ives et al. 2008; Mouradian et al. 2002). For example, Ives and associates found that 77% of patients, who were smokers at 3 months, were also smokers at the end of their 3 year follow-up (Ives et al. 2008). Only 17% of their patients quit smoking immediately after their stroke and stayed abstinent at all subsequent follow-ups (Ives et al. 2008). Similarly, a study by Mouradian and colleagues (2002) found that as high as 89% of ischemic and TIA patients who were identified as smokers at the time of their event continued to be smokers 12 months afterwards (Mouradian et al. 2002). Stemming from this literature, the question as to why smoking cessation in this group of smokers continues to be a challenge needed to be addressed.

The first phase of the research program included two systematic reviews that explored the effectiveness of smoking cessation interventions in increasing cessation rates and the effects of smoking cessation on stroke recurrence. The first review found a non-significant effect of SCIs on quitting (RR 1.19; 95% CI: 0.81 to 1.73; $p=0.38$, $I^2=0.00\%$). Furthermore, results of the second review found a similar non-significant effect of quitting on stroke recurrence (RR 0.5; 95% CI: 0.22 to 1.34; $p=0.12$, $I^2=67.2\%$).

Based on these results we conclude that additional intervention trials, using evidence-based cessation interventions are required. Much larger trials are needed to validate the promising trend of smoking cessation on stroke recurrence. To build upon what we found in the first-phase in possibly explaining why smoking cessation

interventions are not effective in this group of smokers, the question of whether they were differences in the clinical and demographic characteristics of smoking and non-patients with cerebrovascular was explored.

In the second phase of the research program, we found that there were significant differences between smokers and non-smokers with cerebrovascular disease in regards to clinical and demographic characteristics. Smoking status also had a prognostic effect on several important outcomes such as disability, LOS in hospital and mortality.

The results of the previous phase led us to ask another pertinent question: “If smokers with cerebrovascular disease are significantly different from non-smokers, could there be specific correlates of smoking cessation unique to this population?” This question became the aim of the final research phase.

The third-phase of the research program found significant correlates of smoking cessation in Canadians reporting symptoms of a stroke on the Canadian Community Health Survey.

Contributions to Understanding of Population Health

Population health is defined as the “health outcomes of a group and the distributions of such outcomes within the group” (Kindig and Stoddart 2003). It encompasses not only health outcomes but also the patterns of health determinants and policies and interventions that link them together (Kindig and Stoddart 2003). We argue however that population health also aims to improve the health of the entire population or sub-population to reduce inequities among these groups. Based on these definitions, the results of the three-phase research provided further understanding of Population Health for this group of smokers with cerebrovascular disease in the following manner.

First, intervention research to reduce inequities between select groups is considered an important part of population health (Kindig and Stoddart 2003). Results of the first phase of the research program found that effective interventions have not been adequately evaluated to increase cessation rates for this population. The use of pharmacotherapy, along with counselling and follow-up that are considered evidence-based for smoking cessation are not being used by most reported intervention studies. The health of this population may be improved with the use of evidence-based smoking cessation approaches. Quitting may reduce the effects of smoking on atherosclerotic accumulation and progression (Baldassarre et al. 2009; Stoll et al. 2008; Blann et al. 1998; Hankey 1999; Howard et al. 1998).

Second, to improve the health of a particular group or groups, differences must first be identified. We found that smoking and non-smoking patients with cerebrovascular disease were significantly different from each other. These differences in clinical and demographic characteristics between these two populations provide a challenge to health care professionals especially due to the lack of implementation of evidence based smoking cessation approaches.

Third, population health also refers to the multitude of factors that affect health (Kindig and Stoddart 2003). Here we take this idea and apply it to this population by exploring the multiple levels of factors associated with smoking cessation. By using a socio-ecological model, we were able to ascertain that success in cessation is affected by multiple factors at multiple levels ranging from population characteristics to the organizational level.

The results of the three-phase research program have contributed to the field of Population Health as follows: 1) the need for intervention research that utilize evidence-based approaches to smoking cessation has been identified; 2) significant differences in clinical and demographic characteristics between smokers and non-smokers have been determined; and 3) multiple level correlates of smoking cessation have been highlighted for future interventions to address.

Theories used in the research program

The theories of allostatic load (McEwan and Seeman 1993) and the socio-ecological model by Sorensen et al. (2004) aided in directing the second and third phases of the research program. Each model provided guidance regarding possible questions to address and variables to explore.

In regard to the AL model, it provided a possible mechanism by which smoking would lead to increased stroke severity in patients with cerebrovascular disease. We hypothesized that since smoking is a stressor to the body, stress would accumulated through biological changes in the cardiovascular system such as atherosclerotic progression (Baldsarre et al. 2009; Blann et al. 1998; Hankey 1999; Howard et al. 1998; Stoll et al. 2008;) and weakening of structural blood vessels (Quresh et al. 2008) smoking would lead to increased stroke severity. We found that this was not case with our cohort. Based on the ALM, smoking should have increased stroke severity. However, our results do not support this assumption. Further research is required to determine if the ALM can be used as a theoretical basis to explain the effects of smoking on stroke severity.

Socio-ecological models (SEM) provide insight regarding multiple factors and context by which they are interrelated to one another (Oetzel, Ting-Toomey, Rinderle

2006). Specifically, the SEM by Sorensen and associates (2004) provided a framework to study the multiple factors associated with smoking cessation in smokers with cerebrovascular disease. These authors outlined that factors such as population characteristics and socio-economic status, individual, interpersonal, community and organizational were key factors regarding why an individual would smoke or not. We found that smoking cessation was associated with numerous factors at multiple levels.

Clinical Implications and future research

Our results have clinical implications for this population. First, evidence-based smoking cessation approaches need to be implemented and adequately tested in this population. Our systematic reviews found only a few published intervention studies that used recommended approaches such as pharmacotherapy, counselling and follow-up. It is not known whether these approaches are effective in increasing cessation rates in this population and further research is required. Large-scale studies are required to confirm the impact of quitting on stroke recurrences.

Second, patients with cerebrovascular disease often have significant co-morbidities such as depression and alcohol consumption that may hinder their success with respect to smoking cessation. Health care professionals need to be cognizant that an interplay of these co-morbidities may complicate the cessation attempt. Further research is required to determine if co-morbidities should be addressed concurrently during smoking cessation interventions.

Third, interventions need to address the correlates of smoking cessation found in the third phase of the research program. Based on our results, interventions should include pharmacotherapy, counselling, follow-up (access to a GP) and interpersonal

interventions (such as household and vehicle smoking restrictions). Addressing these correlates of smoking cessation may increase the likelihood of quitting in this population.

Gaps filled in the literature

This is the first study to examine the effectiveness of SCIs in this population and the effect of smoking cessation on stroke recurrence. We found that there were few adequately powered intervention studies of proven strategies that help patients quit smoking. Studies that did implement such proven strategies were underpowered and require larger sample sizes to observe an effect of their intervention. We found little evidence on the effect smoking cessation on stroke recurrence and require further research.

We found smokers are clinically and demographically different from those who do not smoke in this population. The significant differences in clinical and demographic characteristics may play a role in why smokers in the stroke population are unsuccessful with their quit attempts. We also found that smoking status has a prognostic effect on disability, length of stay in hospital and mortality but may vary by stroke sub-type.

Finally, there are multi-level correlates of smoking cessation that need to be addressed in future interventions. Further research is required to determine if these correlates can be used to increase cessation rates in smoking cessation interventions.

Conclusion

The aim of this three-phase research program was to better understand the complex association between smoking and cerebrovascular disease. We addressed three important question that filled gaps in the literature. We found that the effectiveness of SCIs in this population has been not established. Furthermore, smoking has a prognostic

influence on disability, LOS in hospital and long-term mortality in various stroke subtypes. Finally further research is required to determine if significant multi-level correlates of smoking cessation can be utilized for a comprehensive intervention.

References

- Adams, H.P. Jr, Davis, P.H., Leira, E.C., Chang, K.C., Bendixen, B.H., Clarke, W.R., Woolson, R.F., Hansen, M.D. (1999). Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 13;53(1):126-31.
- Almeida, O.P., Alfonso, H., Flicker, L., Hankey, G.J., Norman, P.E. (2011). Cardiovascular Disease, Depression and Mortality: The Health In Men Study. *American Journal of Geriatric Psychiatry*. [Epub ahead of print].
- Andersen, K.K., Olsen, T.S., Dehlendorff, C., kammersgaard, L.P. (2009). Hemorrhagic and Ischemic stroke compared: Stroke severity, mortality and risk factors. *Stroke*. 40:2068-2072.
- Asplund, K., Karvanen, J., Giampaoli, S., Jousilahti, P., Niemelä, M., Broda, G., Cesana, G., Dallongeville, J., Ducimetriere, P., Evans, A., Ferrières, J., Haas, B., Jorgensen, T., Tamosiunas, A., Vanuzzo, D., Wiklund, P.G., Yarnell, J., Kuulasmaa, K., Kulathinal, S; MORGAM Project. (2009). Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. *Stroke*. 40 (7): 2319-26.
- Bader, P., Travis, H., and Skinner, H.A. (2006). Smoking cessation among neglected populations: employed and unemployed young adults (18–24 yrs). *American Journal of Public Health*. 97(8): 1434-1444.
- Bak, S., Sindrup, S.H., Alslev, T., Kristensen, O., Christensen, K., Gaist, D. (2002). Cessation of Smoking After First-Ever Stroke: A Follow-Up Study. *Stroke*. 33:2263-2269.
- Baldassarre, D., Castelnuovo, S., Frigerio, B., Amato, M., Werba, J.P., De Jong, A., Ravani, A.L., Tremoli, E., Sirtori, C.R. (2009). Effects of timing and extent of smoking, type of cigarettes, and concomitant risk factors on the association between smoking and subclinical atherosclerosis. *Stroke*. 40(6):1991-8.
- Ballard, J., Kreiter, K.T., Claasen, J., Kowalski, R.G., Connolly, E.S., Mayer, S.A. (2003). Risk Factors for Continued Cigarette Use After Subarachnoid Hemorrhage. *Stroke*. 34:1859-1863.
- Bang, O.Y., Park, H.Y., Lee, P.H., Kim, G.M., Chung, C.S., Lee, K.H. (2007). Improved after atherosclerotic stroke in male smoker. *Journal of Neurological Sciences*. 260:43-48.

- Bauer, J.E., Hyland, A., Li, Q., Steger, C., Cummings, M. (2005). A longitudinal assessment of the impact of smoke-free worksite policies on tobacco use. *American Journal of Public Health*. 95(6):1024-9.
- Benowitz, N.L. (2009). Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annual Review of Pharmacological Toxicology*. 49:57-71.
- Blann, A.D., Kirkpatrick, U., Devine, C., Naser, S., McCollum, C.N. (1998). The influence of acute smoking on leucocytes, platelets and endothelium. *Atherosclerosis*. 141: 133-139.
- Boyajian, R.A., and Otis, S.M. (2000). Acute effects of smoking on human cerebral blood flow: a transcranial Doppler ultrasonography study. *Journal of Neuroimaging*. 10:204-208.
- Burn, J., Dennis, M., Bamford, J., Sandercock, P., Wade, D., Warlow, C. (1994). Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke*. 25(2):333-337.
- Burns, D.M. (2003). Epidemiology of smoking-induced cardiovascular disease. *Progress in Cardiovascular Disease*. 46:11-29.
- Butler-Jones, D. (2008). The Chief Public Health Officer's Report on the State of Public Health In Canada. 2008. Ministry of Health. Internet document retrieved on Mar 23, 2010 from <http://www.phac-aspc.gc.ca/publicat/2008/cpho-aspc/pdf/cpho-report-eng.pdf>.
- Butler-Jones, D. (2011). The Chief Public Health Officer's Report on the State of Public Health in Canada . Ministry of Health. Internet document retrieved on Nov 10, 2011 from <http://www.phac-aspc.gc.ca/cphorsphc-respcaesp/2011/pdf/cpho-resp-2011-eng.pdf>.
- Cahill, K., Stead, L.F., and Lancaster, T. (2007). Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Systematic Review*. (1)(1):CD006103.
- Canadian Tobacco Use Monitoring Survey [CTUMS]. (2006). Information retrieved on Dec 1, 2008 from http://www.hc-sc.gc.ca/hl-vs/tobac-tabac/research-recherche/stat/_ctums-esutc_2006/ann_summary-sommaire-eng.php.
- Celermajer, D., Keld, S., Georgakopoulos, D., Bull, C., Thomas, O., Robinson, J., Deanfield, J. (1993). Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation*. 88: 2149-2155.
- Chang, K., Tseng, M., Weng, H., Lin, Y., Liou, C., Tan, T. (2002). Prediction of Length of Stay of First-Ever Ischemic Stroke. *Stroke*. 33: 2670-2674.

- Critchley, J., Capewell, S. (2004). Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database Systematic Review*. (1):CD003041.
- Cronin, E.M., Kearney, P.M., Kearney, P.P., Sullivan, P., Perry, I.J., Coronary Heart Attack Ireland Registry (CHAIR) Working Group. (2012). Impact of a national smoking ban on hospital admission for acute coronary syndromes: a longitudinal study. *Clinical Cardiology*. 35(4):205-209.
- Domino, E.F. (1997). Tobacco Smoking and Nicotine Neuropsychopharmacology: Some Future Research Directions. *Neuropsychopharmacology*. 18(6): 456- 468.
- Domino, E.F., Minoshima, S., Guthrie, S., Ohl, L., Ni, L., Koeppe, R.A., Zubieta, J.K. (2000). Nicotine effects on regional cerebral blood flow in awake, resting tobacco smokers. *Synapse*. 38:313-321
- Downs, S. H., and Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and nonrandomised studies of health care interventions. *Journal of Epidemiology and Community Health*. 52:377–384.
- Edjoc, R. (2011). The Association between Household Restrictions and Smoking Abstinence: Does age matter? *Journal of Smoking Cessation*. 6(1): 74-78.
- Eggers, M., Davey Smith, G., Atman, D.G. (2001). Systematic Reviews in Health Care: Meta-analyst in context. 2nd edition British Medical Journal Books.
- Eguchi, K., Kario, K., Hoshide, S., Hoshide, Y., Ishikawa, J., Morinari, M., Hashimoto, T., Shimada, K. (2004). Smoking is associated with silent cerebrovascular disease in a high-risk Japanese community-dwelling population. *Hypertension Research*. (10):747-54.
- Eisenberg, M.J., Filion, K.B., Yavin, D., Bélisle, P., Mottillo, S., Joseph, L., et al. (2008). Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *Canadian Medical Association Journal*. 179(2):135-44.
- Ellis, G., McAlpine, C., and Langhorne, P. (2005). The impact of stroke nurse specialist input on risk factor modification: a randomised controlled trial. *Age Ageing*. 34: 389-392.
- Evans, J., and Chen, Y. (2007). The Association Between Home and Vehicle Environmental Tobacco Smoke (ETS) and Chronic Bronchitis in a Canadian Population: The Canadian Community Health Survey, 2005. *Inhalation Toxicology*. 21(4): 244-249.
- Feigin, V., Parag, V., Lawes, C.M.M., Rodgers, A., Suh, I., Woodward, M., Jamrozik, K., Ueshima, H. (2005). Smoking and elevated blood Pressure are the most important risk

- factors for subarachnoid haemorrhage in the Asia-Pacific Region. *Stroke*. 35: 1360-1365.
- Frandsen, N.B., Margit Sørensen, M., Hyldahl, T.K., Rikke Mitzi Henriksen, R.M., & Søren Bak. (2012). Smoking Cessation Intervention After Ischemic Stroke or Transient Ischemic Attack. A Randomized Controlled Pilot Trial. *Nicotine & Tobacco Research*. 14(4): 443–447.
- Granger, C.B. (2000). When is angina good? Preconditioning in acute myocardial infarction. *American Heart Journal*. 39:771–2.
- Evans, M.D., Pryor, W.A. (1994). Cigarette smoking, emphysema and damage to a proteinase inhibitor. *American Journal of Physiology*. 266:593-611.
- Fiore, M.C., Jaen, C.R., Baker, T.B., Bailey, W.C., Benowitz, N.L., Curry, S.J., et al. (2008). Treating tobacco use and dependence: 2008 update. Rockville, MD: U.S. Department of Health and Human Services. *Public Health Service*.
- Furie, K.L., Kasner SE, Adams RJ, et al. (2011). On behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 42:227–76
- Fujita, M., Nakae, I., Kihara, Y., Hasegawa, K., Nohara, R., Ueda, K., et al. (1999). Determinants of collateral development in patients with acute myocardial infarction. *Clinical Cardiology*. 22:595–9.
- Hankey, G.J. (1999). Smoking and risk of stroke. *Journal of Cardiovascular Risk*. 298: 798-794.
- Hankey, G.J., and Warlow, C.P. (1999). Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet*. 354(9188):1457-1463.
- Heaney, C.A. and Israel, B.A. (2008). Chapter 9: Social Networks and Social Support. In *Health Behaviour and Health Education: Theory, Research and Practice*. 4th Ed. John Wiley and Sons.
- Heart and Stroke. (2011). Internet document. Information retrieved on August 26th, 2011 from <http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.3581729/k.359A/Statistics.htm>.

- Hickey, J.V. (2003). *The clinical practice of neurological and neurosurgical nursing* (5th ed.). Philadelphia: Lippincott, Williams & Wilkins.
- Hays, J.T., Croghan, I.T., Schroeder, D.R., Offord, K.P., Hurt, R.D., Wolter, T.D., et al. (1999). Over the counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trials. *American Journal of Public Health*. 89(11):1701-7.
- Hawkins, B.T., Brown, R.C., Davis, T.P. (2002). Smoking and ischemic stroke: a role for nicotine. *Trends in Pharmacological Sciences*. 23(2):78-82.
- Hawkins, B.T., Abbruscato, T.J., Egleton, R.D., Brown, R.C., Huber, J.D., Campos, C.R., Davis, T.P. (2004). Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution. *Brain Research*. 1027 (1-2): 48-58.
- Henningfield, J.E. (1995). Nicotine Medications for Smoking Cessation. *New England Journal of Medicine*. (333): 1196-1203.
- Henningfield, J.E., and Fant, R.V. (1999), Tobacco use as drug addiction: The scientific foundation. *Nicotine Tobacco Research*. 1(1): Suppl 1, 33-35.
- Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerström, K.O. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*. 86(9):1119-27.
- Higgins, J.P., and Thompson, S.G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 21:1539-58.
- Hinkle, J.L., and Bowman, L. (2003). Neuroprotection for ischemic stroke. *Journal of Neuroscience Nursing*. 35 (2): 114-8.
- Hinkle, J.L., and Guanci, M.M. (2007). Acute ischemic stroke review. *Journal of Neuroscience Nursing*. 39(5):285-293, 310.
- Hiscock, R., Bauld, L., Amos, A., Fidler, J.A., Munafò, M. (2011). Socioeconomic status and smoking: a review. *Annals of the New York Academic of Sciences*. doi: 10.1111/j.1749-6632.2011.06202.x. [Epub ahead of print].
- Hoiki, Y., Aoki, N., Kawano, K., Homori, M., Hasumura, Y., Yasumura, T., Maki, A., Yoshino, H., Yanagisawa, A., Ishikawa, K. (2001). Acute effects of cigarette smoking on platelet-dependent thrombin generation. *European Heart Journal*. 22: 56-61.
- Holbrook, A.L., Green, M.C., Krosnick, J.A. (2003). Telephone versus face-to-face interviewing of national probability samples with long questionnaires: Comparisons of respondent satisficing and social desirability response bias. *Public Opinion Quarterly*. 67:79-125.

- Howard, G., Wagenkencht, L.E., Burke, G.L., Diez-Roux, A., Evans, G.W., McGovern, P., Nieto, J. Tell, G.S. (1998). The atherosclerosis risk in communities (ARIC) study. *Journal of the American Medical Association*. 1998. 279: 119-124.
- Hughes, J.R., Stead, L.F., and Lancaster, T. (2007). Antidepressants for smoking cessation. *Cochrane Database Systematic Review*. (1)(1):CD000031.
- Hyman, R., Karalis, D., Ross Jr., J.J., Victor, M., Morris, R. (2006). Pulmonary embolism from in situ right thrombus after coronary artery bypass surgery. *Journal of American Society of Echocardiography*. 10(7): 760-762.
- Institute for Clinical Evaluative Sciences [ICES]. (2010). Information retrieved on August 31st, 2010 from <http://www.ices.on.ca>.
- Ives, S.P., Heuschmann, P.U., Wolfe, C.D.A., Redfern, J. (2008). Patterns of smoking cessation in the first 3 years after stroke: the South London Stroke Register. *European Journal of Cardiovascular Prevention and Rehabilitation*. 15:329-335.
- Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clinical Trials*. 17(1):1-12.
- Jatoi, N.A., Jerrard-Dunne, P., Feely, J., Mahmud, A. (2007). Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 49:981.
- Jiang, B., Wang, W., Chen, H., Hong, Z., Yang, Q., Wu, S., Du, X., Bao, Q.(2006). Incidence and Trends of Stroke and Its Subtypes in China. Results From Three Large Cities. *Stroke*. 37:63-65.
- Johnston, K.C., Connors, A.F., Wagner, D.P., Knaus, W.A., Wang, X-Q., Haley, E.C. (2000). A predictive risk model for outcomes of ischemic stroke. *Stroke*. 31:448-455.
- Jorgensen, H.S., Nakayama, H., Raaschou, H.O., Olsen, T.H. (1997). Acute Stroke and Rehabilitation An analysis of the direct cost and its clinical and social determinants: The Copenhagen Stroke Study. *Stroke*. 28:1138-1141.
- Joubert, J., Reid, C., Barton, D., Cumming, T., McLean, A., Joubert, L., Barlow, J., Ames, D., Davis, S. (2009). *Journal of Neurology, Neurosurgery and Psychiatry*. 80(3): 279-284.
- Kaper, J., Wagena, E.J., Willemsen, M.C., van Schayck, C.P. (2005). Reimbursement for smoking cessation treatment may double the abstinence rate: results of a randomized trial. *Addiction*. 100(7):1012-20.

- Kapral, M., Hall, R., Silver, F., Richards, J., Robertson, A., Fang, J. (2009). Registry of the Canadian Stroke Network: report on the 2004/05 Ontario stroke audit. Internet document accessed on Sep 27th, 2010 from <https://www.rcsn.org/RCSN.aspx>.
- Kawachi I., Colditz, G.A., Stampfer, M.J., Willett, W.C., Manson, J.E., Rosner, B. (1993). Smoking cessation in relation to total mortality rates in women. A prospective cohort study. *Annals of Internal Medicine*. 119(10):992-1000.
- Keuthen, N.J., Niaura, R.S., Borrelli, B., Goldstein, M., Depue, J., Murphy, C., Gastfriend, D., Reiter, S.R., Abrams, D. (2000). Comorbidity, Smoking Behaviour and Treatment Outcome. *Psychotherapy and Psychosomatics*. 69(5):244-250.
- Kindig, DA, Stoddart G. (2003). What is population health? *Am J Public Health*. 93: 366-369.
- Kool, M.J., Hoeks, A.P., Struijker Boudier, H.A., Reneman, R.S., Van Bortel, L.M. (1993). Short- and long-term effects of smoking on arterial wall properties in habitual smokers. *Journal of the American College of Cardiology*. 22: 1881-1886.
- Koning, P., Webbink, D., Martin, N.G. (2010). The Effect of Education on Smoking behaviour: Evidence from smoking durations of a sample of twins. 2010. Internet document retrieved on Nov 10, 2011 from <http://ftp.iza.org/dp4796.pdf>.
- Luijendijk, H.J., Stricker, B.H., Wieberdink, R.G., Koudstaal, P.J., Hofman, A., Breteler, M.M., Tiemeier, H. (2011). Transient Ischemic Attack and Incident Depression. *Stroke*. [Epub ahead of print].
- Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Public Library of Science One*. 6: e1000100. doi:10.1371/journal.pmed.1000100.
- Longstreth, W., Nelson, L., Koepsell, T., van Belle, G. (1992). Cigarette smoking, alcohol use and subarachnoid haemorrhage. *Stroke*. 23: 1242-1249.
- McEwen, B.S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*. 338:171-179.
- McEwen, B.S., and Seeman, T. (1999). Protective and damaging effects of mediators of stress: elaborating and testing the concepts allostatis and allostatic load. *Annals of the New York Academic of Sciences*. 896:30-47.
- McEwen, B.S., and Stellar, E. (1993). Stress and the Individual: Mechanisms leading to disease. *Archives of Internal Medicine*. 153: 2093-2101.

- McManus, J.A., Craig, A., McAlpine, C. *et al.* (2009). Does behaviour modification affect post-stroke risk factor control? Three-year follow-up of a randomized controlled trial. *Clinical Rehabilitation*. 23:99–105.
- Mouradian, M.S., Majumdar, S.R., Senthilselvan, A., Khan, K., Shuaib, A. (2002). How well are hypertension, hyperlipidemia, diabetes, and smoking managed after a stroke or transient ischemic attack? *Stroke*. 6:1656-1659.
- Mynt, P.K., Welch, A.A., Bingham, S.A., Luben, R.N., Wareham, N.J., Day, N.E., et al. (2006). Smoking predicts long-term mortality in stroke: The European Prospective Investigation into Cancer (EPIC)- Norfolk prospective population study. *Preventive Medicine*. 42:128-131.
- Naidoo, B., Stevens, W., McPherson, K. (2000). Modelling the short term consequences of smoking cessation in England on the hospitalisation rates for acute myocardial infarction and stroke. *Tobacco Control*. 9:397–400
- Nidhinandana, S., Sithinamsuwan, P., Chinvarun, Y., Wongmek, W., Supakasem, S., Suwantamee, J. (2010). Prevalence of poststroke depression in Thai stroke survivors studied in Phramongkutklao Hospital. *Journal Medical Association of Thailand*. 93 Suppl 6:S60-4.
- Norusis, M.J. (2008). SPSS 16.0: Statistical Procedures Companion. Prentice Hall Inc. Upper Saddle River, NJ 07458.
- Oetzel, J. G., Ting-Toomey, S., Rinderle, S. (2006). Conflict communication in contexts: A social ecological perspective. In J. G. Oetzel & S. Ting-Toomey (Eds.), *The SAGE handbook of conflict communication*. Thousand Oaks, CA: Sage.
- Ontario Tobacco Research Unit [OTRU]. (2009). Toward a Smoke Free Ontario: Progress and Implications for Future Developments. Internet document accessed on June 23rd, 2012 from http://www.otru.org/pdf/13mr/13mr_no3.pdf.
- Ontario Tobacco Research Unit [OTRU]. (2011). Tobacco Control Funding Commitments. Internet document accessed on June 23rd from <http://www.otru.org/pdf/mr2011/funding2011.pdf>.
- Ovbiagele, B., Weir, C.J., Saver, J.L., Muir, K.W., Lees, K.R. (2006). Effect of smoking status on outcome after acute ischemic stroke. *Cerebrovascular Diseases*. 21:260-265.
- Ortells, M.O., and Arias, H.R. (2010). Neuronal Networks of nicotine addiction. *The International Journal of Biochemistry and Cell Biology*. 42(12):1931-1935.
- Ortells M.O., and Barrantes, G.E. (2010) Tobacco addiction: a biochemical model of nicotine dependence. *Medical Hypotheses*. 74: 884–894.

- Pierce, J.P., Gilpin, E.A., Emery, S.L. White, M.M., Rosbrook, B., Berry, C.C. (1998a). Has the Tobacco Control Program Reduced Smoking? *Journal of the American Medical Association*. 280: 893-899.
- Pierce, J.P., Evans, N., and Farkas, A.J. (1998b). Tobacco use in California: An evaluation of the tobacco control program, 1998-1993. 1994. La Jolla: University of California, San Diego.
- Pai, M., McCulloch, M., Gorman, J.D., Pai, N., Enanoria, W., Kennedy, G., Tharyan, P., Colford Jr, J.M. (2008). Systematic reviews and meta-analyses: An illustrated, step by step guide. *National Medical Journal of India*. 17(2):86-95.
- Pai, M. (2012.). Systematic reviews of non-experimental (observational) studies. Internet document accessed on Nov 5th, 2012 from http://www.medepi.net/meta/lectures/Systematic_Reviews_Observational_Studies.ppt.
- Papadakis, S., Aitken, D., Gocan, S., et al. (2011). Quit- A pilot trial of standardized counselling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention. *BMJ Open*. 1:e000366 doi:10.1136/bmjopen-2011-000366.
- Papadakis, S., McDonald, P., Mullen, K.A., Reid, R., Skulsky, K., Pipe, A. (2010). Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis. *Preventative Medicine*. 51:199-213.
- Pan, A., Okereke, O.I., Sun, Q., Logroscino, G., Manson, J.E., Willett, W.C., Ascherio, A., Hu, F.B., Rexrode, K.M. (2011). Depression and Incident Stroke in Women. *Stroke*. 42:2770-2775.
- Poredos, P., Orehek, M., Tratnik, E. (1999). Smoking is associated with dose-related increase of intima-media thickness and endothelial dysfunction. *Angiology*. 50: 201-208.
- Public Health Agency of Canada [PHAC]. (2010). Tracking Heart Disease and Stroke in Canada. Internet document accessed on Nov 10th, 2010 from www.phac-aspc.gc.ca.
- Quattrocki, E., Baird, A., Yurgelun-Todd, D. (2000). Biological aspects of the link between smoking and depression. *Harvard Review Psychiatry*. 8(3):99-110.
- Rogers, R.L., Meyer, J.S., Judd, B.W., Mortel, K.F. (1985). Abstinence from cigarette smoking improves cerebral perfusion among elderly chronic smokers. *Journal of the American Medical Association*. 253(20):2970-2974.
- Redfern, J., McKeivitt, C., Dundas, R., Rudd, A.G., Wolfe, C.D.A. (2000). Behavioural risk factor prevalence and lifestyle change after stroke: a prospective study. *Stroke*. 31: 1877-1881.

- Reid, R.D., Pipe, A.L., Quinlan, B. (2006). Promoting smoking cessation during hospitalization for coronary artery disease. *Canadian Journal of Cardiology*. 22(9):775-80.
- Reynoso, J., Susabda, A., Cepeda-Benito, A. (2005). Gender Differences in Smoking Cessation. *Journal of Psychopathology and Behavioural Assessment*. 27(3): 227-234.
- Rigotti, N.A., Pipe, A.L., Benowitz, N.L., Arteaga, C., Garza, D., Tonstadt, S. (2010). Efficacy and Safety of Varenicline for Smoking Cessation in Patients with Cardiovascular Disease. *Circulation*. 121: 221-229.
- Rigotti, N., Munafo', M.R., and Stead, L.F. (2008). Interventions for smoking cessation in hospitalised patients. *Archives of Internal Medicine*. 168(18):1950-1960.
- Sallis, J. and Owen, N. (1999). Ecological models, K. Glanz, F. Lewis, B. Rimer, Editors, *Health Behavior and Health Education: Theory, Research, and Practice*, Jossey Bass, San Francisco. pp. 404-424.
- Seeman, T.E., Crimmin, E., Huang, M., Singer Burton Bucur, A., Gruenewald, T., Berkman, L.F., Reuben, D.B. (2004). Cumulative biological risk and socio-economic differences in mortality: MacArthur Studies of Successful Aging. *Social Science Medicine*. 58: 1985-1997.
- Shaohua, H., McAlister, A.L., Meshack, A.F., Margois, J.A. (2003). Physician's views and practices of smoking cessation. *Texas Medicine*.
- Shaikh, N., Parchani, A., Bhat, V., Kattren, M.A. (2008). Fat embolism syndrome: clinical and imaging considerations: Case report and review of literature. *Indian Journal of Crititical Care Medicine*. 12(1): 32-36.
- Shelley, D., Yerneni, R., Hung, D., Das, D., Fahs, M. (2007). The relative effect of household and workplace smoking restriction on health status among Chinese Americans living in New York City. *Journal of Urban Health*. 84(3):360-371.
- Shields, M. (2007). Smoking bans: Influence on smoking prevalence. *Health Reports*. 3:9-24.
- Shinton, R., and Beevers, G. (1989). Meta-analysis of relation between cigarette smoking and stroke. *British Medical Journal*. 298(6676):789-794.
- Smoke Free Ontario Act: Legislation. (2009). Internet document. Retrieved on May 29, 2009 from http://www.mhp.gov.on.ca/english/health/smoke_free/legislation.asp.
- Smoke Free Ontario Act: Legislation. (2009a). Internet document. Retrieved on May 29, 2009 from http://www.mhp.gov.on.ca/english/health/smoke_free/chart.asp

- Smoke Free Ontario Act: Legislation. (2009b). Internet document. Retrieved on May 29, 2009 from http://www.e-laws.gov.on.ca/html/reggs/english/elaws_reggs_060048_e.htm.
- Sorensen, G., Barbeau, E., Hunt, M.K., Emmons, Karen. (2004). Reducing Social Disparities in Tobacco Use: A Social-Contextual Model for Reducing tobacco Use Among Blue-Collar Workers. *American Journal of Public Health*. 94(2):230-239.
- Statistics Canada. (2008). The Canadian Community Health Survey (CCHS) 2007-2008. Statistics Canada. Retrieved on May 13th, 2011 from <http://www.statcan.gc.ca>.
- Stead, L.F., Perera, R., Bullen, C., et al. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database Systematic Review*. (1)(1):CD000146.
- Steiner, I., Gotkine, M., Wirguin, I. (2008). The protective effect of risk factors against stroke severity. *Journal of Neurological Sciences*. 267: 187-189.
- Sterling, P., and Eyer, J. (1998). A New Paradigm to Explain Arousal Pathology. In Fisher, S. and J. Reason, eds. *Handbook of Life Stress, Cognition and Health*. New York, John Wiley & Sons. 629-649.
- Stein, J.H., and Soble, J.S. (1995). Thrombus Associated With Mitral Valve Calcification: A Possible Mechanism for Embolic Stroke. *Stroke*. 26:1697-1699.
- Stoll, G., Kleinschnitz, C., and Nieswandt, B. (2008). Molecular mechanisms of thrombus formation in ischemic stroke: novel insights and targets for treatment. *Blood*. 112(9):3555-62.
- Stone, P., Gottlieb, D., O'Connor, G., Ciccolella, D., Breuer, R., Bryan-Rhadi, J., Shaw, H., Franzblau, C., Snider, G. (1995). Elastin and collagen degradation products in urine of smokers with and without chronic obstructive pulmonary disease. *American Journal of Respiratory Critical Care Medicine*. 151: 952-959.
- Stroup, D.F., Berlin, J.A., Morton, S., Olkin, I., Williamson, G.C., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B. (2000). Meta-analysis of Observational Studies in Epidemiology: A proposal for reporting. *Journal of the American Medical Association*. 283(15):2008-2012.
- Strum, J.W., Donnan, G.A., Dewey, H.M., Macdonell, R.A.L., Gilligan, A.K., Thrift, A.G. (2004). Determinants of Handicap after stroke: The North East Melbourne Stroke Incidence Study. *Stroke*. 35:715-720.
- Tartara, F., Gaetani, P., Tancioni, F., Guagliano, A., Klersy, C., Forlino, A., Marzatico, F., Rodriguez y Baena, R. (1996). Alpha1-antitrypsin activity in subarachnoid haemorrhage. *Life Sciences*. 59- 15-20.

- Tebor, C., Bramer, S., Weiller, C., Rother, J. (2002). Short-term of cigarette smoking in CO₂-induced vasomotor reactivity in man: A study with near infrared spectroscopy and transcranial Doppler sonography. *Journal of the Neurological Sciences*. 205: 15-20.
- The Registry for the Canadian Stroke Network . (2010). Information retrieved on February 06th, 2010 from <http://www.rcsn.org>.
- Volpp, K.G., Troxel, A.B., Pauly, M.V., Glick, H.A., Puig, A., Asch, D.A., et al. (2005). A randomized, controlled trial of financial incentives for smoking cessation. *New England Journal of Medicine*. 360(7):699-709.
- Wannamethee, S.G., Shaper, A.G., Whincup, P.H., Walker, M. (1995). Smoking cessation and the risk of stroke in middle-aged men. *Journal of the American Medical Association*. 274:155-60.
- Weng, W., Huang, W., Chien, Y., Wu, C., Su, F.C., Hsu, H.J., Lee, T., Peng, T. (2011). The impact of smoking on the severity of acute ischemic stroke. *Journal of Neurological Sciences*. [Epub ahead of print].
- White, J. (2006). Communique for the Health Industry: Smoke Free Ontario Act. Internet document. Retrieved on May 29, 2009 from http://www.millerthomson.ca/docs/Health_Communicu__May_31_2006.pdf.
- Wolf, P.A., D'Agostino, R.B., Kannel, W.B., Bonita, R., Belanger, A.J. (1988). Cigarette smoking as a risk factor for stroke. The Framingham Study. *Journal of the American Medical Association*. 259(7):1025-1029.
- Wolfe, C.D., Redfern, J., George Rudd, A., et al. (2010). Cluster Randomized Controlled Trial of a Patient and General Practitioner Intervention to Improve Management of Multiple Risk Factors After Stroke: Stop Stroke. *Stroke*. 41:2470-2476.
- Xu, G., Liu, X., Wu, W., Zhang, R., Yin, Q. (2007). Recurrence after Ischemic Stroke in Chinese Patients: Impact of Uncontrolled Modifiable Risk Factors. *Cerebrovascular Disease*. 23:117-120.
- Yamishita, K., Kobayashi, S., Yamaguchi, S., Kitani, M., Tsunematsu, T. (1988). Effect of smoking on regional cerebral blood flow in the normal aged volunteers. *Gerontology*. 34:199-204.
- Yeh, D.D. and Waters, D.D. (2008). Preventing and Treating and Transient Ischemic Attack. *American Journal of Cardiology*. 101(2):270-273.
- Young, J.M., and Ward, J.E. (2001). Implementing guidelines for smoking cessation advice in Australian general practice: opinions, current practices, readiness to change and perceived barriers. *Family Practice*. 18(1):14-20.

Zwar, N.A., Richmond, R.L. (2006). Role of the general practitioner in smoking cessation. *Drug and Alcohol Review*. 25(1):21-26.

Appendix A: Systematic review search strategy

- 1 Smoking Cessation/ (15369)
- 2 ((stop or quit or cease* or cessation*) adj2 smok*).ti,ab. (15378)
- 3 1 or 2 (22000)
- 4 cerebrovascular disorders/ (41249)
- 5 cerebrovascular.ti,ab. (31127)
- 6 exp brain ischemia/ (69234)
- 7 ((brain or cerebral) adj2 (ischemi* or infarc*)).ti,ab. (35310)
- 8 tia.ti,ab. (4080)
- 9 intracranial hemorrhages/ (2362)
- 10 ((brain or intracranial) adj1 hemorrhag*).ti,ab. (5150)
- 11 exp cerebral hemorrhage/ (24534)
- 12 ((cerebrum or cerebral) adj2 hemorrhag*).ti,ab. (3715)
- 13 exp subarachnoid hemorrhage/ (14146)
- 14 exp stroke/ (62633)
- 15 stroke*.ti,ab. (112322)
- 16 exp "Intracranial Embolism and Thrombosis"/ (16617)
- 17 ((brain or intracranial) adj2 (emboli* adj3 thromb*)).ti,ab. (14)
- 18 or/4-17 (251175)
- 19 mortality/ or morbidity/ or sudden death/ (48184)
- 20 (death or mortality or morbidity).ti,ab. (735687)
- 21 diabetes.ti,ab. or exp diabetes mellitus/ (344577)
- 22 carotid stenosis/ or (carotid adj2 (stenos* or narrow*)).ti,ab. (12091)
- 23 (depression or depressive).ti,ab. or depression/ (212356)
- 24 (alzheimer disease or alzheimer* or dementia).ti,ab. (99695)
- 25 revascularization.mp. (33817)
- 26 (high blood pressure or hypertensi*).ti,ab. or hypertension/ (311650)
- 27 (dyslipidemia* or hyperlipidemia*).ti,ab. or hyperlipidemias/ (36941)
- 28 emergency service, hospital/ and utilization.fs. (6599)
- 29 (emergency adj4 (readmission* or readmit or utiliz*)).ti,ab. (1000)
- 30 ((emergency room or er) adj2 visit*).ti,ab. (1634)

31 patient readmission/ or ((patient* or hospital) adj2 readmission*).ti,ab. (6798)
32 alcohol*.mp,hw. (255918)
33 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (1862932)
34 3 and 18 and 33 (367)
35 comparative studies/ (1511188)
36 follow-up studies/ (416493)
37 change*.tw. (1713838)
38 evaluat*.tw. (1687962)
39 prospective*.tw. (332455)
40 retrospective.tw. (197723)
41 reviewed.tw. (274974)
42 baseline.tw. (241109)
43 cohort.tw. (158672)
44 consecutive*.tw. (237244)
45 (compare* or compara*).tw. (2226405)
46 or/35-45 (6050097)
47 randomized controlled trial.pt. (302106)
48 controlled clinical trial.pt. (81976)
49 randomized.ab. (218153)
50 placebo.ab. (126254)
51 clinical trials as topic.sh. (152808)
52 randomly.ab. (160915)
53 trials.ti. (36533)
54 or/47-53 (708775)
55 (46 or 54) and 34 (229)
56 limit 55 to english language (199)

Appendix B: Tables

Table 1: Characteristics of included studies for 1st systematic review

Study identification	Type of SCI/Control	Patient Characteristics	Jadad score	Cessation rate
Wolfe et al. (2010)	SCI: Advice on NRT use Control: Usual care Follow-up: 1 year	Intervention: 61 (22.3%) over 80 years, 126 (46.2%) female, 76 (27.9%) smokers. Control: 50 (20.2%) over 80 years, 118 (47.8%) female, 78 (32.2%) smokers.	3	Nintervention=21 out of 76 (27.6%) Ncontrol=22 out of 78 (28.2%)
McManus et al. (2010)	SCI: Discussion with nurse specialist on lifestyle modification in regards to smoking cessation Control: Usual care Follow-up: 42 months	Intervention: 64.3 (62.4- 66.1, 95% CI) mean age, 54 (54.0%) male, 36 (36.0%) smokers. Control: 65.8 (64.0-67.5 95% CI) mean age, 52 (49.5%) male, 42 (40.0%) smokers.	4	Nintervention =1 out of 36 (2.8%) Ncontrol=0 out of 42 (0.0%)

Table 1: Characteristics of included studies for 1st systematic review continued

Study identification	Type of SCI/Control	Patient Characteristics	Study Quality (Jadad score)	Cessation rate
Papadakis et al. (2011)	SCI: Counseling and cost free quit smoking medications (NRT, Bupropion, Varenicline) with follow-up Control: Usual care + prescriptions to pharmacotherapy Follow-up: 26 weeks	Intervention: 55.4 (12.4 SD) mean age, 53.3% male, 15 (53.6%) smokers. Control: 53.5 (8.1 SD), mean age, 69.2% male, 13 (46.4%) smokers.	4	Nintervention=4 out of 15 (26.6%) Ncontrol=2 out of 13 (15.4%)
Frandsen et al. (2012)	SCI: Counseling and cost-free NRT (gum, tablets, patches, nasal spray) with follow-up Control: 1 time 30 min counseling support Follow-up: 6 months	Intervention: 29 (59.2%) age 50-65, 17 (34.7%) female, 49 smokers. Control: 21 (46.7%) 50-65 age, 22 (48.9%) female, 45 smokers.	4	Nintervention=16 out of 49 (32.7%) Ncontrol=13 out of 45 (28.9%)

Table 2: Characteristics of included studies for 2nd systematic review

Study Identification	Stroke diagnosis	Patient demographics and smoking status	Period of Follow-up	Modified Downs and Black score (out of 19)	Main findings related to smoking
Xu et al. (2007)	Lacunar (n=181) Athero-thrombotic(n=226) Cardioembolic(n=192) Undetermined (n=235)	N=834 Mean age: 68.5 +/- 12.4 Smoking Status by stroke diagnosis N=369 with history of smoking N _{current} =211 N _{former} =158	NR	14	First year recurrence rate was 11.2%. Ceasing smoking for more than 1 yr reduced hazard ratio of recurrence from 1.71 to 1.39
Eguchi et al. (2004)	Silent cerebral infarct (n=75)	N=170 Mean age:67.2 +/- 9.5 Smoking status by stroke diagnosis N _{current} =15 N _{former} =3	1 yr	17	Number of infarcts in current smokers were higher than in former smokers (1.9 +/- 2.2 vs. 0.5 +/-0.8; p=0.01)

Table 3: Characteristics of smoking and non-smoking patients

Variables	All	No (Smoking status)	Yes (Smoking status)	P value
Socio-demographics				
Current Smoking	20523	16894	3629	
Age (Mean±SD (n))	71.2±14.11 (20523)	73.2±13.5 (16894)	61.8±13.2 (3629)	<0.0001
Age group				
12-39 - n/N (%)	535/20523 (2.6%)	357/16894 (2.1%)	178/3629 (4.9%)	<0.0001
40-59 - n/N (%)	3689/20523 (18%)	2309/16894 (13.7%)	1380/3629 (38.0%)	
60-79 - n/N (%)	9709/20523 (47.3%)	7949/16894 (47.1%)	1760/3629 (48.5%)	
80+ - n/N (%)	6590/20523 (32.1%)	6279/16894 (37.2%)	311/3629 (8.6%)	
Sex				
Female - n/N (%)	9828/20523 (47.9%)	8535/16894 (50.5%)	1293/3629 (35.6%)	<0.0001
Male - n/N (%)	10695/20523 (52.1%)	8359/16894 (49.5%)	2336/3629 (64.4%)	
Stroke Type				
ICH - n/N (%)	2599/20523 (12.7%)	2215/16894 (13.1%)	384/3629 (10.6%)	<0.0001
Ischemic - n/N (%)	12349/20523 (60.2%)	9946/16894 (58.9%)	2403/3629 (66.2%)	
Tia - n/N (%)	5575/20523 (27.2%)	4733/16894 (28.0%)	842/3629 (23.2%)	
Stroke severity (CNS)				
Severe: 0-5.5 - n/N (%)	4331/20523 (21.1%)	3722/16894 (22.0%)	609/3629 (16.8%)	<0.0001
Moderate: 6.0-8.0 - n/N (%)	2673/20523 (13%)	2185/16894 (12.9%)	488/3629 (13.4%)	
Mild: 8.5+ - n/N (%)	13519/20523 (65.9%)	10987/16894 (65.0%)	2532/3629 (69.8%)	
Medications				
Anti-platelet -n/N (%)	8161/20523 (39.8%)	6964/16894 (41.2%)	1197/3629 (33.0%)	<0.0001
Anti-coagulation -n/N (%)	2264/20523 (11%)	2070/16894 (12.3%)	194/3629 (5.3%)	
Anti-thrombotic -n/N (%)	9895/20523 (48.2%)	8547/16894 (50.6%)	1348/3629 (37.1%)	
Co-morbidities				
Depression -n/N(%)	1099/20523 (5.4%)	836/16894 (4.9%)	263/3629 (7.2%)	<0.0001
Diabetes-n/N (%)	4742/20523 (23.1%)	3986/16894 (23.6%)	756/3629 (20.8%)	0.0003
Hyperlipidemia- n/N(%)	6919/20523 (33.7%)	5708/16894 (33.8%)	1211/3629 (33.4%)	0.62
Hypertension- n/N (%)	13416/20523 (65.4%)	11316/16894 (67.0%)	2100/3629 (57.9%)	<0.0001
Atrial Fibrillation -n/N (%)	3017/20523 (14.7%)	2790/16894 (16.5%)	227/3629 (6.3%)	<0.0001
Stroke History -n/N (%)	3904/20523 (19%)	3350/16894 (19.8%)	554/3629 (15.3%)	<0.0001
Dementia	1648/20523 (8%)	1535/16894 (9.1%)	113/3629 (3.1%)	<0.0001
AlcoholConsumption				
<2/day - n/N (%)	1787/20523 (8.7%)	1261/16894 (7.5%)	526/3629 (14.5%)	<0.0001
>2/day - n/N (%)	1103/20523 (5.4%)	518/16894 (3.1%)	585/3629 (16.1%)	

Table 4: Univariate analyses by smoking status and outcomes of interest (Stroke severity, disability, mortality, LOS)

Outcomes of interest	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI	Chi-square
Stroke Severity (Severe vs. Mild)	0.79	0.73	0.85	<.0001
Disability (Severe vs. No symptoms)	0.87	0.82	0.93	<.0001
Mortality				
30 days	0.56	0.50	0.64	<.0001
90 days	0.56	0.5	0.63	<.0001
1 yr.	0.62	0.56	0.68	<.0001

Table 4a: Univariate analyses by smoking status and outcome of interest (LOS)

Outcomes of interest	Estimate	Lower 95% CI	Upper 95% CI	Chi-square
Intercept	2.28	2.28	2.29	<0.0001
LOS	-0.01	-0.02	0.002	0.01

Table 5: Multivariate analyses on smoking and outcomes of interest (stroke severity, disability and mortality)

Outcome	Effect	Ischemic				TIA				ICH			
		Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square	Odds Ratio	Lower 95% CI	Upper 95% CI	Chi-Square
Stroke Severity (CNS score)	Smoking*	0.99	0.90	1.10	0.99	1.20	0.81	1.77	0.37	0.73	0.59	0.91	0.01
Disability (No disability vs. Severe disability; MRs)	Smoking#	1.10	1.01	1.20	0.03	1.29	1.09	1.54	<0.0001	0.98	0.79	1.21	0.86
Mortality at 30 days	Smoking#	1.00	0.78	1.15	0.56	0.86	0.41	1.81	0.68	1.08	0.79	1.46	0.64
Mortality at 90 days	Smoking#	1.00	0.83	1.17	0.88	1.04	0.62	1.75	0.88	1.19	0.89	1.60	0.25
Mortality at 1 year	Smoking#	1.08	0.93	1.25	0.31	0.62	0.88	1.75	0.62	1.33	1.00	1.76	0.05

*Effect of smoking controlled for age, sex, co-morbidities

#Effect of smoking controlled for age, sex, co-morbidities and stroke severity

Table 5a: Multivariate analyses on smoking and outcome of interest (LOS)

Outcome	Effect	Ischemic				TIA				ICH			
		Estimate (# of days)	Std Error	Lower, Upper 95% CI	Chi- Square	Est. (# of days)	Std Error	Lower, Upper 95% CI	Chi- Square	Est. (# of days)	Std Error	Lower, Upper 95% CI	Chi- Square
LOS	Intercept	0.02	0.01	0.02, 2.77	2.85	1.02	0.10	0.82, 1.23	<.0001	3.05	0.03	2.99, 3.11	<.0001
	Smoking *	0.05(17.2)	0.01	0.01,0.03	0.07	0.35 (5.7)	0.03	0.30,0.40	<0.001	21.4	0.02	0.01,0.07	0.03

*Effect of smoking controlled for Age, Sex, Co-morbidities and stroke severity

Table 6: Phase 3 study cohort characteristics

<i>Covariates</i>	<i>Non-Smoker</i> (n=211 549)	<i>Smoking (%)</i> (n=62 960)	<i>Quit Smoking (%)</i> (n=109 395)	<i>P-values</i>
Males	107 191 (50.7)	35 521 (56.4)	68 798 (62.9)	<0.0001
Females	104 358 (49.3)	27439 (43.6)	40 597 (37.1)	<0.0001
Age				
12-19	1975 (0.9)	314 (0.5)	0.0	<0.001
20-34	2259 (1.1)	2432 (3.9)	1649 (1.5)	<0.001
35-54	11 070 (5.2)	12 830 (20.4)	3375 (3.1)	<0.001
55-69	44 277 (20.9)	24 079 (38.2)	26 660 (24.4)	<0.001
70-80+	89 613 (42.4)	19 515 (31.0)	50 456 (46.1)	<0.001
Education				
< secondary	40 722 (19.3)	11 913 (18.9)	19 917 (18.2)	<0.001
Secondary	26 478 (12.5)	7244 (11.5)	14 902 (13.6)	<0.001
Some post secondary	10 367 (4.9)	2390 (3.8)	5583 (5.1)	<0.001
Income				<0.001
None or < 20 000	33 607 (15.9)	13 029 (20.7)	15 686 (14.3)	
20 000 -39 000	56 858 (26.9)	15 931 (25.3)	32 083 (29.3)	
40 000 – 59 000	34 765 (16.4)	11 993 (19.1)	18 891 (17.3)	
60 000 – 79 000	14 422 (6.8)	3928 (6.24)	7712 (7.1)	
80 000 +	26 714 (12.6)	6617 (10.5)	14 739 (13.5)	
Fagerstrom Nicotine Dependency				<0.0001
Very Low				
Low	0.0	562 (0.89)	0.0	
Medium	0.0	482 (0.8)	0.0	
High	0.0	137 (0.2)	0.0	
Very High	0.0	1288 (2.0)	0.0	
	0.0	326 (0.5)	0.0	

Table 6a: Phase 3 study cohort contd.

<i>Covariates</i>	<i>Non-Smoker</i> (n=211 549)	<i>Smoking (%)</i> (n=62 960)	<i>Quit Smoking (%)</i> (n=109 395)	<i>P-values</i>
Smoking restrictions				
Household	163 099 (77.1)	22 364 (35.5)	80 983 (74.0)	<0.0001
Workplace	23 845 (11.3)	18 740 (29.8)	11 470 (10.5)	0.004
Vehicle	210 504 (99.5)	0.0	102 527 (93.7)	<0.0001
Public	209 436 (99.0)	0.0	102 032 (93.3)	<0.0001
Have access to GP	202 460 (95.8)	55 563 (86.7)	103 830 (94.9)	<0.0001
Smoking cessation aids				
Nicotine replacement therapy (NRT) gum	0.0	0.0	0.0	-
NRT patch	0.0	0.0	65.9 (0.1)	<0.0001
Zyban/Buprion	0.0	0.0	486 (0.4)	<0.0001
MD counseling	0.0	2853 (4.5)	511 (0.5)	<0.0001
One-to-One referral	0.0	326 (0.5)	0.0	<0.0001
Referral to smoking cessation group	0.0	0.0	0.0	-
Alcohol drinking (> 2 drinks/day)	82 752 (39.1)	30 923 (49.1)	4984 (7.9)	0.03
Depression	69 425 (32.8)	26 239 (41.7)	38 989 (35.6)	<0.0001
Diabetes	18 256 (8.6)	13 029 (20.7)	9823 (8.9)	0.21
Hypertension	50 217 (23.7)	4984 (7.9)	22 263 (20.4)	0.02

Table 7: Correlates of smoking cessation of study cohort

<i>Correlates of smoking cessation</i>	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI
Population characteristics			
Female Sex	0.4	0.41	0.42
Age 12-19	-	-	-
Age 20-34	0.02	0.02	0.03
Age 35- 54	0.03	0.025	0.027
Age 55- 69	1.1	1.10	1.19
Age 70- 80	1.6	1.61	1.67
Socio-economic status			
Less than secondary	0.91	0.88	0.93
Secondary education	1.3	1.22	1.29
Some post-secondary education	1.2	1.23	1.24
Post-secondary	1.1	1.10	1.15
No income or less 20 000	0.7	0.63	0.73
\$20 000- 39 000	1.3	1.24	1.29
\$40 000- 59 000	1.1	1.06	1.11
\$60 000- 79 000	1.5	1.45	1.51
\$80 000+	0.7	0.66	0.70
Individual level			
Alcohol Consumption (> 2 drinks/day)	0.70	0.69	0.71
Depression	0.89	0.88	0.91
Hypertension	1.2	1.18	1.24
Diabetes	1.4	1.34	1.38
Fagerstrom Nicotine Dependency	-	-	-

Table 7a: Correlates of smoking cessation of study cohort cntd.

<i>Correlates of smoking cessation</i>	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI
Interpersonal level			
Household smoking restrictions	1.1	1.05	1.08
Vehicle smoking restrictions	2.8	2.72	2.86
Access to GP	1.3	1.24	1.31
Community level			
Public smoking restrictions	-	-	-
Workplace smoking restrictions	-	-	-
Organizational level			
Nicotine replacement therapy (NRT) gum	-	-	-
NRT patch	-	-	-
Zyban/Bupropion	15.4	13.9	17.0
MD counselling	3.7	3.37	4.03

Appendix C: Canadian Community Health Survey: stroke symptoms variable operationalization

Variable Name	CCC_151	Length	1	Position	136
Question Name	CCC_Q151				
Concept	Suffers from the effects of a stroke				
Question	Do you suffer from the effects of a stroke?				
Universe	All respondents				

Note

<u>Content</u>	<u>Code</u>	<u>Sample</u>	<u>Population</u>
YES	1	2,039	304,595
NO	2	128,845	27,681,957
DON'T KNOW	7	135	19,167
REFUSAL	8	14	4,981
NOT STATED	9	28	6,671
	Total	131,061	28,017,372

Appendix D: Canadian Community Health Survey: depression variable operationalization

Variable Name	DPS_02	Length	1	Position	1179
Question Name	DEP_Q02				
Concept	Felt sad/blue/depressed - 2 weeks or more - 12 mo				
Question	During the past 12 months, was there ever a time when you felt sad, blue, or depressed for 2 weeks or more in a row?				
Universe	Respondents with DPSFOPT = 1				
Note					
<u>Content</u>		<u>Code</u>		<u>Sample</u>	<u>Population</u>
YES		1		5,997	1,369,774
NO		2		38,305	9,083,352
NOT APPLICABLE		6		84,930	17,079,233
DONT KNOW		7		87	15,838
REFUSAL		8		159	41,084
NOT STATED		9		1,583	428,091
		Total		131,061	28,017,372

Appendix E: Figures

Figure 1: Effects of nicotine on microcirculation

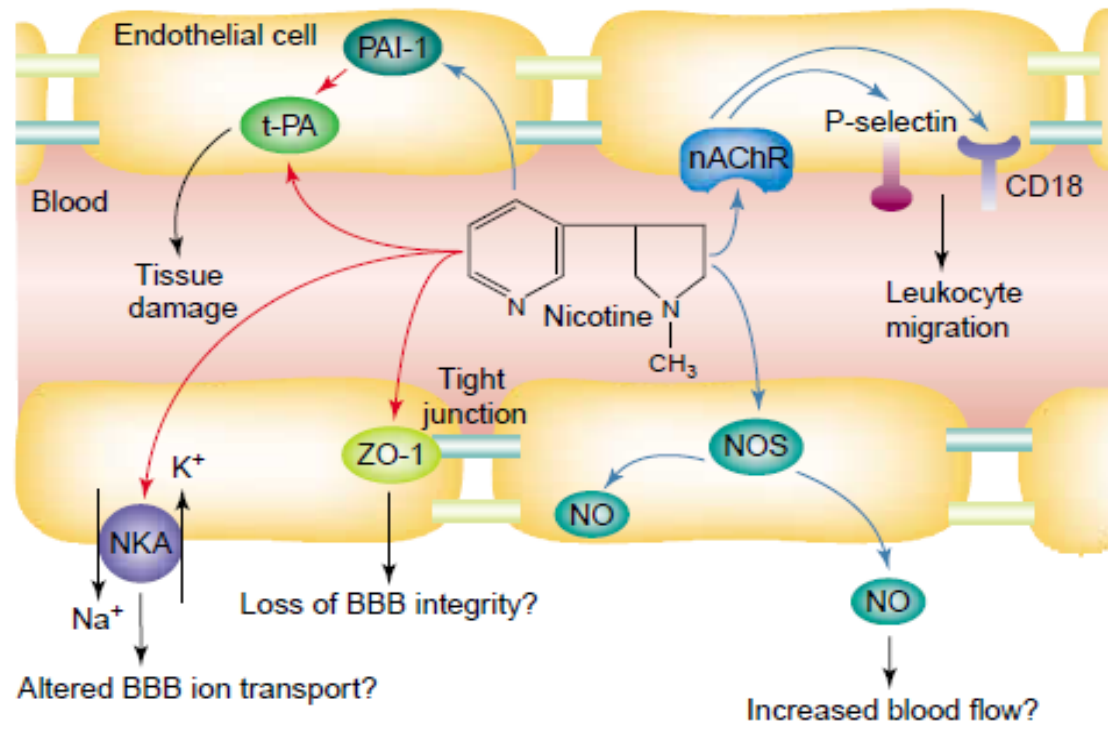


Figure 2: Exclusion criteria and paper selection procedure for the 1st systematic review

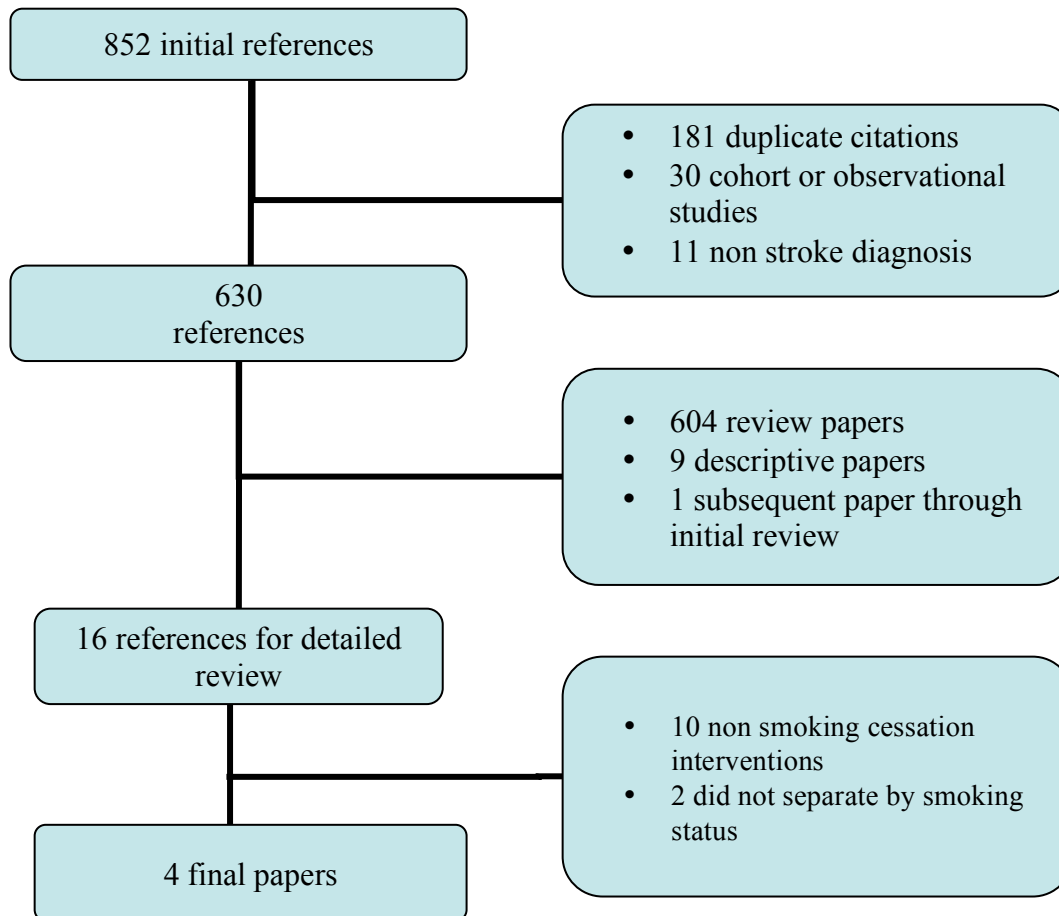


Figure 2a: Exclusion criteria and paper selection procedure for 2nd systematic review

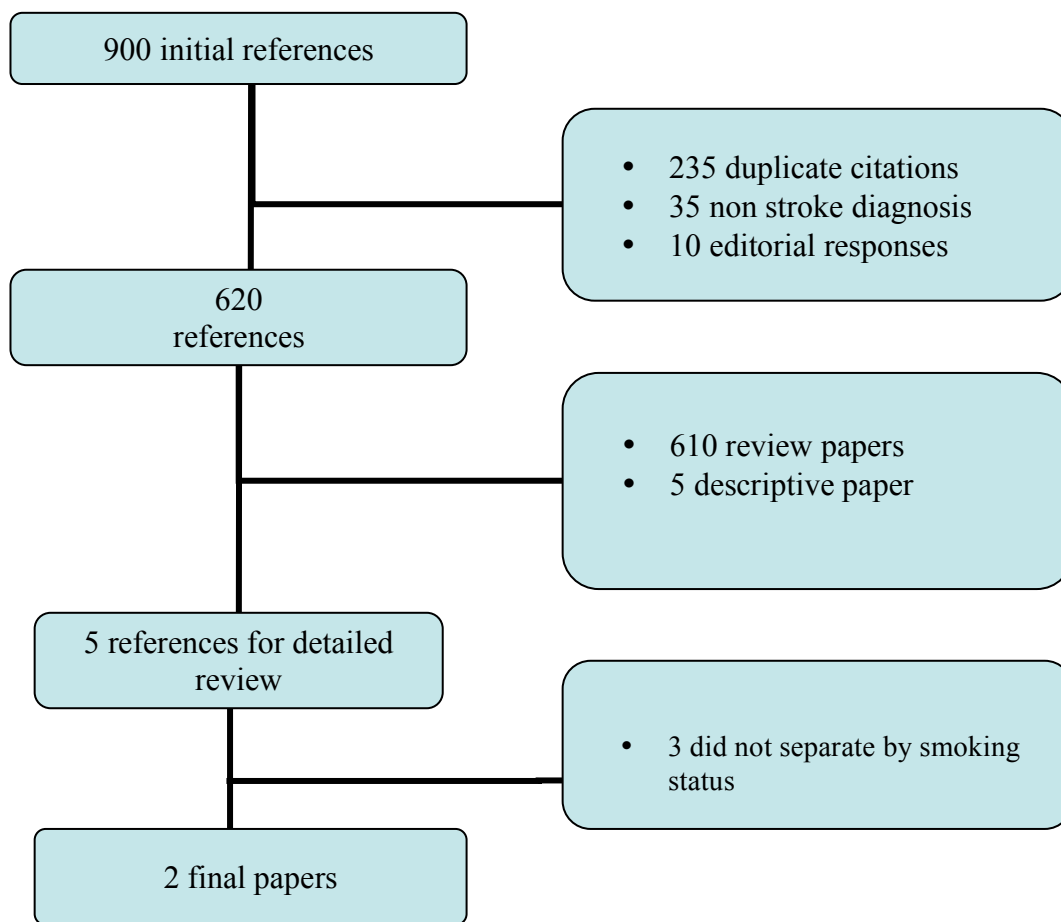


Figure 3: The effect of SCIs on long term quit rates

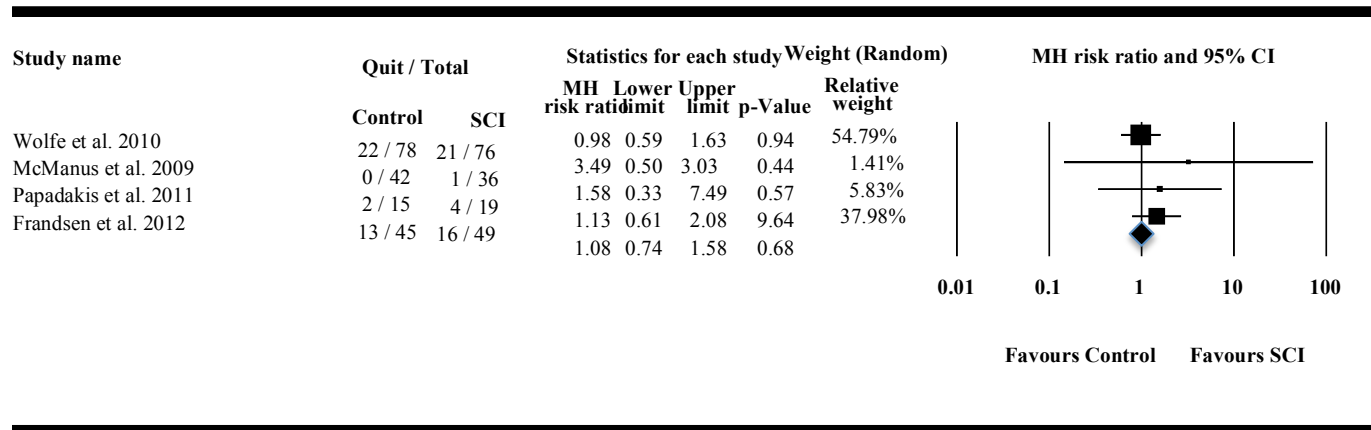


Figure 4: The effect of smoking cessation on stroke recurrence

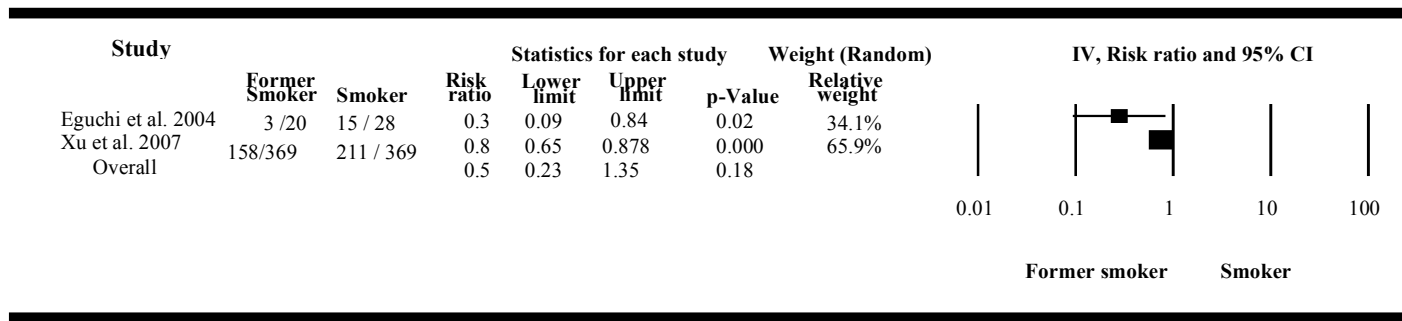


Figure 5: Socio-ecological model for multi-level correlates of smoking cessation in smokers with cerebrovascular disease

