Risk of Carotid Stroke after Chiropractic Care: A Population-Based Case-Crossover Study

J. David Cassidy, DC, PhD, DrMedSc,*,†,‡ Eleanor Boyle, PhD,*,‡ Pierre Côté, DC, PhD,‡,§ Sheilah Hogg-Johnson, PhD,‖,¶ Susan J. Bondy, PhD,‡ and Scott Haldeman, MD, PhD#

Background: Chiropractic manipulation is a popular treatment for neck pain and headache, but may increase the risk of cervical artery dissection and stroke. Patients with carotid artery dissection can present with neck pain and/or headache before experiencing a stroke. These are common symptoms seen by both chiropractors and primary care physicians (PCPs). We aimed to assess the risk of carotid artery stroke after chiropractic care by comparing association between chiropractic and PCP visits and subsequent stroke. *Methods:* A population-based, case-crossover study was undertaken in Ontario, Canada. All incident cases of carotid artery stroke admitted to hospitals over a 9-year period were identified. Cases served as their own controls. Exposures to chiropractic and PCP services were determined from health billing records. *Results:* We compared 15,523 cases to 62,092 control periods using exposure windows of 1, 3, 7, and 14 days prior to the stroke. Positive associations were found for both chiropractic and PCP visits and subsequent stroke in patients less than 45 years of age. These associations tended to increase when analyses were limited to visits for neck pain and headache-related diagnoses. There was no significant difference between chiropractic and PCP risk

From the *Department of Sports Science and Clinical Biomechanics, Faculty of Health, University of Southern Denmark, Odense, Denmark; †Division of Health Care and Outcomes Research, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; ‡Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; §Faculty of Health Sciences, University of Ontario Institute of Technology and UOIT-CMCC Centre for Disability Prevention and Rehabilitation, Oshawa, Ontario, Canada; ‖Institute for Work and Health, Toronto, Ontario, Canada; ¶Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; and #Department of Neurology, University of California, Irvine, California.

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Address correspondence to J. David Cassidy, DC, PhD, DrMedSc, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, Odense M 5230, Denmark. E-mail: dcassidy@health.sdu.dk.

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estimates. We found no association between chiropractic visits and stroke in those 45 years of age or older. *Conclusions:* We found no excess risk of carotid artery stroke after chiropractic care. Associations between chiropractic and PCP visits and stroke were similar and likely due to patients with early dissection-related symptoms seeking care prior to developing their strokes. **Key Words:** Stroke—stroke prevention—risk factor—spinal manipulation.

Introduction

Neck pain and headache are common and related symptoms in the general population and can cause considerable health burden.[1,2] Many individuals with these symptoms attend chiropractors and family doctors.[3] Chiropractic care usually involves manual manipulation of the cervical spine,[4] and although there is evidence that manipulation can improve neck pain and certain headaches, there is concern that it might damage cervical arteries and cause dissection-related stroke.[5] Indeed, there are multiple case reports of both vertebrobasilar and carotid artery dissection-related strokes occurring after cervical manipulation.[6] This concern has prompted some neurologists to warn against chiropractic manipulation of the neck.[7] More recently, the American Heart and Stroke Associations released a consensus statement concerning cervical artery dissections associated with cervical spine manipulation.[8] In their view, patients should be informed of a statistical association between cervical dissections and spinal manipulation prior to undergoing manipulation of the cervical spine.

Although case reports can raise concerns and hypotheses about risk, a study design with a control group is required to test these hypotheses and quantify the risk. There are several challenges in this respect. Internal carotid artery dissection is a relatively rare event with an annual incidence estimated at 1.72 per 100,000 population (95% confidence interval [CI] 1.13-2.32).[9] Furthermore, the dissections that are most likely to be diagnosed are those that result in hospitalization for stroke.[10] To date, there are no reported cases of stroke as an adverse event in the published trials of cervical spine manipulation, but these trials are too small to detect rare events. Although about 12% of North American adults seek chiropractic care annually,[11] it would require a very large cohort study to accrue enough cases to investigate this problem. As an alternative, the case–control study design is well suited to address rare events, and 5 such studies have been published. Two used Canadian health services data,[12,13] and the others used Californian stroke registries,[14] the Medicare Advantage data from the United States,[15] and cervical artery dissections seen at 18 neurology departments in 8 countries.[16] Three studies showed strong associations between chiropractic care and vertebrobasilar artery (VBA) stroke and 1 study found no association. Another study showed an association between cervical manipulative therapy and cervical dissections (i.e., defined as affecting either the carotid artery, vertebral artery, or both arteries).[16] However, only 1 study included results specific to carotid artery dissection strokes (n = 26), and they were not associated with neck manipulation.[14]

Another challenge is the potential for protopathic bias.[17] This occurs when an exposure (e.g., health care) is delivered in the early prodrome of a disease (e.g., for dissection-related neck pain or headache) before it is diagnosed (e.g., before the dissection causes a symptomatic ischemic event). In case–control studies, protopathic bias can lead to the illusion that the exposure caused the outcome, even though it is not on the causal pathway.[18] Cassidy et al addressed this issue in their study by comparing the association between both chiropractic services and primary care physician (PCP) services prior to VBA stroke.[13] They hypothesized that patients with dissection-related neck pain and headache would attend both chiropractors and PCPs prior to developing their strokes. Furthermore, if associations were greater for chiropractors than for PCPs, then chiropractic care would be implicated as a cause of VBA stroke. Their results confirmed strong associations between chiropractic services and stroke in those less than 45 years of age, but similar associations were seen for PCP services. They also did an analysis limited to services coded for neck pain and/or headaches that showed an increase in these associations. This suggests that protopathic bias explains the link between chiropractic care and VBA stroke.

Our study aims to investigate associations between chiropractic exposures and carotid artery-related stroke and compare them to PCP exposures in the same analyses. We hypothesize that if chiropractic care increases the risk of carotid stroke, associations between chiropractic visits and stroke will exceed those between PCP visits and stroke. In addition, we hypothesize that if associations between healthcare visits and carotid stroke increase when analyses are limited to visits provided for neck pain and headache-related diagnoses, protopathic bias is a likely explanation.

Methods

Study Design and Source Population

We conducted a population-based case-crossover study using administrative healthcare data. In this design, cases serve as their own controls by sampling control periods

before the index stroke date. This design is most appropriate when a brief exposure (e.g., healthcare visit) causes a transient change in risk (i.e., hazard period) of a rare event (e.g., carotid stroke).[19] The within-person comparisons provide better control for unmeasured risk factors (e.g., potential confounding due to obesity, smoking, physical activity, general health, etc.). The source population was all adults, 18 years of age and older, residents in the province of Ontario, Canada (population between 12 and 13 million during the study period), and eligible to receive health care under the provincial health insurance plan.

Data Sources

We used administrative data from the Discharge Abstract Database (DAD) from the Canadian Institute for Health Information, the Ontario Health Insurance Plan (OHIP) database, and the Registered Persons Database (RPDB). The DAD is a record of all hospital discharges, and includes up to 8 discharge diagnoses coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to 4 digits only. These diagnoses were used to identify stroke cases. OHIP contains billing codes submitted for services rendered by clinicians. At the time of this study, doctor of chiropractic (DC) services were covered by OHIP. For each encounter, clinicians submit the date, fee code(s), and an ICD code for the responsible condition. The RPDB is a registry of all individuals who have healthcare coverage under OHIP, and it was used to identify the age and sex of our cases. The University Health Network Research Ethics Board approved our study (REB number 05-0533-AE).

Cases

All incident carotid artery stroke cases (ICD-9-CM: 433.1—occlusion and stenosis of the carotid artery) discharged from hospitals between April 1, 1993 and March 31, 2002 were eligible for the study. We included cases with at least 1 year of healthcare coverage prior to the date of the incident stroke. Cases who had a previous hospital admission(s) with a discharge diagnosis of stroke were excluded. We also excluded cases who had concurrent stroke discharge diagnoses (i.e., ICD-9-CM 430, 431, 432.1, 432.9, 433.0, 433.2, and 435.0) because we could not be sure if the main stroke was related to carotid artery injury (Table 1). All decisions regarding codes were made in consultation with stroke experts and epidemiologists familiar with coding in Ontario. We further excluded cases who were in a long-term care facility during the year prior to their incident strokes, as these individuals would be

Table 1. *ICD-9-CM codes used to exclude previous strokes and concurrent strokes*

Code	Description	Exclusion type	
		Previous stroke	Concurrent stroke
430	Subarachnoid hemorrhage	X	X
431	Intracerebral hemorrhage	X	X
432.0	Other and unspecified intracranial hemorrhage: nontraumatic extradural hemorrhage	X	
432.1	Other and unspecified intracranial hemorrhage: subdural hemorrhage	X	X
432.9	Other and unspecified intracranial hemorrhage: unspecified intracranial hemorrhage	X	X
433.0	Occlusion and stenosis of precerebral arteries: basilar artery	X	X
433.1	Occlusion and stenosis of precerebral arteries: carotid artery	X	
433.2	Occlusion and stenosis of precerebral arteries: vertebral artery	X	X
433.3	Occlusion and stenosis of precerebral arteries: multiple and bilateral arteries	X	
433.8	Occlusion and stenosis of precerebral arteries: other specified precerebral artery	X	
433.9	Occlusion and stenosis of precerebral arteries: unspecified precerebral artery	X	
434.0	Occlusion of cerebral arteries: cerebral thrombosis	X	
434.1	Occlusion of cerebral arteries: cerebral embolism	X	
434.9	Occlusion of cerebral arteries: cerebral artery occlusion, unspecified	X	
435.0	Transient cerebral ischemia: basilar artery syndrome	X	X
435.1	Transient cerebral ischemia: vertebral artery syndrome	X	
435.3	Transient cerebral ischemia: vertebrobasilar artery syndrome	X	
435.8	Transient cerebral ischemia: other specified transient cerebral ischemia	X	
435.9	Transient cerebral ischemia: unspecified transient cerebral ischemia	X	
436.0	Acute, but ill-defined, cerebrovascular disease	X	
437.1	Other and ill-defined cerebrovascular disease: other generalized ischemic cerebrovascular disease	X	
438.0	Late effects of cerebrovascular disease	X	
900.9	Injury to blood vessels of head and neck: unspecified blood vessel of head and neck	X	

Abbreviation: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

sicker than individuals living in the community and would be less likely to access chiropractic services.

For descriptive purposes, we used the OHIP database to extract all services related to comorbid conditions that might be related to stroke during the year prior to the stroke (i.e., hypertension, heart disease, peripheral vascular diseases, diabetes, hypercholesterolemia, cerebrovascular diseases, overweight, and addiction) and history of stroke or transient ischemic attack.

Exposures

We extracted all ambulatory DC and PCP fee codes from OHIP for the year prior to the index stroke. We further identified specific visits for neck pain or headache-related services and redid our analyses to investigate protopathic bias. For chiropractors, we identified neck or headache-related encounters using their unique diagnostic codes (i.e., C01-C06 cervical and cervicothoracic subluxation, C13-C15 multiple site subluxation, C30 cervical sprain/strain, C40 cervical neuritis/neuralgia, C44 arm neuritis/neuralgia, C50 brachial radiculitis, C51 cervical radiculitis, and C60 headache). For the PCP visits, we identified neck or headache-related encounters by ICD-9 codes (i.e., 307 tension headaches; 346 migraine headaches; 722 intervertebral disc disorders; 780 headache except tension headache and migraine; 729 fibrositis, myositis, and muscular rheumatism; and 847 whiplash sprain/strain and other traumas associated with neck).

Control Periods

Using a time-stratified approach, 4 control periods were randomly chosen during the year prior to the stroke for each case.[20] The year was divided into disjoint strata with 2-week intervals between strata because chiropractic care is often delivered in episodes of care, and a 2-week separation in sampling would limit overlap bias associated with time trends in this exposure.[21] The control periods were matched to exposure windows of 1, 3, 7, and 14 days, depending on the hazard period under examination.

Statistical Analysis

We used conditional logistic regression to estimate associations between stroke and healthcare visits. Separate models were built for all visits and for neck or headache-related visits for each different hazard period. A 4-level exposure variable was created: no exposure as the referent, DC only visit, PCP only visit, and both DC and PCP visits. We excluded PCP visits that occurred on the day of the stroke because individuals may have seen their PCPs after their strokes, but prior to hospital admission. Conversely, DC visits on the day of the stroke were included in our analyses.

We built separate models for younger (age <45 years) and older (age ≥45 years) cases based on previous studies indicating an increased risk of stroke after chiropractic care in those less than 45 years of age.[12,13] Separate models were also built for 1-, 3-, 7-, and 14-day exposure periods. We report our results as odds ratios (ORs) with their 95% CIs and bias-corrected bootstrapped CI. We performed contrasts to test whether the ORs for DC visits were significantly different from the comparable ORs for PCP visits (i.e., null hypothesis of equality). All analyses were done using STATA/SE version 12.1.[22]

Results

A total of 15,523 carotid artery stroke cases met our inclusion/exclusion criteria. The mean age of the cases was 69.9 years and 61.4% were male. Only 214 (1.4%) of cases occurred in those less than 45 years of age. There were a lower proportion of men in the younger age group compared with the older age group (48.6% versus 61.6%, respectively). In the 14 days preceding their strokes, 5,433 cases (35%) had received only PCP services, 186 cases (1.2%) had received only DC services, and 116 cases (.7%) had received both services. As expected, older cases had received more services coded for comorbid conditions, and those who saw a DC tended to have fewer comorbidities (Table 2).

Overall, there were few cases exposed to chiropractic care prior to their strokes. Six cases less than 45 years of age saw a chiropractor within 14 days of their strokes, compared to 70 cases who saw a PCP (Table 3). With such few exposed cases in the DC group, it was not possible to bootstrap 95% CI for all estimates (Tables 4 and 5). When considering all DC and PCP visits in those less than 45 years of age, there is an association with stroke for both groups (Table 4). However, there is no significant difference between PCP and DC estimates (i.e., fail to reject the null hypothesis of similar effects for either provider type). There were no younger cases who saw both practitioners less than 7 days before their strokes, and too few cases saw both practitioners in the 7- and 14-day exposure periods to calculate the estimate. For stroke cases 45 years of age and older, there is no positive association with chiropractic care, or with the combination of DC and PCP care. However, there is a consistent but weak association with PCP care in the older group.

When we restricted our analyses to visits that were coded for neck pain and/or headache, the ORs increased considerably for all DC and PCP exposures in those less than 45 years of age, with 1 exception (Table 5). For the exposure period of 3 days before the stroke, both the DC and the PCP estimates were about the same as those for all services for the same exposure period. Again, there is no significant difference between DC and PCP estimates. There were no younger cases who saw both a DC and a PCP. For those more than 45 years of age, the estimates were very similar to those seen when all service visits were considered (Table 5). The odds of seeing a

Table 2. *Age, sex, comorbid conditions, and exposure history of cases*

	Age group			Exposure history during the 14-day hazard period			
Variable (Ontario ICD physician billing codes)	All n = 15,523	<45 years n = 214	≥45 years n = 15,309	None n = 9778	DC only n = 186	PCP only n = 5443	DC and PCP n = 116
Age: mean (SD)	69.6 (9.9)	38.2 (5.8)	70.0 (9.2)	69.6 (9.8)	67.5 (9.9)	69.7 (10.0)	69.6 (9.0)
Men: n (%)	9,529 (61.4)	104 (48.6)	9,425 (61.6)	6,117 (62.6)	122 (65.6)	3,226 (59.3)	64 (55.2)
Hypertension: n (%) (ICD 401, 402, 403)	7,799 (50.2)	37 (17.3)	7,762 (50.7)	4,546 (46.5)	77 (41.4)	3,115 (57.2)	61 (52.6)
Heart disease: n (%) (ICD 410, 412, 413, 426, 427, 428, 429)	8,357 (53.8)	48 (22.4)	8,309 (54.3)	5,059 (51.7)	94 (50.5)	3,135 (57.6)	69 (59.5)
Peripheral vascular diseases: n (%) (ICD 440, 441, 443, 446, 447)	6,516 (42.0)	34 (15.9)	6,482 (42.3)	4,125 (42.2)	79 (42.5)	2,265 (41.6)	47 (40.5)
Diabetes: n (%) (ICD 250)	3,292 (21.2)	17 (7.9)	3,275 (21.4)	1,909 (19.5)	34 (18.3)	1,328 (24.4)	21 (18.1)
Hypercholesterolemia: n (%) (ICD 272)	2,106 (13.6)	15 (7.0)	2,091 (13.7)	1,275 (13.0)	29 (15.6)	784 (14.4)	18 (15.5)
Cerebrovascular diseases: n (%) (ICD 432, 435, 436, 437)	12,609 (81.2)	158 (73.8)	12,451 (81.3)	7,877 (80.6)	146 (78.5)	4,498 (82.6)	88 (75.9)
Obesity: n (%) (ICD 278)	256 (1.7)	8 (3.7)	248 (1.6)	144 (1.5)	Cell sizes less than 6 (cannot be reported)		
Addiction: n (%) (ICD 303, 304, 305)	368 (2.4)	11 (5.1)	357 (2.3)	203 (2.1)	6 (3.2)	153 (2.8)	6 (5.2)
More than or equal to one of the above conditions: n (%)	15,179 (97.8)	182 (85.1)	14,997 (98.0)	9,518 (97.3)	177 (95.2)	5,369 (98.6)	115 (99.1)

Abbreviations: DC, doctor of chiropractic; ICD, International Classification of Diseases; PCP, primary care physician; SD, standard deviation.

Table 3. *Number (n) and percentage (%) of DC and PCP visits before the stroke date*

	Entire cohort		Age <45 years		Age ≥45 years	
Exposures	Cases N = 15,523	Control periods N = 62,092	Cases n = 214	Control periods n = 856	Cases n = 15,309	Control periods n = 61,236
Most recent DC visit						
0-1 day: n (%)	32 (.2%)	238 (.4%)	Cell size less than 6 cannot be reported.			
0-3 days: n (%)	95 (.6%)	570 (.9%)				
0-7 days: n (%)	183 (1.2%)	923 (1.5%)	6 (2.8%)	13 (1.5%)	177 (1.2%)	910 (1.5%)
0-14 days: n (%)	302 (1.9%)	1,418 (2.3%)	6 (2.8%)	15 (1.8%)	296 (1.9%)	1,403 (2.3%)
Most recent PCP visit						
1-1 day: n (%)	670 (4.3%)	1,357 (2.2%)	18 (8.4%)	20 (2.3%)	650 (4.2%)	1,339 (2.2%)
1-3 days: n (%)	1,615 (10.4%)	4,170 (6.7%)	30 (14.0%)	43 (5.0%)	1,585 (10.4%)	4,127 (6.7%)
1-7 days: n (%)	3,295 (21.2%)	9,225 (14.9%)	48 (22.4%)	87 (10.2%)	3,247 (21.2%)	9,138 (14.9%)
1-14 days: n (%)	5,559 (35.8%)	16,553 (26.7%)	70 (32.7%)	193 (22.5%)	5,489 (35.9%)	16,360 (26.7%)

Abbreviations: DC, doctor of chiropractic; PCP, primary care physician.

chiropractor prior to stroke remained below 1 across exposure periods whereas the odds of seeing a PCP were above 1. There were no older cases seen by both practitioners within 1 day of their stroke, and for the other exposure periods, the odds of seeing both practitioners indicate no association with stroke.

Discussion

Our study is the first population-based, controlled study to address the risk of carotid artery strokes after chiropractic care. Using a case-crossover methodology, we have shown an increased association between DC and PCP visits and subsequent hospitalization for strokes coded as occlusion and stenosis of the carotid artery in those less than 45 years of age. Although the point estimates are different for DC and PCP visits, there is no statistical difference between them. Furthermore, these associations increased when analyses were limited to service codes for neck pain and headache-related diagnoses. Taken together, our results suggest that the association between chiropractic care and carotid artery stroke is explained

Table 4. *Odds ratios and 95% CI and bootstrapped 95% CI of the association between DC and PCP visits and carotid stroke for all services*

	Age <45 years (n = 214 cases)		Age ≥45 years (n = 15,309 cases)	
Exposure groups*	Odds ratio (95% CI)	Bootstrapped 95% CI	Odds ratio (95% CI)	Bootstrapped 95% CI
One day before†				
DC only	2.00 (.18-22.06)	‡	.53 (.36-.77)	.36-.77
PCP only	4.95 (2.52-9.72)	2.35-10.46	1.99 (1.81-2.19)	1.80-2.20
Both	No exposures		No exposures	
Three days before				
DC only	6.93 (1.24-38.62)	‡	.59 (.46-.76)	.46-.76
PCP only	3.37 (2.01-5.65)	1.93-5.57	1.62 (1.52-1.73)	1.53-1.73
Both	No exposures		1.04 (.59-1.82)	.56-1.80
Seven days before				
DC only	2.70 (.79-9.24)	.84-13.26	.72 (.59-.89)	.59-.89
PCP only	2.76 (1.83-4.16)	1.73-4.17	1.59 (1.52-1.67)	1.52-1.67
Both	‡	‡	1.15 (.82-1.62)	.81-1.62
Fourteen days before				
DC only	3.14 (.81-12.11)	.45-26.10	.81 (.67-.97)	.68-.96
PCP only	1.97 (1.36-2.84)	1.32-2.86	1.66 (1.59-1.73)	1.59-1.73
Both	‡	‡	1.13 (.90-1.41)	.89-1.43

Abbreviations: CI, confidence interval; DC, doctor of chiropractic; PCP, primary care physician.
*Reference is no exposure.
†Includes the day of the stroke for DC exposures, but only the day before the stroke for PCP exposures (see Methods).
‡Unable to compute because of small numbers.

Table 5. *Odds ratios and 95% CI and bootstrapped 95% CI of the association between DC and PCP visits and carotid stroke for services related to head or neck pain diagnoses*

	Age <45 years (n = 214 cases)		Age ≥45 years (n = 15,309 cases)	
Exposure groups*	Odds ratio (95% CI)	Bootstrapped 95% CI	Odds ratio (95% CI)	Bootstrapped 95% CI
One day before†				
DC only	4.00 (.25-63.95)	‡	.73 (.41-1.30)	.39-1.33
PCP only	8.00 (.73-88.23)	‡	3.72 (2.55-5.42)	2.59-5.61
Both	No exposures		No exposures	
Three days before				
DC only	6.00 (1.06-33.92)	‡	.65 (.47-.90)	.46-.90
PCP only	3.20 (.86-11.92)	.67-20.00	2.56 (2.01-3.27)	1.97-3.20
Both	No exposures		.76 (.09-6.54)	‡
Seven days before				
DC only	8.72 (1.65-46.00)	2.76-23.21	.80 (.63-1.02)	.77-.88
PCP only	4.72 (1.55-14.36)	4.33-8.06	2.15 (1.80-2.57)	2.07-2.40
Both	No exposures	No exposures	.76 (.09-6.50)	‡
Fourteen days before				
DC only	7.41 (1.39-39.67)	3.24-15.23	.75 (.60-.94)	.75-.77
PCP only	6.56 (2.59-16.59)	6.00-16.28	1.86 (1.62-2.12)	1.73-2.10
Both	No exposures	No exposures	1.58 (.56-4.51)	‡

Abbreviations: CI, confidence interval; DC, doctor of chiropractic; PCP, primary care physician.
*Reference is no exposure.
†Includes the day of the stroke for DC exposures, but only the day before the stroke for PCP exposures (see Methods).
‡Unable to compute because of small numbers.

by protopathic bias. In other words, younger patients with an impending carotid artery stroke could be seeking care for dissection-related pain in the head and neck prior to developing stroke. Under this scenario, any care provided by chiropractors or PCPs is coincidental to the stroke and not on the causal pathway.

Another potential explanation of our results is that both DC and PCP care increase the risk of these strokes. However, because PCPs do not usually manipulate the cervical spine, or provide other care that significantly increases the risk of stroke in young people, this explanation is unlikely. It is likely that the weak associations seen between PCP care and stroke in older individuals are due to comorbid disease, as sicker, older individuals are more likely to consult a PCP than a DC.

To our knowledge, there is one other controlled study assessing the association between chiropractic care and carotid dissection-related stroke. Smith et al used 2 Californian academic stroke registries to investigate the relationship between chiropractic treatment and both vertebrobasilar and carotid artery dissection-related strokes.[14,23] Twenty-six carotid dissection-related strokes or transient ischemic attacks were compared to 100 other non–dissection-related strokes using a case–control study design. Although cases were more likely to complain of pain before their ischemic event (OR 4.7; 95% CI 1.7-13.0), the authors reported no significant association with previous cervical spine manipulation. However, the small sample size would have limited their ability to test this relationship.

Headache and neck pain are common presenting symptoms in patients with cervical artery dissection,[9,24] and in some cases are the only presenting symptoms.[25] They are also common and recurrent in the general population.[26,27] Although some ischemic events are preceded by sudden intense neck and/or head pain, in many cases it is less sudden and severe and likely indistinguishable from less serious causes.[24,28] In the absence of neurological signs and symptoms, there are no practical, clinically valid screening tests to identify underlying dissections in patients with head or neck pain.[29] This leaves clinicians who treat these conditions vulnerable to misdiagnosis, providing inappropriate treatment and subsequent malpractice lawsuits.[6] Fortunately, internal carotid artery dissection is rare,[9] but this makes it difficult to study and a challenge to identify in the absence of neurological signs.

A strength of our study is the case-crossover design, which allows better control of time-independent confounding factors, both known and unknown, than the traditional case–control method. As many stroke risk factors are not captured in health administrative data (e.g., smoking, obesity, physical inactivity, genetic susceptibility, and undiagnosed hypertension and connective tissue disorders), our self-controlled design compensates for this. We also measured DC and PCP exposures

independent of case definition by merging separate databases, which would limit diagnostic selection bias.[30] We addressed the issue of protopathic bias by including PCP exposures in our analysis as a measure of the background risk of becoming a case. Our subgroup analysis, which limited visits to diagnostic codes related to conditions that would cause head or neck pain, suggests the presence of protopathic bias. We also found very few cases who had seen both DCs and PCPs during exposure periods, thus limiting misclassification of exposures. We also excluded from our analyses cases who presented to PCPs the day of their stroke hospitalization, but included those who had been seen by a chiropractor. As a result, our findings include acute onset stroke after seeing a chiropractor, but exclude cases seen by a PCP on the day of their strokes. Finally, our study base includes the entire population of Ontario, Canada, over a 9-year period, representing 109,020,875 person-years of observation, and the results should be generalizable to other populations where chiropractic treatment is offered. Nevertheless, because of the small number of exposed cases, we could not bootstrap all our CIs.

There are also limitations with using administrative data. We can not be certain that all chiropractic visits resulted in manipulation to the cervical spine. We were able to exclude visits coded for radiographic examination, and more than 80% of patients seeing chiropractors in Ontario receive spinal manipulation.[4] However, there is potential for visits to be misclassified as cervical spinal manipulation exposures that are not, which could result in an underestimation of the DC–stroke association. In addition, the positive predictive value of our case definition of carotid stroke is not known, raising the potential of misclassification of strokes.[31] However, any misclassification would be nondifferential across exposure groups, which would equally attenuate risk estimates in the PCP and DC groups.[32] Several limitations might bias our estimates in favor of an increased association between stroke and chiropractic care. These include excluding PCP visits on the same day of the stroke from our analysis and diagnostic work-up bias in cases that present to hospital after chiropractic care.[30] Alternatively, there is some evidence that recent infection is associated with cervical artery dissection,[33,34] and patients with infection might be more likely to consult their PCPs than a DC. If this were the case, our estimates of the association between stroke and PCPs would be elevated by selection bias. Finally, our results are based on a small proportion of exposed cases, and this is reflected in our wide CIs.

In conclusion, our study suggests that the association between chiropractic care and carotid artery stroke could be due to care being delivered for dissection-related neck pain and/or headache, prior to the ischemic event. However, stroke is a serious disorder, and all practitioners treating patients with neck pain and headache should be aware that it could occur. Although these events are rare, they can result in serious impairment or death.

References

1. Hagen K, Einarsen C, Zwart JA, et al. The co-occurrence of headache and musculoskeletal symptoms amongst 51 050 adults in Norway. Eur J Neurol 2002;9:527-533.
2. Martin BI, Deyo RA, Mirza SK, et al. Expenditures and health status among adults with back and neck problems. JAMA 2008;299:656-664.
3. Chevan J, Riddle DL. Factors associated with care seeking from physicians, physical therapists, or chiropractors by persons with spinal pain: a population-based study. J Orthop Sports Phys Ther 2011;41:467-476.
4. Hurwitz EL, Coulter ID, Adams AH, et al. Use of chiropractic services from 1985 through 1991 in the United States and Canada. Am J Public Health 1998;88:771-776.
5. Cassidy JD, Bronfort G, Hartvigsen J. Should we abandon cervical spine manipulation for mechanical neck pain? No. BMJ 2012;344:e3680.
6. Haldeman S, Carey P, Townsend M, et al. Arterial dissections following cervical manipulation: the chiropractic experience. CMAJ 2001;165:905-906.
7. Jones J. Neurologists warn about link between chiropractic, stroke. CMAJ 2002;166:794.
8. Biller J, Sacco RL, Albuquerque FC, et al. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3155-3174.
9. Lee VH, Brown RD Jr, Mandrekar JN, et al. Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67:1809-1812.
10. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 2001;344:898-906.
11. Hurwitz EL, Chiang LM. A comparative analysis of chiropractic and general practitioner patients in North America: findings from the joint Canada/United States Survey of Health, 2002-03. BMC Health Serv Res 2006; 6:49.
12. Rothwell DM, Bondy SJ, Williams JI. Chiropractic manipulation and stroke: a population-based case-control study. Stroke 2001;32:1054-1060.
13. Cassidy JD, Boyle E, Cote P, et al. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. Spine 2008;33:S176-S183.
14. Smith WS, Johnston SC, Skalabrin EJ, et al. Spinal manipulative therapy is an independent risk factor for vertebral artery dissection. Neurology 2003;60:1424-1428.
15. Kosloff TM, Elton D, Tao J, et al. Chiropractic care and the risk of vertebrobasilar stroke: results of a case-control study in U.S. commercial and Medicare Advantage populations. Chiropr Man Therap 2015;23:19.
16. Engelter ST, Grond-Ginsbach C, Metso TM, et al. Cervical artery dissection: trauma and other potential mechanical trigger events. Neurology 2013;80:1950-1957.
17. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med 1980;68: 255-258.
18. Korhonen MJ, Huupponen R, Ruokoniemi P, et al. Protopathic bias in observational studies on statin effectiveness. Eur J Clin Pharmacol 2009;65:1167-1168.

19. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144-153.
20. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. Am J Epidemiol 1995;142:91-98.
21. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. Epidemiology 2005;16:717-726.
22. StataCorp. Stata base reference manual. 12th ed. College Station, Texas: Stata Press, 2011.
23. Chung CL, Cote P, Stern P, et al. The association between cervical spine manipulation and carotid artery dissection: a systematic review of the literature. J Manipulative Physiol Ther 2015;38:672-676.
24. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 2009;8:668-678.
25. Arnold M, Cumurciuc R, Stapf C, et al. Pain as the only symptom of cervical artery dissection. J Neurol Neurosurg Psychiatry 2006;77:1021-1024.
26. Côté P, Cassidy JD, Carroll LJ, et al. The annual incidence and course of neck pain in the general population: a population-based cohort study. Pain 2004;112:267-273.
27. Boardman HF, Thomas E, Croft PR, et al. Epidemiology of headache in an English district. Cephalalgia 2003;23:129-137.
28. Thomas LC, Rivett DA, Attia JR, et al. Risk factors and clinical features of craniocervical arterial dissection. Man Ther 2011;16:351-356.
29. Kerry R, Taylor AJ, Mitchell J, et al. Cervical arterial dysfunction and manual therapy: a critical literature review to inform professional practice. Man Ther 2008;13:278-288.
30. Boyle E, Cote P, Grier AR, et al. Examining vertebrobasilar artery stroke in two Canadian provinces. Spine 2008;33:S170-S175.
31. Cai X, Razmara A, Paulus JK, et al. Case misclassification in studies of spinal manipulation and arterial dissection. J Stroke Cerebrovasc Dis 2014;23:2031-2035.
32. Cassidy JD, Cote P. Re: Cai et al, Case misclassification in studies of spinal manipulation and arterial dissection (letter). J Stroke Cerebrovasc Dis 2015;24:901-902.
33. Guillon B, Berthet K, Benslamia L, et al. Infection and the risk of spontaneous cervical artery dissection: a case-control study. Stroke 2003;34:e79-e81.
34. Rubinstein SM, Peerdeman SM, van Tulder MW, et al. A systematic review of the risk factors for cervical artery dissection. Stroke 2005;36:1575-1580.