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The association between cervical artery dissection and spinal manipulation among US adults

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Abstract

Purpose—Cervical artery dissection (CeAD), which includes both vertebral artery dissection (VAD) and carotid artery dissection (CAD), is the most serious safety concern associated with cervical spinal manipulation (CSM). We evaluated the association between CSM and CeAD among US adults.

Methods—Through analysis of health claims data, we employed a case–control study with matched controls, a case–control design in which controls were diagnosed with ischemic stroke, and a case-crossover design in which recent exposures were compared to exposures in the same case that occurred 6–7 months earlier. We evaluated the association between CeAD and the 3-level exposure, CSM versus office visit for medical evaluation and management (E&M) versus neither, with E&M set as the referent group.

Results—We identified 2337 VAD cases and 2916 CAD cases. Compared to population controls, VAD cases were 0.17 (95% CI 0.09 to 0.32) times as likely to have received CSM in the previous week as compared to E&M. In other words, E&M was about 5 times more likely than CSM in the previous week in cases, relative to controls. CSM was 2.53 (95% CI 1.71 to 3.68) times as likely as E&M in the previous week among individuals with VAD than among individuals experiencing a stroke without CeAD. In the case-crossover study, CSM was 0.38 (95% CI 0.15 to 0.91) times as likely as E&M in the week before a VAD, relative to 6 months earlier. In other words, E&M was approximately 3 times more likely than CSM in the previous week in cases, relative to controls. Results for the 14-day and 30-day timeframes were similar to those at one week.

Conclusion—Among privately insured US adults, the overall risk of CeAD is very low. Prior receipt of CSM was more likely than E&M among VAD patients as compared to stroke patients. However, for CAD patients as compared to stroke patients, as well as for both VAD and CAD

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patients in comparison with population controls and in case-crossover analysis, prior receipt of E&M was more likely than CSM.

Keywords

Cervical artery dissection; Vertebral artery dissection; Carotid artery dissection; Spinal manipulation; Chiropractic

Introduction

Cervical artery dissection (CeAD) can occur in either the carotid or vertebral arteries. CeAD occurs when deterioration of the arterial lining allows blood to penetrate and accumulate between the layers of the arterial wall. The dissection and associated thrombus can occlude the artery, or the thrombus may embolize and cause an ischemic stroke [1, 2]. Patients with CeAD may be asymptomatic, but frequently present with neck pain or headache. CeADs are uncommon, with a reported annual incidence rate of 1.72 per 100,000 population for carotid artery dissection (CAD) and 0.97 per 100,000 population for vertebral artery dissection (VAD) [3], accounting for approximately 2% of all ischemic strokes [4, 5]. However, the incidence of CeADs appears to be increasing in recent years, possibly due to increased sensitivity and utilization of imaging technologies [6]. Blunt or penetrating trauma may lead to CeAD but the etiology of spontaneous CeAD is unclear [7, 8]. A systematic review of the risk factors for CeAD found strong associations between CeAD-associated stroke and 'trivial trauma' in the form of manipulation of the cervical spine (adjusted OR = 3.8, 95% CI = 1.3–11.0) [9], making CeAD the most serious safety concern associated with cervical spinal manipulation (CSM).

CAD is generally more common than VAD, although there is a reported 3:1 predominance of VADs over CADs following CSM [10]. It has been hypothesized that CSM may cause VAD through rotation and extension of the neck that stretches the vessel where it penetrates either the atlas or posterior atlanto-occipital membrane [11]; however, no direct evidence has been found to support this hypothesis. A retrospective review of medical legal cases of stroke temporally associated with CSM found no apparent dose–response relationship between CSM and CeAD [12]. A case–control study of 165 patients < 50 years old with ischemic strokes found that headache and neck pain were associated with diagnosis of CeAD [13]. Thus, an alternative hypothesis for the association between CSM and VAD is that the onset of neck pain may represent a dissection in progress, causing a patient to seek CSM.

CSM is a common treatment for neck pain. The task-force on neck pain and its associated disorders recommend CSM for managing neck pain in older adults [14]. Other clinical practice guidelines recommend SMT for management of neck pain [15], neck pain-associated disorders [16], and headache associated with neck pain [17]. However, the American Heart Association (AHA) and the American Stroke Association (ASA) have issued recommendations that patients should be informed of the association between CSM and CeAD [18]. The true risk of CeAD related to CSM remains unclear and a rigorous examination of the potential relationship between CSM and CeAD is warranted. However,

a recent systematic review found that much larger sample sizes would be required to fully assess the safety of CSM and noted that observational studies on CSM for neck pain are "important for building the evidence base in which randomized trials are lacking or are insufficient for the task" [19]. Because CeAD is rare, assessing risk of CeAD via an interventional study would be prohibitively expensive; a case–control design offers a feasible approach. The current availability of very large datasets of private health insurance claims presents an opportunity to conduct analyses with sufficient power to better quantify the risk of CeAD associated with CSM.

In this study, to better inform US policymakers, providers, and patients, we analyzed claims data spanning a nine-year period, and employed case–control and case-crossover designs to evaluate the association between CSM and CeAD among privately insured US adults aged 18+ . Previous studies of the association between CSM and CeAD have been criticized regarding choice of control groups [2]. Because there is no obvious best choice of controls, we used three different control groups to assess the sensitivity of results to choice of control, and given the observational nature of the data, we employed advanced statistical approaches to control for potential confounding.

Methods

Design

We hypothesized that the explanation for the association between CSM and CeAD is that the onset of neck pain may represent a dissection in progress, causing a patient to seek CSM. We followed the STROBE statement as a guideline for conducting observational research. We examined the association between CSM and CeAD using three observational designs; (1) a case–control study with matched controls from a general population of insurance beneficiaries; (2) a case–control design in which controls were all individuals diagnosed with an ischemic stroke but without associated CeAD; and (3) a case-crossover design, in which exposures that occurred at 2 weeks and 30 days prior to diagnosis of CeAD are compared to exposures in the same person 6 months earlier.

Population

The study population consists of adults (18 and up) who were insured by a health insurance provider that contributed health claims data to the Health Care Cost Institute (HCCI) for the years 2007–2015. The HCCI data warehouse consists of de-identified administrative claims data from multiple healthcare settings on approximately 40 million individuals each year. We included all individuals with at least one claim in a calendar year during each of two consecutive years.

The cases

The primary outcome was the occurrence of a CeAD diagnosed as either (1) vertebral artery dissection (VAD) or (2) carotid artery dissection (CAD). The cases were identified as beneficiaries with a new (not recorded in the prior year) diagnosis of International Classification of Disease (ICD-9) code 443.24 (VAD) or 443.21 (CAD) in the primary

diagnosis field on at least one inpatient hospital claim, or the primary/secondary diagnosis for outpatient hospital claims on at least two separate days.

The controls

There were three different groups of controls. For population controls, we matched beneficiaries without CeAD, which we refer to as population controls, to the CeAD cases in a 10:1 ratio. Controls were matched for age (in years), sex, and having at least one claim within one week of the case. Controls were excluded if they ever had a diagnosis of CeAD. For the ischemic stroke controls, we identified beneficiaries with a diagnosis code for non-CeAD-associated ischemic stroke (ICD-9 codes 431, 432, 434, 433.10, or 433.11) in the primary diagnosis field on at least one inpatient hospital claim or primary/secondary diagnosis for outpatient claims on at least two separate days. For the case-crossover study, we abstracted claims services for the cases that occurred in the same individuals 6–7 months prior to diagnosis of CeAD.

Index date

The index date is defined as the date of diagnosis of CeAD in the cases, as the corresponding date in the population controls, and as the date of diagnosis of ischemic stroke in the stroke controls. In the case-crossover analysis, the index date for the control period is 180 days prior to the occurrence of CeAD.

Exposures

The primary exposure was CSM, as identified by Current Procedural Terminology (CPT) codes 98940-98942 (indicating spinal manipulation by a doctor of chiropractic) associated with a primary diagnosis of headache (ICD-9 code 339. xx) or neck pain (ICD-9 codes 721.0, 721.1, 722.0, 722.4, 722.71, 722.81, 722.91, 723.1-723.8, 739.1, 756.16, 839.0x, 847.0, 953.0, or 953.4) or other disorders of the head or neck pain that are commonly treated by spinal manipulation (ICD-9 codes 739.1, 723.1, 739.0, 722.4, 839.xx, 723.3, 847.0, or 839.00) in order to try to localize the manipulation to the cervical region. The comparison was the occurrence of an encounter for Evaluation and Management (E&M) as indicated by ICD-9 codes 99201-99205 and 99211-99215 with the same associated diagnoses discussed above.

We created a 3-level categorical variable for the exposure, (i) CSM, (ii) E&M but no CSM and (iii) neither CSM nor E&M. The E&M only category is used as the referent group, i.e., the odds of CeAD in individuals who received CSM are compared to the odds of CeAD in individuals who received E&M (but no CSM).

Timeframes for the exposure

We created the 3-level exposure described above for each of the following time frames, up to 7, 14 and 30 days prior to the index event. For instance, for the 7-day time window, the 3-level categorical exposure is (i) CSM in the 7 days before index, (ii) E&M but no CSM in the 7 days before index, and (iii) neither CSM nor E&M in the 7 days before index.

Covariates

Covariates included demographics age, sex and calendar year (race was not available). To capture comorbidities, we considered all diagnoses 14 to 365 days preceding the index date, grouped using the Multi-level Clinical Classification Software (CCS) of the Healthcare Cost and Utilization Project [20]. ICD-9 codes were grouped into categories using the third level of the multi-level classification.

Statistical methods

We calculated odds ratios to quantitate the association between CeAD and the 3-level exposure, CSM versus E&M versus neither, with E&M set as the referent group. To control for the covariates described above, we applied multivariable logistic regression to the dataset consisting of CeAD cases and ischemic stroke controls. To control for covariates in the analysis comparing CeAD cases to matched population controls we used multivariable conditional logistic regression. The conditional logistic regression estimates the odds ratios conditional on the sex-age-year matches, in addition to race and diagnostic covariates. Sex, age and calendar year therefore have null coefficients due to matching on them.

Due to large number of diagnostic covariates (over 430), we used variable selection methods. To select predictors of CeAD cases, we employed least absolute shrinkage and selection operator (LASSO) for logistic models. We employed tenfold cross-validation to determine the LASSO penalty parameter based on optimization of the binomial deviance (analogous to log-likelihood). To select predictors of CeAD cases versus population controls that accounts for matching by sex, age and year, we employed stepwise conditional logistic regression (we are not aware of a LASSO adaptation to conditional logistic regression). This approach to covariate selection served to identify any comorbidities that predict diagnosis of CeAD and are potential confounders.

We tested if there was an association of the exposure (CSM vs. E&M vs. neither) with CeAD in the case-crossover analysis using conditional logistic regression conditioning on subject (e.g., the pair of observations from CeAD and 6 months earlier).

All analyses above were repeated for each of the three time-windows for exposure to CSM and E&M (7, 14 and 30 days). That is, we report odds ratios that (i) compare CSM to E&M but no CSM and (ii) compare neither CSM nor E&M to E&M (but no CSM) exposure in each of these time periods.

As an additional analysis, we employed a propensity score approach to estimate the odds ratio relating CeAD to CSM. This consisted of the following steps. Using data from the population controls, we modeled the occurrence of CSM in the 7 days before index as a function of demographics and comorbidities using logistic regression. The predicted probabilities (fitted values) from this logistic regression were used to calculate the inverse weighted propensities. The final step was to employ a weighted logistic regression to estimate the odds ratio relating VAD (or CAD) to CSM in the previous 7 days.

Statistical software employed was R (including libraries, tidyverse, & glmnet) as well as SAS 9.4. The project protocols were reviewed and approved by the Committee for Protection of Human Subjects, Dartmouth College.

Minimal detectable odds ratio

Our study, which utilized all cases of CeAD in a panel of over 300 million person-years, was powered (at 80%) to detect odds ratios of 1.30 or more for the association of VAD with CSM in the previous week (approximate prevalence of 2/1000) relative to E&M (approximate prevalence of 1/1000) in the 10:1 matched population case–control. The corresponding minimal detectable odds ratio for the association of CAD with CSM relative to E&M is 1.28. The detectable odds ratios using the Ischemic stroke controls are slightly smaller as we had more than 10 of those controls per CAD case.

Results

We identified 2337 VAD cases and 2916 CAD cases. Males and females were approximately equally represented among the CAD and VAD cases. The 45–54 age group had the highest number of VAD cases (24%) and CAD cases (29%). Table 1 shows sex and age groupings for the cases, population-matched controls and ischemic stroke controls.

Compared to population-matched controls, individuals experiencing a VAD were 0.17 (95% CI 0.09 to 0.32) times as likely to have had a CSM in the previous week than they were to have had an E&M. In other words, E&M was about 5 times more likely than a CSM in the previous week in cases, relative to controls. (Table 2) Similarly, CSM was less likely in the previous 14 and 30 days relative to E&M in cases compared to controls, as shown in Table 2. The odds of CAD in individuals undergoing a CSM in the previous week were 0.08 (95% CI 0.04 to 0.16) times the odds of E&M in the previous week. In other words, E&M was approximately 10 times more likely than CSM in the previous week in cases relative to controls. The corresponding odds ratios for the 14- and 30-day timeframes were similar. Using an inverse weighted propensity approach, the odds of VAD in individuals who received CSM in the previous week were 0.10 (95% CI 0.05 to 0.22) times as likely as those who received E&M in the previous week. The corresponding odds ratio for CAD was 0.09 (95% CI 0.04 to 0.22). Thus, using an inverse weighted propensity approach for both VAD and CAD, E&M was approximately 10 times more likely than CSM in the previous week in cases relative to controls. There was no evidence that the relative effects of CSM versus E&M on CeAD were different between individuals less than age 65 and those 65 and over ($P > 0.10$).

Table 3 shows the findings when cases are compared to ischemic stroke controls. CSM was 2.53 (95% CI 1.71 to 3.68) times as likely as E&M in the previous week among individuals experiencing a VAD than among individuals experiencing a stroke without CeAD. This relative increased likelihood of CSM was also observed for the 14- and 30-day periods as shown in Table 3. CSM was not significantly more likely ($P = 0.23$) than E&M in the previous week when CAD cases were compared to the ischemic stroke controls, nor was it in the 14- and 30-day periods.

Table 4 reports the results of the case-crossover study. CSM was 0.38 (95% CI 0.15 to 0.91) times as likely as E&M in the week before a VAD, relative to the week 6 months earlier. In other words, E&M was approximately 3 times more likely than CSM in the previous week in cases relative to controls. For the corresponding 14-day and 30-day timeframes, CSM was also significantly less likely ($P = 0.003$ and $P < 0.001$ respectively) than E&M. For CAD, the odds of receiving CSM were 0.29 (95% CI 0.13 to 0.68) times as likely as receiving E&M in the previous week compared to the corresponding period 6 months earlier. Thus, for both CAD and VAD, E&M was approximately 3 times more likely than CSM in the previous week in cases relative to controls. This decreased odds of CeAD in those receiving CSM relative to E&M were also observed in the 2-week ($P < 0.001$) and 4-week periods ($P < 0.001$).

Table 5 displays multivariable adjusted odds ratios by age subgroup (< 65 years; > = 65 years) comparing VAD and CAD with ischemic stroke controls at the 30-day time window. Among patients aged 18–65, the risk of VAD was significantly higher for CSM as compared to E&M (OR 2.37; 95% CI 1.74–3.20). This finding was nearly identical to the findings for the full cohort, while the OR for the over 65 group was somewhat lower at 1.7 and was not statistically significant; however, the test for interaction showed no significant difference in result between the two age groups. For both older and younger patients with either CAD or VAD, the OR was significantly lower among those who received neither CSM nor E&M, as compared to recipients of E&M.

Discussion

Prior to this research project, the largest study of the association of CSM with CeAD consisted of 966 cases [21]. In this study, the sample size was more than five times as large at 5253, providing a statistical advantage for studying an uncommon condition [22]. The pattern of reduced risk associated with neither CSM nor E&M is consistent with the hypothesis that patients may be seeking out treatment for neck related symptoms leading up to their diagnosis of CeAD.

Multiple approaches to analysis failed to demonstrate any consistent increased risk of CeAD associated with CSM and in fact showed a significantly decreased risk of CSM compared to E&M in the population controls and case-crossover analyses. The one exception was that prior receipt of CSM was more likely than E&M among VAD patients as compared to ischemic stroke patients; these results were similar when examined between subgroups aged over and under 65 years old. In a prior analysis using Medicare Claims for beneficiaries aged 65+, we found no significant difference in the odds of CSM versus E&M among VAD patients compared to ischemic stroke controls [23]. Given the reduced risk seen compared to the population controls and in the case-crossover analyses, it is difficult to attribute the increased risk compared to ischemic stroke controls to a direct causal effect of CSM. The results were very sensitive to choice of controls, perhaps due to differences in the underlying burden of vascular disease and its associated healthcare seeking behaviors. As can be seen in Table 2, more of the population controls sought CSM for neck pain as compared to E&M. Table 3 however illustrates an opposite pattern of patient care seeking: more of the ischemic stroke controls sought E&M (conventional medical evaluation) as compared to CSM. Thus,

patients with a greater underlying burden of vascular disease and comorbidity were more likely to seek medical attention for their neck pain, as compared to the general population with neck pain, and these patterns of care-seeking behavior influenced the odds ratios reported in Tables 2 and 3. Even if we posit a direct effect of CSM on the risk of CeAD compared to ischemic stroke, the overall risk of CeAD remains very low. The incidence of VAD is estimated to be about 1 per 100,000 person-years, which is equivalent to 1 per 5 million person-weeks. Thus, if CSM increased the risk of CAD threefold in the week following a CSM, this risk increases from 1 to 3 per 5 million, or an absolute (additive) increase of 2 in 5 million, and the number of CSM treatments needed to result in VAD in the following week would be approximately 2.5 million. Given the potential for stroke following CeAD, the effect of each case is potentially devastating. However, for purposes of informed clinical decision-making, clinicians and patients should interpret estimates of comparative risk in the context of incidence.

Among previous studies, only four [21, 24–26] were large enough to inform the AHA/ASA position paper on the association between CSM and CeAD [18]. These studies have been criticized for controls which, although age- and sex-matched, were much healthier than the cases [27]. Further, the two largest studies were based on the same dataset from the 1990s, which may have misidentified CeAD [28]. While these two studies found a strong relationship between CSM and posterior circulation stroke among patients aged 45 or younger, a temporal association of CSM preceding stroke was not demonstrated; moreover, a lack of adjustment for comorbidities may have obscured a similar relationship in older patients. In the present study, we controlled for diagnostic groups based upon patient comorbidities and leveraged the statistical power of analyzing a multi-year claims dataset. Moreover, by using E&M visit for cervical spine related issues as the main comparator, we controlled for the potential tendency for patient with early or impending dissection to seek treatment for the associated symptoms, with either a physician or a chiropractor.

Our findings therefore strongly suggest that the association between CSM and CeAD is not causal in nature. It is more likely that in the period leading up to their diagnosis of CeAD, patients with neck pain and related symptoms seek out care from a CSM provider, a medical provider or both, rather than having a specific risk for CeAD imparted by receipt of CSM.

Limitations

General limitations of using health claims data for research include inconsistencies in billing practices and coding of procedures. Because there is no procedure code specific to CSM, we identified CSM as spinal manipulation in patients with neck pain and related diagnoses. Because this was a retrospective study, the subjects were not randomized and there may have been systematic differences between the groups. However, we minimized confounding through use of advanced statistical methods intended to control for differences between groups.

Conclusions

Among privately insured US adults, the overall risk of CeAD is very low. Prior receipt of CSM was more likely than E&M among VAD patients as compared to stroke patients.

However, for CAD patients as compared to stroke patients, as well as for both VAD and CAD patients in comparison with population controls and in case-crossover analysis, prior receipt of E&M was more likely than CSM.

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Table 1

Age and sex of cervical artery dissection cases and controls

	VAD (*n* = 2337)	VAD-Matched population controls (*n* = 23,343)	CAD (*n* = 2916)	CAD-matched population controls (*n* = 29,107)	Stroke controls (*n* = 376,338)
Age (Years)					
18–24	62 (2.65%)	620 (2.66%)	66 (2.26%)	660 (2.27%)	1188 (0.32%)
25–34	333 (14.25%)	3330 (14.27%)	173 (5.93%)	1730 (5.94%)	3179 (0.84%)
35–44	542 (23.19%)	5420 (23.23%)	539 (18.48%)	5390 (18.52%)	10,691 (2.84%)
45–54	561 (24.01%)	5605 (24.02%)	856 (29.36%)	8542 (29.35%)	31,413 (8.35%)
55–64	397 (16.99%)	3965 (16.99%)	623 (21.36%)	6224 (21.38%)	63,264 (16.81%)
65–74	232 (9.93%)	2313 (9.91%)	354 (12.14%)	3521 (12.10%)	94,654 (25.15%)
75–84	158 (6.76%)	1561 (6.69%)	238 (8.16%)	2370 (8.14%)	109,703 (29.15%)
85 +	52 (2.23%)	519 (2.22%)	67 (2.30%)	670 (2.30%)	62,246 (16.54%)
Sex					
Female	1132 (48.44%)	11,317 (48.48%)	1438 (49.31%)	14,346 (49.29%)	194,750 (51.75%)
Male	1205 (51.56%)	12,026 (51.52%)	1478 (50.69%)	14,761 (50.71%)	181,588 (48.25%)

VAD, vertebral artery dissection; CAD, carotid artery dissection

Table 2

Association of cervical artery dissection with cervical spinal manipulation relative to E&M using 10:1 sex- and age-matched population controls

	Vertebral artery dissection				Carotid artery dissection			
	***n* controls**	***n***	**Odds ratio (95% CI)**	***p*-value**	***n* controls**	***n***	**Odds ratio (95% CI)**	***p*-value**
Exposure Past 7 days								
E&M Only	27	113	Ref.		30	114	Ref.	
Any CSM	60	47	0.17 (0.09, 0.32)	< 0.001	69	25	0.08 (0.04, 0.16)	< 0.001
Neither CSM nor E&M	23,256	2177	0.02 (0.01, 0.04)	< 0.001	29,008	2777	0.03 (0.02, 0.04)	< 0.001
Exposure Past 14 days								
E&M Only	61	168	Ref.		67	197	Ref.	
Any CSM	95	63	0.27 (0.17, 0.43)	< 0.001	34	34	0.09 (0.06, 0.16)	< 0.001
Neither CSM nor E&M	23,187	2106	0.04 (0.03, 0.05)	< 0.001	28,919	2685	0.04 (0.03, 0.05)	< 0.001
Exposure Past 30 days								
E&M Only	109	223	Ref.		146	268	Ref.	
Any CSM	155	80	0.32 (0.22, 0.47)	< 0.001	185	48	0.16 (0.10, 0.24)	< 0.001
Neither CSM nor E&M	23,079	2034	0.06 (0.05, 0.08)	< 0.001	28,776	2600	0.07 (0.06, 0.09)	< 0.001

E&M, evaluation and management; Ref, referent group; CI, confidence interval

Table 3

Association of cervical artery dissection with cervical spinal manipulation relative to E&M using ischemic stroke controls

	n controls	Vertebral artery dissection			Carotid artery dissection		
		n	**Odds ratio (95% CI)**	***p*-value**	***n***	**Odds ratio (95% CI)**	***p*-value**
Exposure past 7 days							
E&M Only	4248	113	Ref.		114	Ref.	
Any CSM	829	47	2.53 (1.71, 3.68)	< 0.001	25	1.32 (0.82, 2.05)	0.23
Neither CSM nor E&M	371,261	2177	0.41 (0.33, 0.50)	< 0.001	2777	0.47 (0.39, 0.58)	< 0.001
Exposure past 14 days							
E&M Only	7451	168	Ref.		197	Ref.	
Any CSM	1372	63	2.35 (1.68, 3.23)	< 0.001	34	1.10 (0.73, 1.60)	0.65
Neither CSM nor E&M	367,515	2106	0.48 (0.40, 0.57)	< 0.001	2685	0.49 (0.42, 0.57)	< 0.001
Exposure past 30 days							
E&M Only	12,628	223	Ref.		268	Ref.	
Any CSM	2191	80	2.22 (1.66, 2.93)	< 0.001	48	1.15 (0.82, 1.59)	0.4
Neither CSM nor E&M	361,519	2034	0.57 (0.49, 0.67)	< 0.001	2600	0.60 (0.52, 0.69)	< 0.001

E&M, evaluation and management; Ref, referent group; CI, confidence interval

Table 4

Association of CAD with CSM relative to E&M using case-crossover design

	Vertebral artery dissection		Carotid artery dissection	
	Odds ratio (95% CI)	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Exposure past 7 days				
E&M Only	Ref.		Ref.	
Any CSM	0.38 (0.15, 0.91)	0.031	0.29 (0.13, 0.68)	0.004
Neither CSM nor E&M	0.10 (0.05, 0.18)	< 0.001	0.16 (0.10, 0.26)	< 0.001
Exposure past 14 days				
E&M Only	Ref.		Ref.	
Any CSM	0.33 (0.16, 0.69)	0.003	0.21 (0.10, 0.43)	< 0.001
Neither CSM nor E&M	0.10 (0.06, 0.17)	< 0.001	0.14 (0.09, 0.21)	< 0.001
Exposure past 30 days				
E&M Only	Ref.		Ref.	
Any CSM	0.32 (0.18, 0.60)	< 0.001	0.26 (0.14, 0.48)	< 0.001
Neither CSM nor E&M	0.12 (0.08, 0.18)	< 0.001	0.15 (0.11, 0.22)	< 0.001

E&M, evaluation and management; Ref, referent group; CI, confidence interval

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Table 5

Association of cervical artery dissection with cervical spinal manipulation relative to E&M, by age category in the population-matched case–control

Age	Visit type	Vertebral artery dissection		Carotid artery dissection	
		Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
< 65	E&M Only	Ref.		Ref.	
	Any CSM	2.37 (1.74, 3.20)	< 0.001	1.19 (0.83, 1.68)	0.32
	Neither CSM nor E&M	0.59 (0.50, 0.70)	< 0.001	0.57 (0.49, 0.67)	< 0.001
≥65	E&M Only	Ref.		Ref.	
	Any CSM	1.70 (0.71, 3.69)	0.2	0.87 (0.29, 2.07)	0.77
	Neither CSM nor E&M	0.44 (0.29, 0.68)	< 0.001	0.53 (0.38, 0.79)	< 0.001

CSM, exposure to cervical spine manipulation within 30 days prior to diagnosis; E&M, exposure to evaluation and management within 30 days prior to diagnosis; Ref, referent group; CI, confidence interval