Original Research

RISK OF STROKE AFTER CHIROPRACTIC SPINAL MANIPULATION IN MEDICARE B BENEFICIARIES AGED 66 TO 99 YEARS WITH NECK PAIN



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Abstract

Objective: The purpose of this study was to quantify risk of stroke after chiropractic spinal manipulation, as compared to evaluation by a primary care physician, for Medicare beneficiaries aged 66 to 99 years with neck pain. Methods: This is a retrospective cohort analysis of a 100% sample of annualized Medicare claims data on 1 157 475 beneficiaries aged 66 to 99 years with an office visit to either a chiropractor or primary care physician for neck pain. We compared hazard of vertebrobasilar stroke and any stroke at 7 and 30 days after office visit using a Cox proportional hazards model. We used direct adjusted survival curves to estimate cumulative probability of stroke up to 30 days for the 2 cohorts. **Results:** The proportion of subjects with stroke of any type in the chiropractic cohort was 1.2 per 1000 at 7 days and 5.1 per 1000 at 30 days. In the primary care cohort, the proportion of subjects with stroke of any type was 1.4 per 1000 at 7 days and 2.8 per 1000 at 30 days. In the chiropractic cohort, the adjusted risk of stroke was significantly lower at 7 days as compared to the primary care cohort (hazard ratio, 0.39; 95% confidence interval, 0.33-0.45), but at 30 days, a slight elevation in risk was observed for the chiropractic cohort (hazard ratio, 1.10; 95% confidence interval, 1.01-1.19).

Conclusions: Among Medicare B beneficiaries aged 66 to 99 years with neck pain, incidence of vertebrobasilar stroke was extremely low. Small differences in risk between patients who saw a chiropractor and those who saw a primary care physician are probably not clinically significant. (J Manipulative Physiol Ther 2015;38:93-101) Key Indexing Terms: Stroke; Spinal Manipulation, Adverse Effects; Neck Pain; Chiropractic; Vertebral Artery Dissection; Medicare

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Risk of Stroke After Spinal Manipulation

regarding the safety of cervical spine manipulation.²



anipulation of the cervical spine is a treatment for neck pain often performed by chiropractic physicians, but the safety of cervical spine manipulation has been questioned because observational studies have linked cervical spine manipulation to vertebral artery dissection and subsequent vertebrobasilar stroke (VBS).¹⁻³ A considerable amount of controversy persists

Vertebrobasilar stroke is an uncommon type of stroke, with a reported population incidence of 0.97 cases per 100 000.⁵ The likelihood of VBS after spinal manipulation has been examined in 3 studies using case-control designs, an approach well suited to the evaluation of rare conditions such as VBS. Smith et al³ compared patients with ischemic stroke or transient ischemic attack, with and without vertebral artery dissection, and concluded that spinal manipulation is an independent risk factor for vertebral artery dissection. Rothwell

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et al² studied 582 cases of VBS and found that patients with stroke younger than 45 years were 5 times more likely than controls to have visited a chiropractor within 1 week of the stroke. Cassidy et al¹ also found an increased association between chiropractic visits and vertebrobasilar artery stroke in patients younger than 45 years, but the association was no greater than that associated with visits to primary care physicians. Taken together, the results of these case-control studies constitute the strongest evidence regarding the association between spinal manipulation and VBS.

More subject to bias in favor of a stronger association with spinal manipulation was an observational study of 1897 subjects conducted by Engelter et al,⁶ who used a questionnaire to assess for "prior cervical trauma." Spinal manipulation was found to be a determinant of cervical (vertebral or carotid) artery dissection but not an independent risk factor. Also with greater potential for bias—in either direction—was the use of an ecological study design by Boyle et al,⁷ who found that marked increases in the rates of VBS in 2 Canadian provinces in 2000 were unassociated with increased utilization of chiropractic services.

Several recent systematic reviews on the safety of chiropractic care and spinal manipulation have been largely inconclusive with regard to risk of adverse events in general and stroke in particular. In 2005, Rubinstein et al⁸ evaluated risk factors for cervical artery dissection. They found strong associations for "trivial trauma" (including spinal manipulation) but conducted no meta-analysis. They urged caution with regard to attributing cervical artery dissection to spinal manipulation, pending further research.⁸ In 2007, in a systematic review on the adverse effects of spinal manipulation, Ernst⁹ concluded that spinal manipulation can cause vertebral artery dissection, but in 2012, a replication of that review found numerous errors and omissions that threatened its validity.¹⁰ A review of the safety of chiropractic interventions published in 2009 found no robust data on the incidence of adverse reactions after chiropractic care. Estimates of the risk of serious adverse events such as stroke ranged from 0.05 to 1.46 per 10 000 000 manipulations.¹¹ A systematic review published in 2010 was also unable to draw any conclusions regarding the risk of adverse events associated with manipulation of the cervical spine for care of neck pain in adults.¹² Similarly, a review published in 2012 found the evidence inadequate to either confirm or refute a significant association between manipulation of the cervical spine and stroke.¹³

Age as a Risk Factor for VBS After Spinal Manipulation

Efforts to identify either risk factors or populations at risk for VBS have been largely unsuccessful.^{14,15} The risk of stroke in general increases with age,¹⁶ but it is not known how age might affect the risk of stroke after spinal manipulation.¹⁷ Current best knowledge of the risk of stroke temporally associated with spinal manipulation in older patients is based upon the work of Rothwell et al² and Cassidy et al,¹⁸ who

collectively found only 53 patients older than 45 years with stroke after spinal manipulation, of a total of 1400 cases of VBS. Rothwell et al analyzed 582 cases of VBS and found no significant association between VBS and chiropractic care for those 45 years and older. Cassidy et al analyzed 818 cases of VBS, stratified by age, and also found no association between VBS and chiropractic care for those 45 years and older.¹ Subsequently, Choi et al¹⁷ examined patient demographic data in 3 case series and 3 surveys on characteristics of patients with stroke after spinal manipulation. Where reported, mean patient age in these studies ranged from 34.0 years $(n = 10)^{19}$ to 44 years (n = 74).²⁰ However, Choi et al¹⁷ found a population at risk that was significantly older than that previously reported: in a population-based case series of 93 patients with VBS who had visited a chiropractor in the previous year, mean patient age was 57.6 years.

Risk of Stroke After Chiropractic Spinal Manipulation in Elderly US Adults

No population-based studies of risk of stroke after spinal manipulation have been conducted in the United States or focused upon older adults. In this study, we sought to answer the research question: "In Medicare beneficiaries aged 66-99 with neck pain, what is the probability of stroke following chiropractic spinal manipulation, as compared to a control group of subjects evaluated for neck pain by a primary care physician?" Among Medicare beneficiaries aged 66 to 99 years, we hypothesized no difference in risk of stroke between those exposed to chiropractic spinal manipulation for neck pain and those exposed to evaluation by a primary care physician for neck pain. Because chiropractors frequently treat neck pain with spinal manipulation and the temporal association between provider office visits and stroke has been observed to be stronger in patients with neck pain,¹⁸ we limited our sample to beneficiaries with neck pain. (Choi et al¹⁷ found that among 93 patients with VBS and a chiropractic visit within the previous year, the most common comorbidities [reported by 67%] were neck pain and headache.) An understanding of the relationship between spinal manipulation and stroke among US Medicare beneficiaries should help facilitate the safe and appropriate utilization of chiropractic care for neck pain in older adults. Thus, the purpose of this study was to quantify risk of stroke after chiropractic spinal manipulation, as compared to evaluation by a primary care physician, for Medicare beneficiaries aged 66 to 99 years with neck pain.

Methods

The Dartmouth College Committee for Protection of Human Subjects reviewed and approved the research plan. This study was supported by the National Institutes of Health under Award Number K01AT005092.

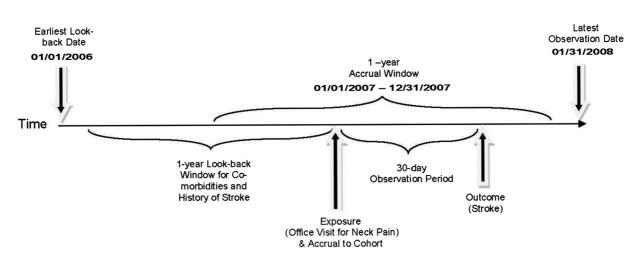


Fig 1. Cohort accrual.

Data Sources and Sampling

We conducted a retrospective cohort study using Medicare administrative data. Our data sources were 100% of *Denominator* files (for beneficiary demographics), *Carrier* files (for outpatient claims), and *MEDPAR* files (for inpatient claims) for the years 2006 to 2008. The data files were merged on unique beneficiary identifiers to generate the analytic files.

Cohort Definition

Each included beneficiary was assigned to 1 of 2 cohorts, in which beneficiaries with neck pain used either chiropractic care or primary care exclusively:

Chiropractic cohort: Beneficiaries with at least 1 allowed Medicare B claim in 2007 for chiropractic office visit with spinal manipulation, identified as claim with provider specialty code number 35, with current procedural terminology code for spinal manipulation (98940, 98941, or 98942), but without a primary care office visit for neck pain in 2007.

Primary care cohort: Beneficiaries with at least 1 allowed Medicare B claim in 2007 for primary care office visit for evaluation and management, but without a chiropractic office visit for neck pain in 2007. (Primary care visits were identified as claims associated with the provider specialty code for family medicine [08], internal medicine [11], or general practice [01].) Evaluation and management services were identified by *BETOS Code* "M".

Exposures

We included all beneficiaries covered under the Medicare B fee for service plan, aged 66 to 99 years, and living as of January 1 of each year, with at least 1 allowed Medicare B claim in 2007 for an office visit associated with

a diagnosis of neck pain to either a chiropractor or primary care physician. Neck pain was identified by any of the following International Classification of Diseases, Ninth Revision (ICD-9), codes: 721.0, 721.1, 722.0, 722.4, 722.71, 722.81, 722.91, 723.0, 723.1, 723.2, 723.3, 723.5, 723.7, 723.8, 723.9, 739.1, 756.16, 756.2, 839.00, 839.01, 839.02, 839.03, 839.04, 839.05, 839.06, 839.07, 839.08, 847.0, 953.0, or 953.4. We excluded duplicate claims for the same patient, provider, procedure, and date of service. We also excluded beneficiaries with a previous history of cerebrovascular disease (in Part A or Part B data) at any time during the 1-year period before the date of first exposure and accrual to cohort. Prior cerebrovascular disease was identified by any of the following codes for stroke (ICD-9 430, 431, 432-432.9, 433-433.9, 434-434.9, 436, 437.1, 443.21, 443.24, or 900-900.9), transient cerebral ischemia (ICD-9 435-435.9), or late effects of cerebrovascular diseases (ICD-9 438-438.9). A 1-year look back window from first exposure to office visit for neck pain and accrual to cohort served to exclude beneficiaries with a recent history of cerebrovascular disease and to calculate Charlson comorbidity scores for risk adjustment (Fig 1). The Charlson comorbidity index is a validated prognostic tool based upon the risk of mortality associated with a range of comorbid chronic diseases. For each patient, individual conditions are assigned scores, which are summed to provide a total score.

Medicare allows coverage for chiropractic spinal manipulation of up to 5 spinal regions (cervical, thoracic, lumbar, sacral, and pelvic). It is not possible to specifically identify manipulation of the cervical spine through analysis of Medicare data because the procedure codes for chiropractic spinal manipulation identify the number of spinal regions manipulated but not the specific spinal regions at which the manipulations were performed. However, Medicare does require that the level at which the manipulation is performed

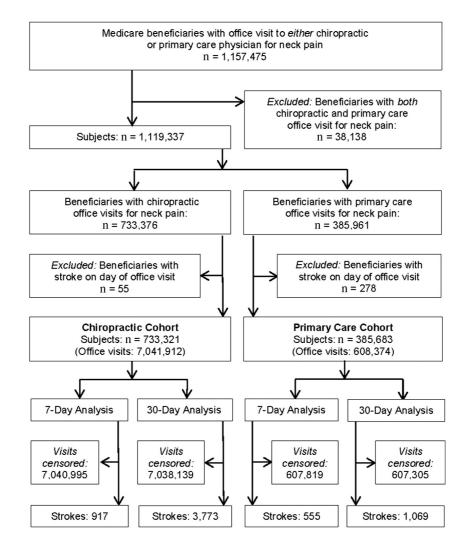


Fig 2. Exclusions and censoring.

must be tied to the patient's complaint.²¹ Therefore, assuming compliance with Medicare clinical practice guidelines, a patient complaint of neck pain should be associated with the delivery of cervical spine manipulation.

Outcomes Measurement

The hazard (observation) period for identifying outcomes was a 30-day window after each exposure to an office visit for neck pain. We set the hazard period at 30 days to allow for comparison of our results with the findings of previous reports.¹ The primary outcome measure was VBS within 30 days of office visit for neck pain. However, because of the potential for bias resulting from the imprecise use of diagnosis codes in claims data, we also analyzed for any type of stroke. We identified stroke by *ICD-9* codes 430, 431, 432–432.9, 433-433.9, 434-434.9, 436, 437.1, 443.21, 443.24, or 900-900.9, recorded in hospital emergency department or inpatient claims. We categorized strokes as VBS and non-VBS-identifying VBS by diagnosis code 433.00, 433.01, 433.20, or 433.21-all other stroke codes were categorized as non-VBS. As a secondary outcome measure, among those diagnosed with stroke, we also evaluated for death within 30 days of office visit. For each successive office visit, we evaluated for days to diagnosis of stroke and censored the previous visit. Subjects were removed from follow-up upon occurrence of their first stroke. Evaluation of risk by office visit allowed comparison of risk between cohorts while allowing for the high degree of variability in number, frequency, and timing of office visits. For analysis of hazard of stroke within 30 days, we excluded subjects who were hospitalized for stroke on the same day as the office visit because these patients likely presented with signs or symptoms of stroke (Fig 2). The data used in this study were analyzed in accordance with a data user agreement with The Centers for Medicare and Medicaid

Table I. Subject Characteristics

Cohort	Chiropractic	Primary Care	Difference (A-B)	95% CI
Subjects	733 321	385 683	347 638	
Office visits for neck pain	7 041 912	608 374	6 433 538	
Subjects with stroke	3773	1069	2704	
Age in years				
% 66-69	29.27	24.25	5.02 ^a	4.84-5.19
% 70-74	29.16	25.45	3.71 ^a	3.54-3.88
% 75-79	21.46	21.99	-0.53 ^a	-0.69 to -0.37
% 80-84	12.83	16.22	-3.39 ^a	-3.52 to -3.25
% 85-99	7.27	12.08	-4.80 ^a	-4.92 to -4.39
% Male	38.77	33.57	5.20 ^a	5.02-5.39
Race				
% White	96.62	86.98	9.63 ^a	9.54-9.74
% Black	1.41	6.98	-5.56 ^a	-5.64 to -5.47
% Other	1.96	6.04	-4.08^{a}	-4.15 to -4.01
Mean Charlson comorbidity score	0.92	1.29	-0.37 ª	-0.38 to -0.36

CI, confidence interval.

^a P < .05.

Services. Rules for the conduct of Medicare-approved research projects stipulate that specific quantities may not be disclosed if the unit of observation contains less than 11 subjects.

Analysis

We initially measured incidence of first stroke after exposure to office visit and analyzed for 30-day mortality after stroke. We compared the hazard of stroke within 30 days between patients visiting chiropractors and those visiting primary care physicians, using a Cox proportional hazards model. The model was adjusted for subject age, sex, race and Charlson comorbidity index. We used the same approach to estimate the hazard ratio of stroke within the first 7 days (by right censoring all subjects at 7 days). To estimate the cumulative probability of stroke up to 30 days for the chiropractic and primary care physician groups while adjusting for the covariates stated above, we used direct adjusted survival curves, as described by Zhang et al.^{22,23} We performed data analyses in SAS (SAS Institute, Inc, Cary, NC).

Results

We found 1 157 475 Medicare beneficiaries with an office visit to either a chiropractic or primary care physician for neck pain (Fig 2). Of these, 38 138 (3%) had seen both types of providers: we excluded these subjects from the study population, thus creating 2 mutually exclusive cohorts of chiropractic and primary care patients. We excluded 55 patients (7.5 per 100 000) from the chiropractic cohort and 278 patients (72 per 100 000) from the primary care cohort who were diagnosed with stroke on the same day as an office visit for neck pain. The chiropractic cohort (n = 733 321) was nearly twice as large as the primary care cohort (n = 385 683), and the number of chiropractic office visits (7 041 912) was more than 11 times greater than the number of primary care office visits (608 374).

The 2 cohorts also differed with regard to age, sex, race, and comorbidity score (Table 1). The chiropractic cohort was younger, with a significantly greater proportion of subjects younger than 75 years and a lesser proportion older than 80 years. The chiropractic cohort also was composed of a higher proportion of males and significantly lower proportions of blacks and other minorities. The chiropractic cohort appeared to be healthier than the primary care cohort, as indicated by a significant difference in Charlson comorbidity scores (0.92 vs 1.29; difference, -0.37; 95% confidence interval [CI] -0.38 to -0.36).

The specific incidence of VBS was too small to report and thus precluded further analysis. The proportion of subjects with stroke of any type in the chiropractic cohort was 1.2 per 1000 at 7 days after office visit for neck pain and 5.1 per 1000 at 30 days. In the primary care cohort, the proportion of subjects with stroke of any type was 1.4 per 1000 at 7 days after office visit for neck pain and 2.8 per 1000 at 30 days (Fig 2). Among subjects who sustained any type of stroke, there was no significant difference in 30-day mortality between cohorts (chiropractic cohort, 9.65%; primary care cohort, 9.1%; difference, 0.52%; 95% CI, -1.88to 2.93).

From the day after office visit (day 1) to day 24, the probability of stroke was lower in the chiropractic cohort as compared to the primary care cohort (2 vs 7 strokes per 100 000 subjects, respectively, at day 1; 110 vs 111 strokes per 100 000 subjects, respectively, at day 24). However, on days 25 to 30, the probability of stroke for the chiropractic cohort exceeded that for the primary care cohort (116 vs 115 strokes per 100 000 subjects, respectively, at day 25; 162 vs 134 strokes per 100 000 subjects, respectively, at day 25; 162 vs 134 strokes per 100 000 subjects, respectively, at day 30). Figure 3 illustrates the adjusted probability of stroke for the 2 cohorts over the 30-day hazard period. The unadjusted hazard ratio for the chiropractic cohort vs the primary care cohort was 0.33 (95% CI, 0.28-0.37) at 7 days

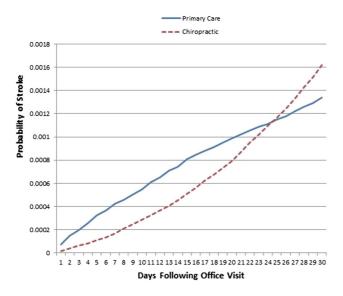


Fig 3. Adjusted probability of stroke over the first 30 days after office visit for neck pain. Day 1 = Day after the day of office visit.

and 0.91 (95% CI, 0.85-0.99) at 30 days. With adjustment for differences in patient characteristics, however, hazard ratios at days 7 and 30 (Table 2) reflected the crossover effect illustrated in Figure 3. In the chiropractic cohort, risk of stroke was significantly lower at 7 days as compared to the primary care cohort (hazard ratio, 0.39; 95% CI, 0.33-0.45), but at 30 days, a slight but statistically significant elevation in risk was observed for the chiropractic cohort (hazard ratio, 1.10; 95% CI, 1.01-1.19). Male sex, increasing age category, and increased Charlson comorbidity score were all associated with increased risk of stroke in the study population.

Discussion

Because risk of stroke in general increases with age, understanding the relationship between cervical spine manipulation and stroke and in older adults will help assure the safe utilization of chiropractic care in this vulnerable population. This is the first study to focus upon the risk of stroke after spinal manipulation in older adults, so the results are not directly comparable to previous studies, but our results are consistent with reports by Rothwell et al² and Cassidy et al,²⁴ which suggest that VBS is uncommon in older adults. Aging may be protective against VBS stroke, as compared to other types of stroke. With regard to risk of any type of stroke, we found that increasing age category was associated with increased risk of any type of stroke, consistent with morbidity data published by The National Institutes of Health.²⁵

The specific incidence of VBS was too low to report, but the incidence was less than 9.8 per million Medicare part B beneficiaries aged 66 to 99 years with office visit for neck pain. This result is remarkably consistent with the incidence rate of 9.7 cases of VBS per 1 000 000 population reported by Lee et al.⁵ Because vertebral artery dissection and associated thromboembolism are the most plausible mechanism by which spinal manipulation could cause stroke, our findings support current best evidence suggesting that manipulation of the cervical spine is unlikely to be a significant cause of stroke in older adults.^{1,26,27}

Blacks, Hispanics, and Native Americans are known to be at higher risk for stroke than Asians and non-Hispanic whites,²⁸ and the lack of effect of race in this study is most likely due to the fact that minorities were underrepresented in the study population because minorities comprise only 3% to 4% of chiropractic users under Medicare.²⁹ The increased risk associated with increased Charlson comorbidity score is likely due to the well-established increased risk of stroke associated with cardiovascular disease, diabetes, and previous history of cerebrovascular disease.²⁸

We found that the probability of any type of stroke on the day of office visit (day 0) was much lower in the chiropractic cohort as compared to the primary care cohort. With exclusion of strokes that occurred on the same day of office visit, the adjusted probability of stroke remained lower in the chiropractic cohort until day 25, when relative risk was reversed and remained higher in the chiropractic cohort for the remainder of the hazard period. At day 0, the higher probability of stroke in the primary care cohort may have been due to a propensity to seek medical rather than chiropractic care among patients with neck pain who also had other symptoms potentially related to stroke. The differences between cohorts in the timing of the diagnosis of stroke may also be related to differences in diagnostic practices between chiropractic and primary care physicians. Song et al³⁰ reported that significant differences in physician's diagnostic practices may be unrelated to patient characteristics. The observed between-cohort differences in probability of stroke may be due to earlier and more aggressive diagnostic testing practices among primary care physicians as compared to chiropractic physicians. It is possible that the short-term increase in hazard of stroke in the primary care cohort was associated with increased treatment of neck pain with nonsteroidal anti-inflammatory drugs, which have been linked to increased risk of ischemic stroke.³¹ Although a purely speculative observation, investigation of this potential association may be indicated.

Regardless of the reason for the observed differences, with the exclusion of same-day strokes, the maximum observed effect size (observed at day 15) was an additional risk of 3 strokes per 10 000 office visits for the primary care cohort. Although statistically significant, this difference as well as the crossover effect seen in Figure 3 may not be clinically significant. The lack of a mechanism by which an office visit might cause a non-VBS stroke and the decreasing likelihood of a causal relationship over 30 days also cast doubt upon the clinical significance of these between-cohort differences in results.

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	7 d			30 d	
	Hazard Ratio	95% CI		Hazard Ratio	95% CI
Chiropractic (vs primary care)	0.39 ^a	0.33	0.45	1.10 ^a	1.01-1.19
Male sex (vs female)	1.44 ^a	1.27	1.62	1.37 ^a	1.29-1.45
Age category (vs 66-69)					
70-74	1.29 ^a	1.04	1.60	1.16 ^a	1.04-1.29
75-79	1.90 ^a	1.54	2.34	1.93 ^a	1.74-2.14
80-84	3.03 ^a	2.46	3.742	2.50 ^a	2.25-2.78
85+	3.70 ^a	2.96	4.63	3.59 ^a	3.21-4.00
Race (vs white)					
African American	1.21	0.85	1.71	1.2	0.99-1.46
Other	1.11	0.79	1.57	1.03	0.85-1.25
Charlson comorbidity score	1.08 ^a	1.05	1.12	1.13 ^a	1.11-1.15

CI, confidence interval.

^a P < .05.

The true probability of stroke is probably unaffected by an office visit to either type of provider and likely resides between the 2 trend lines seen in Figure 3. Chiropractic physicians must be able to recognize symptoms of stroke to provide early detection and when necessary refer patients for appropriate treatment.²⁴ In a retrospective case series, 6 of approximately 500 active chiropractic patients presented with symptoms and signs of stroke.³² Among respondents to a survey of 2000 randomly selected US chiropractors, first recognition of undiagnosed life-threatening conditions, including stroke, reportedly occurred in the normal course of practice at a rate of 1 case every 2.5 years.³³

Limitations

In designing this study, we strove to reduce bias due to inaccurate diagnostic coding by including any type of stroke as an outcome of interest (despite the lack of evidence for a relationship between spinal manipulation and stroke other than VBS), but it is possible that our analysis may have been biased by an underrepresentation in claims data of the true incidence of VBS. However, patients presenting to a hospital with symptoms of stroke and a recent history of visiting a chiropractor may be subjected to a more aggressive workup for VBS, and consequent bias toward increased diagnosis of VBS.7 Therefore, because diagnostic misclassification in the chiropractic cohort is more likely to result in more claims for VBS rather than fewer, we are confident that our results do not significantly underestimate the risk of VBS stroke in this study population. The results for the chiropractic cohort reflect the risk of stroke after chiropractic spinal manipulation, not that after all clinical encounters with chiropractors, who routinely screen patients for contraindications to spinal manipulation and withhold manipulation from those perceived as being at risk.²¹ Finally, because not all Medicare beneficiaries are enrolled in Medicare Part B, the subjects did not represent a random sample of older US

adults. However, the study population does represent the population of older US adults who are eligible to receive chiropractic services under Medicare Part B, and the very large sample size of more than 1 million subjects provided the analysis with high statistical power.

Conclusions

This is the first population-based study in the United States on risk of stroke after spinal manipulation and the first such study to focus on older adults. Among Medicare B beneficiaries aged 66 to 99 years with neck pain, the incidence of vertebrobasilar stroke was too low to allow further analysis. Chiropractic cervical spine manipulation is unlikely to cause stroke in patients aged 66 to 99 years with neck pain. For patients who saw a chiropractic physician, the adjusted probability of any type of stroke was lower than those who saw a primary care physician at days 1 through 24 after office visit, but higher at days 25 to 30, but these temporal associations are of doubtful clinical significance.

Practical Applications

- Among Medicare B beneficiaries aged 66 to 99 years with neck pain, the incidence of vertebrobasilar stroke was extremely low.
- Among subjects with stroke, there was no difference in mortality between cohorts.
- In the chiropractic cohort, the adjusted risk of stroke was significantly lower at 7 days as compared to the primary care cohort, but at 30 days, a slight elevation in risk was observed for the chiropractic cohort.

Funding Sources and Potential Conflicts of Interest

This study was supported by the National Institutes of Health under award number K01AT005092. No conflicts of interest were reported for this study.

Contributorship Information

Concept development (provided idea for the research); J.W. Design (planned the methods to generate the results); J.W., T.L.

Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript); J.W., J.L., R.P., T.L.

Data collection/processing (responsible for experiments, patient management, organization, or reporting data); J.W., Y.S.

Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results); J.W., Y.S., T.M., R.P.

Literature search (performed the literature search); J.W. Writing (responsible for writing a substantive part of the manuscript); J.W., T.M.

Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking); J.W., J.L., Y.S., T.M., T.L., R.P.

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