Case Misclassification in Studies of Spinal Manipulation and Arterial Dissection

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Background: Spinal manipulation has been associated with cervical arterial dissection and stroke but a causal relationship has been questioned by population-based studies. Earlier studies identified cases using International Classification of Diseases Ninth Revision (ICD-9) codes specific to anatomic stroke location rather than stroke etiology. We hypothesize that case misclassification occurred in these previous studies and an underestimation of the strength of the association. We also predicted that case misclassification would differ by patient age. *Methods:* We identified cases in the Veterans Health Administration database using the same strategy as the prior studies. The electronic medical record was then screened for the word "dissection." The presence of atraumatic dissection was determined by medical record review by a neurologist. *Results:* Of 3690 patients found by ICD-9 codes over a 30-month period, 414 (11.2%) had confirmed cervical artery dissection with a positive predictive value of 10.5% (95% confidence interval [CI] 9.6%-11.5%). The positive predictive value was higher in patients less than 45 years of age vs 45 years of age or older (41% vs 9%, $P < .001$). We reanalyzed a previous study, which reported no association between spinal manipulation and cervical artery dissection (odds ratio [OR] = 1.12, 95% CI .77-1.63) and recalculated an odds ratio of 2.15 (95% CI .98-4.69). For patients less than 45 years of age, the OR was 6.91 (95% CI 2.59-13.74). *Conclusions:* Prior studies grossly misclassified cases of cervical dissection and mistakenly dismissed a causal association with manipulation. Our study indicates that the OR for spinal manipulation exposure in cervical artery dissection is higher than previously reported. **Key Words:** Stroke—stroke prevention—risk factor—spinal manipulation.

Spinal manipulation therapy (SMT) is administered to 8% of American adults annually.[1] It is associated with adverse neurologic outcomes including cervical artery dissection (CAD) and stroke.[2–4] The magnitude of risk has been estimated at a high of 1 in 958 manipulations[5] to a low of 1 in 5.85 million manipulations.[6] The causal link between SMT and CAD has been questioned.[7] In 2001, a large case-control study by Rothwell et al[8]

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demonstrated an association between posterior circulation stroke and chiropractic visits in patients less than 45 years of age but found no relationship in those who were 45 years of age or older. In 2008, Cassidy et al replicated Rothwell's results and also demonstrated an association between case status and visits to primary care physicians (PCP). Cassidy suggested that the observed associations are because of reverse causation bias whereby patients with dissections seek treatment from chiropractors or PCPs for dissection-related symptoms like neck pain.

In the earlier studies, cases were identified by using *International Classification of Diseases Ninth Revision* (ICD-9) codes that were specific for a neurovascular location (posterior circulation) rather than codes for a vascular diagnosis (dissection). As a result, they likely classified patients with stroke due to conventional mechanisms described in posterior circulation registries as their cases. Assuming that this case misclassification was random with respect to SMT exposure, it is likely that both the Rothwell and the Cassidy studies underestimated the association between dissection risk and SMT.[9] Furthermore, it is known that patients with vascular risk factors will have more frequent contact with their PCPs.[10] If the cases in the Cassidy study were mostly patients with atherosclerosis, then an association with PCP visits is expected. Finally, given the higher prevalence of dissection as a stroke mechanism in younger patients (those <45 years) and the increased prevalence of atherosclerosis with age more than 40,[11–13] we hypothesized that the extent of case misclassification would differ by patient age, with older patients more likely to be misclassified than younger ones. We sought to evaluate the magnitude of case misclassification in the Rothwell/Cassidy studies by employing their ICD-9–based case identification strategy followed by refined case assessment with detailed medical record review to identify those with true CAD overall and within age strata (<45 years and ≥45 years).

Materials and Methods

By accessing the encounter diagnosis table in the clinical data warehouse we identified all patients in the Veterans Health Administration (VA) electronic medical record (EMR), a population of 15,779,020 veterans, with ICD-9 codes used by the Rothwell/Cassidy studies for the period January 2009 to August 2011[8,14] (Table 1). The earlier studies omitted the dissection-specific codes (443.xx) in their case definition because they were not in use in Ontario at the time (*personal communication, Navin Goocool, April 30, 2013*). The population in our study did have these codes available, and therefore, to avoid an overestimation of case misclassification, we included the 3 additional dissection codes in our initial EMR query ("modified Rothwell/Cassidy strategy"). The entire record of each patient associated with one of those 8 ICD-9 codes was then searched for the presence of the word "dissection" in the EMR using Medical Domain Web Services. Available sources included discharge summaries, radiology reports, consultation notes, outpatient records, and any other record containing text. A study physician then reviewed the extracts from the EMR that included the word "dissection" to determine whether a vertebral or carotid dissection had been diagnosed. The adjudication was supplemented by reviewing neuroimaging studies and other EMR records as needed. Data collected included patient age at the time of the index event and the location of a dissection if present (vertebral, carotid, or both). The definition of atraumatic CAD used during the record review was a clinical presentation consistent with dissection, no competing stroke diagnoses, and confirmation of dissection following appropriate confirmatory investigations. *Atraumatic* was defined as not associated with vertebral fracture in the cervical spine. *Clinical presentation consistent with dissection* includes any of the following: asymptomatic, sudden onset meningismus secondary to subarachnoid hemorrhage, new onset headache or asymmetric neck pain, lower cranial neuropathy, Horner syndrome, and cerebral or retinal ischemia (transient ischemic attack or stroke). We estimated the proportion of ICD-9–detected cases likely to be true CAD events (positive predictive value) with corresponding 95% confidence intervals (CIs) in the entire population and within strata by age (<45 and ≥45 years). Information about exposure to SMT for individual patients was not available in the VA database and was not collected.

To anticipate the impact of misclassification on prior epidemiologic studies of SMT and CAD, we conducted a sensitivity analysis by applying the positive predictive

Table 1. *ICD-9 codes and definitions*

ICD-9 codes	Definition
Codes used in Rothwell/Cassidy studies	
433.00	Occlusion and stenosis of basilar artery without cerebral infarction
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.20	Occlusion and stenosis of vertebral artery without cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
900.9	Injury to unspecified blood vessel of head and neck
Additional dissection-specific codes	
443.21	Dissection of carotid artery
443.24	Dissection of vertebral artery
443.29	Dissection of other artery

Abbreviation: ICD-9, International Classification of Diseases Ninth Revision.