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# Association between cervical spondylosis and migraine: A nationwide retrospective cohort study

**Running Head:** Cervical spondylosis and migraine

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**Conflict of Interest**

All authors report no conflicts of interest.

**Abbreviations:**

CS: cervical spondylosis; HR: hazard ratio; CI: confidence interval; NHIRD: National Health Insurance Research Database; LHID2000: Longitudinal Health Insurance Database 2000; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

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**Abstract**

**Background:** Few studies have investigated the longitudinal association between cervical spondylosis (CS) and migraine by using a nationwide population-based database.

**Methods:** We conducted a retrospective cohort study from 2000 to 2011 identifying 27,930 cases of cervical spondylosis and 111,720 control subjects (those without cervical spondylosis) from a single database. The subjects were frequency-matched on the basis of sex, age, and diagnosis date. The non- cervical spondylosis cohort was four times the size of the cervical spondylosis cohort. To quantify the effects of cervical spondylosis on the risk of migraine, univariate and multivariate Cox proportional hazard regression analyses were used to calculate the hazard ratio (HR) and 95% confidence interval (CI).

**Results:** After a 10-year follow-up controlling for potential confounding factors, overall migraine incidence was higher in the cervical spondylosis cohort than in the non- cervical spondylosis cohort (5.16 and 2.09 per 1,000 people per year, respectively; crude hazard ratio = 2.48, 95% confidence interval = 2.28–2.69) with an adjusted hazard ratio of 2.03 (95% confidence interval = 1.86–2.22) after accounting for sex, age, comorbidities, and medication. Individuals with myelopathy in the cervical spondylosis cohort had a 2.19 times (95% confidence interval = 1.80–2.66) higher incidence of migraine compared than did those in the non- cervical spondylosis cohort.

**Conclusion:** Individuals with cervical spondylosis exhibited a higher risk of migraine than those without cervical spondylosis. The migraine incidence rate was even higher among individuals with cervical spondylotic myelopathy.

**Keywords:** cervical spondylosis; migraine; retrospective cohort study, population-based

## Introduction

Migraine is the most prevalent and incapacitating neurovascular disorder worldwide, affecting approximately one billion people, exerting a considerable impact on quality of life, and representing a significant socioeconomic burden[1-3]. The pathophysiology of migraines is largely unknown. Speculated origins of pain are cortical neuronal hyperexcitability[4], modulatory dysfunction of brainstem and diencephalic systems[5], and peripheral activation[6], all of which lead to the release of vasoactive neuropeptides in the trigeminovascular system to process pain[7,8].

Although many hypotheses regarding migraine triggers have been proposed, the significance of causal relationships between triggers is obscured[9,10]. Among these triggers, cervical pathologies may initiate the sequence of events that results in migraine symptoms. The extensive functional convergence of upper cervical spinal cord from the descending fibers in the trigeminal nucleus caudalis, which terminates within the trigeminocervical nucleus, and the afferent fibers from the upper cervical roots, which communicate in this region, accounting for the bi-directional pathway of pain between the neck and head. This interaction refers the cervical pathologies to the head, which is the activity also proposed to cause cervicogenic headache.[11]. Constantly noxious cervical afferent irritation via this pathway is a possible key element causing migraines.

Neck pain and muscle tension are common migraine symptoms and both could be sequelae of neck injuries according to the musculoskeletal anatomy[11,12]. Moreover, administering multiple injections in targeted head and neck regions is sometimes considered important for the management of migraines, cervicogenic headaches, and myofascial referred pain[11,13-16], indicating that headache and neck pain may share some

common pathways.

Although a previous report indicated that cervical spondylosis (CS) accounts for 15.9% of migraineurs[17], until now epidemiological evidence of a link between CS and the risk of migraine is minimal. Therefore, we conducted this nationwide retrospective cohort study to investigate the longitudinal causal relationship between CS and migraines and CS severity in relation to the risk of developing migraine.

## Methods

### Data Source

The data used in this retrospective study was retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000) of Taiwan, a subdataset of the National Health Insurance Research Database (NHIRD) that comprises 1,000,000 randomly selected people from the NHIRD. The NHIRD of Taiwan contains the detailed health care data of more than 99% of the Taiwanese population (more than 23.74 million residents)[18]. The LHID2000 has been successfully applied in numerous studies[19,20]. The present study based diagnosis on codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

### Ethics Statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions.

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Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR2). The IRB also specifically waived the consent requirement.

**Data Availability Statement**

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

**Sampled Participants**

We selected individuals aged ≧18 years diagnosed with CS without (ICD-9-CM code 721.0) or with (ICD-9-CM code 721.1) myelopathy from 2000 to 2010 as the CS cohort. The CS diagnosis date was defined as the index date. Control subjects (non-CS cohort) were randomly selected from the LHID2000 and matched with the CS cohort at a 4:1 ratio on the basis of sex, age (measured in 5-year spans), and year of CS diagnosis. Participants in both cohorts with previous migraine diagnoses (ICD-9-CM code 346) were excluded.

**Outcome and Comorbidities**

We followed the participants in the CS and non-CS cohorts until migraine diagnoses were made or the participants were censored because of withdrawal from the National Health Insurance (NHI) program or until December 31, 2011. Pre-existing comorbidities for each individual included hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2–296.3, 300.4, 311), coronary artery disease (ICD-9-CM codes 410–414), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, 309.81), sleep disorders (ICD-9-CM codes 307, 780.5), irritable bowel syndrome (ICD-9-CM code 564.1), diabetes (ICD-9-CM code 250), and fibromyalgia (ICD-9-CM code 729.1).

**Statistical Analysis**

Demographic factors including sex and age and comorbidities were compared between the CS and non-CS cohorts by conducting a Chi-square test for the categorical variables and Student's *t* test for the continuous variables. Cumulative incidences of migraines in both cohorts were compared using the Kaplan-Meier method and variations between the two cohorts were compared using a log-rank test. We calculated the incidence rate of migraines based on various risk factors and stratified the results based on sex, age, and comorbidities. Univariate and multivariate Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the influence of CS on the risk of migraine. The multivariate Cox models were adjusted for age, sex, and the comorbidities of hypertension,

hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, and fibromyalgia. In addition, the relative risk of migraine development stratified based on sex, age, and comorbidities in both cohorts was analyzed for comparison. All statistical analyses were conducted using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

**Results**

The CS and non-CS cohorts comprised 27,930 and 111,720 cases of migraine, respectively. Among all the participants, 56.9% were women and 73.7% were aged under 64 years (Table 1). The mean ages of both cohorts were 44.8 ± 16.6 (CS) and 44.5 ± 16.8 years (non-CS). The CS cohort exhibited higher prevalence of all baseline comorbidities. During the mean follow-up of 6.13 (standard deviation (SD) = 3.19) years for the CS cohort and 6.07 (SD = 3.20) years for the non-CS cohort, the cumulative incidence of migraines was higher among individuals with CS than those without (log-rank test $p <$ 0.001) (Figure 1).

The migraine incidence rates were 5.16 and 2.09 per 1,000 people per year in the CS and non-CS cohorts, respectively (Table 2). The risk of migraine was higher in the CS cohort than in the non-CS cohort (adjusted HR (aHR) = 2.03, 95% CI = 1.86–2.22). Compared with individuals aged ≥65 years, individuals aged 20–49 years (aHR = 1.81, 95% CI = 1.58–2.06) and 50–64 years (aHR = 1.40, 95% CI = 1.24–1.58) had a higher risk of developing migraine. The aHR values revealed that the risk of developing migraine was 1.92 times higher among women than men. The multivariate Cox model

revealed that the risk of migraine was higher among individuals with the comorbidities of hypertension, hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, diabetes, and fibromyalgia.

The incidence and risk of migraine in both cohorts were compared based on the variables of sex, age, and comorbidities (Table 3). For all variables, the risk of migraine remained higher in the CS cohort than those in the non-CS cohort.

Table 4 shows the incidence and aHR values of migraine associated with different various forms of CS. The participants with myelopathy in the CS cohort exhibited a 2.19 times higher risk of migraine (95% CI = 1.80–2.66) than those in the non-CS cohort, whereas those without myelopathy exhibited a 2.01 times higher risk in the CS cohort (95% CI = 1.83–2.20).

## Discussion

This study is the first to use a population-based database to demonstrate the long-term risk of migraine in individuals with CS. The primary findings support our hypothesis that individuals with CS are at a higher risk of developing migraine than those without CS. The cumulative migraine frequency at the conclusion of the follow-up period was higher in the CS cohort than in the non-CS group. The migraine rates among 1,000 people per year were 5.16 and 2.09 in the CS and non-CS cohorts, respectively. Moreover, the CS cohort exhibited a 2.03 times higher risk of migraine (95% CI = 1.86–2.22) than the non-CS cohort. Furthermore, in the CS cohort, the participants with myelopathy were at a higher risk of developing migraine than those without myelopathy.

Cervical musculoskeletal abnormalities and headache disorders were a bi-directional comorbidity, with nearly two-thirds of migraineurs coexisted with neck pain or stiffness, and one-fifth of patients with cervicogenic headache in pain clinics[21,22]. Previous studies have disclosed that almost 90% patients with headache accepted anterior cervical operation for the treatment of symptoms with cervical myelopathy or radiculopathy[23,24]. Furthermore, the authors observed that patients with headache disorders presented the myofascial trigger points, clear-cut areas of muscle tenderness and posture changes, compared with non-headache control[21,25]. Thus, our results corroborate those of previous studies on the linking between cervical spine disorder and migraine, emphasizing the importance of assessment for migraine at first and follow-up period in CS patients due to the increasing risk for the development of migraine.

Regarding the effects of age and gender on migraine development, our results correlate with those of previous studies[3,26], which have demonstrated that young and middle-aged women with CS develop migraine more easily than do other individuals. Adjustments for the factors of sex, age, hypertension, hyperlipidemia, depression, anxiety, sleep disorders, coronary artery disease, irritable bowel syndrome, and fibromyalgia achieved statistical significance. Only the result of diabetes was insignificant. Although CS is an age-related disorder affecting the discs and vertebrae of the cervical spine, notably, the HR of the migraine occurrence did not increase with age[27]. First, we assumed that the inflammatory effects of the nucleus rather than the degenerative factor in female adults aged under 50 years might play a role in migraine development[27]. Persistent peripheral nociceptive impulses may induce neuroplastic changes in the spinal cord and brain, causing central sensitization and pain. Therefore, the

combination of tonic nociceptive input and central disinhibition may play a role in migraine development[28]. In vivo, a slow progressive cord irritation resulted in complement-mediated response, contributing to the synapse destruction, neuronal and oligodendrocyte death[29,30]. Moreover, recent imaging advances also demonstrated that patients with more severe CS correlated with higher inflammation volumes[31]. The findings indicated that inflammatory cascade might serve the potential molecular mechanisms underlying the pathogenesis of cervical spondylotic myelopathy, leading to migraine attack. Second, increased inflammation in the cervical spine due to the proinflammatory molecules release into the bloodstream upregulated the hypothalamic-pituitary-adrenal axis, causing the hypothalamic dysfunction[32]. This process intensified the sensitivity to pain in the brain, which may lead to predisposition to migraine.

Understanding of the precise mechanisms of the relationship between CS and migraine risk remains limited. Cervical vertebral degenerative processes can compromise the capsular ligaments of facet joints, thereby contributing to the hypermobility of upper cervical vertebrae[33]. Such cervical instability causes dysregulation of the vertebrobasilar arteries, which leads to migraines[34,35]. Watson and Drummond assessed the effects of sustained pressure on the atlanto-occipital segments and C2-3 zygapophyseal joints to relieve migraines[36]. In addition, several studies have reported that myofascial trigger points could reproduce migraine symptoms[37,38], Moreover, an increasing amount of evidence shows that dyscoordination between the dorsal horns of the upper cervical spinal cord and trigeminal nucleus caudalis may induce cervicogenic headaches. The prolonged irritated inputs implicate in the pain processing through trigeminovascular system, which can provoke and worsen the symptoms of migraine[39,40].

Regarding CS severity, our results revealed in the CS cohort, the participants with myelopathy may be at a greater risk of developing migraine than those without myelopathy. Revanappa et al. demonstrated that more than 50% of individuals with cervical spondylotic myelopathy also had concomitant autonomic dysfunction[41], where sympathetic postganglionic fibers exit through cervical posterior longitudinal ligaments[42]. In these individuals, once the ligaments had been compressed, abnormal activities in the middle cervical ganglia occurred[43], which could partially explain the progression of autonomic dysfunction due to cervical spondylotic myelopathy. Such structural and functional alternations in the cervical spinal cord may upregulate the associated nociceptive expressions, which could contribute to migraine development.

Although this study has the advantage of feasibility and generalizability because of the large sample size and low dropout rate, it had several flaws. First, the NHIRD has limitations, particularly in relation to biographical information such as clinical features, imaging findings, laboratory studies, personal lifestyle, and medication, all of which are irretrievable. Second, the diagnostic accuracy of CS and migraine were totally dependent based on ICD-9-CM codes. In theory, the diagnosis of CS should be on the basis of the appropriate imaging together with physical examinations and history taking. Generally, neurologists in Taiwan developed a headache diary as well as a structured intake form to do the headache survey (clinical headache pattern, psychological comorbidities, medication use and treatment response, functional disability and quality of life)[44], making the diagnosis of migraine according to the second edition of the International Classification of Headache Disorders (ICHD-2) criteria. However, no one could confirm whether patients with the coding were accurately diagnosed due to the inherent weakness

for all studies based on databank. Nonetheless, our results remain reliable because the NHI administration ministry randomly samples the medical charts routinely, verifying the coding in NHIRD dataset from every contracted medical institution. Furthermore, validation study of the diagnostic codes for migraine in NHIRD was performed[45]. Third, our database was derived from the NHI program in Taiwan, which predominantly enrolls Taiwanese citizens. The genetic factor of our participants would have been minimized in our study. However, there was no corresponding ICD-9-CM code for any particular type of migraine. Relationship between CS any particular type of migraine (with and without aura) could not be substantiated, the more definite coding is required to strengthen the association between CS and migraine subtype.

## Conclusion

CS increases the risk of migraine, especially in individuals with cervical spondylotic myelopathy. We showed that young to middle-aged women with CS and comorbidities were at the highest risk of migraine. Although the precise underlying mechanisms of this longitudinal association remain unknown, our results expand the understanding of this association, which requires further careful consideration by clinical practitioners.

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**Figure Legend:**

Figure 1. Cummulative incidence of migraine in individuals with and without CS

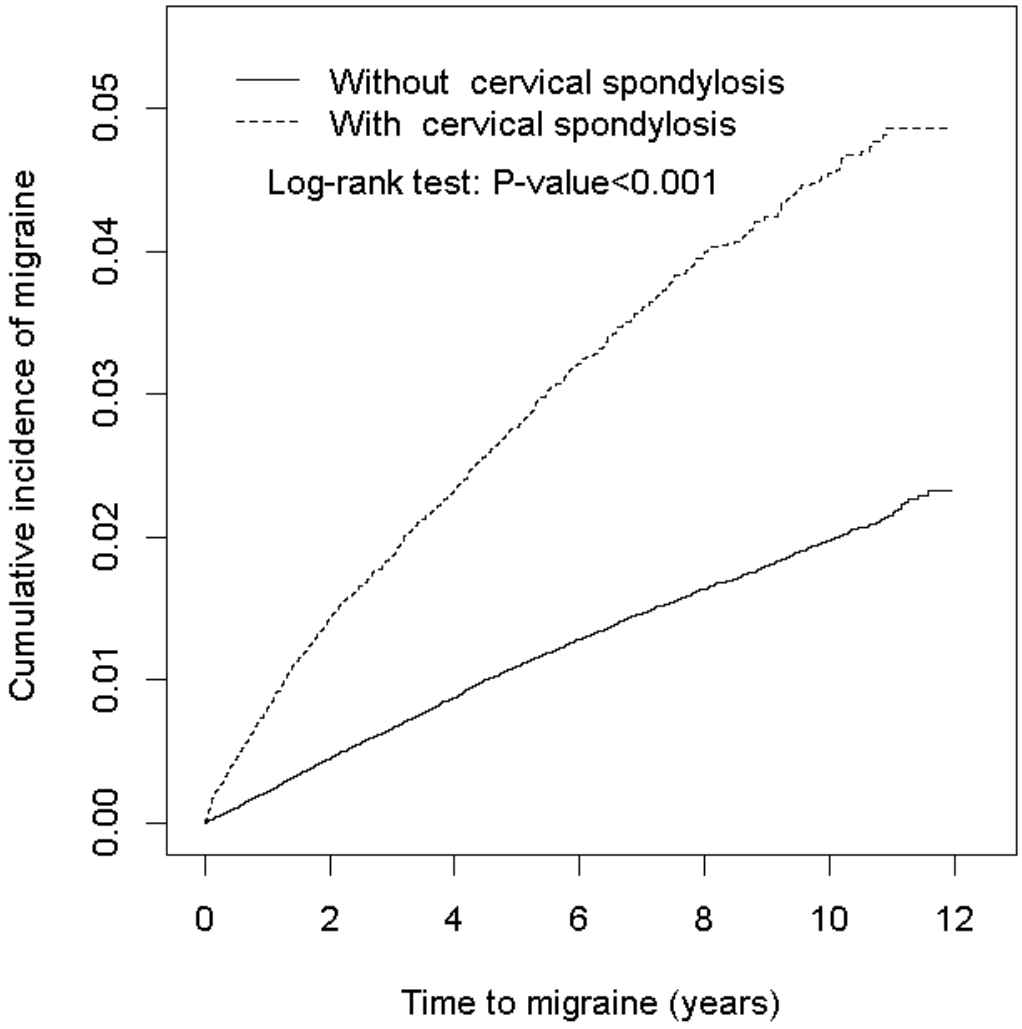

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Table 1. Comparisons of demographic characteristics and comorbidities in individuals with and without CS.

| | **Cervical spondylosis** | | |
|---|---|---|---|
| | **No** | **Yes** | |
| | **(N =111720)** | **(N =27930)** | **Standard mean difference** |
| **Sex** | | | 0.99 |
| Women | 63592(56.9) | 15898(56.9) | |
| Men | 48128(43.1) | 12032(43.1) | |
| **Age stratified** | | | 0.99 |
| ≤ 49 | 40452(36.2) | 10113(36.2) | |
| 50-64 | 41880(37.5) | 10470(37.5) | |
| 65+ | 29388(26.3) | 7347(26.3) | |
| **Age, mean±SD** [a] | 55.1(14.0) | 55.6(13.6) | <0.001 |
| **Comorbidity** | | | |
| Hypertension | 36886(33.0) | 11658(41.7) | <0.001 |
| Hyperlipidemia | 22730(20.4) | 8887(31.8) | <0.001 |
| Depression | 4498(4.03) | 2252(8.06) | <0.001 |
| Coronary artery disease | 17160(15.4) | 6941(24.9) | <0.001 |
| Anxiety | 10300(9.22) | 5607(20.1) | <0.001 |
| Sleep disorder | 20851(18.7) | 9450(33.8) | <0.001 |
| Irritable bowel syndrome | 4969(4.45) | 2487(8.90) | <0.001 |
| Diabetes | 10876(9.74) | 3182(11.4) | <0.001 |
| Fibromyalgia | 4599(4.12) | 2984(10.7) | <0.001 |

Chi-square test; [a] *t* test

CS cohort follow-up time mean = 6.13 (3.19)
Non-CS cohort follow-up time mean = 6.07 (3.20)

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Table 2. Migraine incidences and risk factors.

| Variable | Event | PY | Rate[#] | Crude HR (95% CI) | Adjusted HR[&] (95% CI) |
|---|---|---|---|---|---|
| **Cervical spondylosis** | | | | | |
| No | 1414 | 677913 | 2.09 | 1.00 | 1.00 |
| Yes | 883 | 171179 | 5.16 | 2.48(2.28, 2.69)*** | 2.03(1.86, 2.22)*** |
| **Age group, year** | | | | | |
| 20−49 | 997 | 330050 | 3.02 | 1.46(1.31, 1.64)*** | 1.81(1.58, 2.06)*** |
| 50−64 | 874 | 317220 | 2.76 | 1.32(1.18, 1.48)*** | 1.40(1.24, 1.58)*** |
| ≥ 65 | 426 | 201822 | 2.11 | 1.00 | 1.00 |
| **Sex** | | | | | |
| Female | 1719 | 494959 | 3.47 | 2.14(1.95, 2.35)*** | 1.92(1.74, 2.11)*** |
| Male | 578 | 354133 | 1.63 | 1.00 | 1.00 |
| **Comorbidity** | | | | | |
| **Hypertension** | | | | | |
| No | 1465 | 570275 | 2.57 | 1.00 | 1.00 |
| Yes | 832 | 278816 | 2.98 | 1.15(1.06, 1.25)** | 1.06(0.95, 1.18) |
| **Hyperlipidemia** | | | | | |
| No | 1698 | 668229 | 2.54 | 1.00 | 1.00 |
| Yes | 599 | 180862 | 3.31 | 1.29(1.17, 1.41)*** | 1.01(0.91, 1.12) |
| **Depression** | | | | | |
| No | 2090 | 813829 | 2.57 | 1.00 | 1.00 |
| Yes | 207 | 35263 | 5.87 | 2.24(1.94, 2.58)*** | 1.13(0.97, 1.32) |
| **Coronary artery disease** | | | | | |
| No | 1800 | 711569 | 2.53 | 1.00 | 1.00 |
| Yes | 497 | 137523 | 3.61 | 1.42(1.28, 1.56)*** | 1.20(1.07, 1.35)** |
| **Anxiety** | | | | | |
| No | 1785 | 764303 | 2.34 | 1.00 | 1.00 |
| Yes | 512 | 84789 | 6.04 | 2.53(2.30, 2.80)*** | 1.48(1.32, 1.66)*** |
| **Sleep disorder** | | | | | |
| No | 1444 | 690750 | 2.09 | 1.00 | 1.00 |
| Yes | 853 | 158342 | 5.39 | 2.52(2.31, 2.74)*** | 1.81(1.64, 1.99)*** |
| **Irritable bowel syndrome** | | | | | |
| No | 2105 | 809522 | 2.60 | 1.00 | 1.00 |
| Yes | 192 | 39569 | 4.85 | 1.83(1.57, 2.12)*** | 1.24(1.06,1 .44)** |
| **Diabetes** | | | | | |
| No | 2112 | 775714 | 2.72 | 1.00 | 1.00 |
| Yes | 185 | 73378 | 2.52 | 0.91(0.78, 1.05) | - |
| **Fibromyalgia** | | | | | |
| No | 2127 | 808699 | 2.63 | 1.00 | 1.00 |
| Yes | 170 | 4093 | 4.21 | 1.57(1.34, 1.83)*** | 1.08(0.92, 1.27) |

CI: confidence interval; HR: hazard ratio; PY: people per year; [#]: incidence rate per 1,000 people per year; [&]: model was adjusted for age, sex, and the comorbidities of hypertension, hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, and fibromyalgia by using Cox proportional hazards regression. $^{**}p < 0.01$; $^{***}p < 0.001$

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Table 3. Comparison of incidence rate of migraine HR between individuals with and without CS based on demographic characteristics and comorbidities.

| | Cervical spondylosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | | |
| | Event | PY | Rate# | Event | PY | Rate# | Crude HR (95% CI) | Adjusted HR& (95% CI) |
| **Sex** | | | | | | | | |
| Women | 1082 | 395676 | 2.73 | 637 | 99282 | 6.42 | 2.35(2.13, 2.59)*** | 1.93(1.74, 2.14)*** |
| Men | 332 | 282237 | 1.18 | 246 | 71896 | 3.42 | 2.91(2.47, 3.44)*** | 2.32(1.95, 2.76)*** |
| **Stratify age** | | | | | | | | |
| ≤ 49 | 620 | 264087 | 2.35 | 377 | 65963 | 5.72 | 2.44(2.14, 2.77)*** | 1.94(1.70, 2.23)*** |
| 50-64 | 532 | 253619 | 2.10 | 342 | 63600 | 5.38 | 2.56(2.24, 2.94)*** | 2.05(1.78, 2.36)*** |
| 65+ | 377 | 160207 | 1.64 | 164 | 41615 | 3.94 | 2.42(1.99, 2.94)*** | 2.08(1.70, 2.55)*** |
| **Comorbidity‡** | | | | | | | | |
| No | 520 | 342246 | 1.52 | 180 | 49454 | 3.64 | 2.40(2.02, 2.84)*** | 2.36(1.99, 2.80)*** |
| Yes | 894 | 335667 | 2.66 | 703 | 121725 | 5.78 | 2.19(1.98, 2.41)*** | 2.10(1.91, 2.32)*** |

Rate#: incidence rate per 1,000 people per year; Crude HR: relative hazard ratio; Adjusted HR&: crude HR mutually adjusted for age, sex, and the comorbidities of hypertension, hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, and fibromyalgia by using Cox proportional hazards regression. Comorbidity‡: individuals with any one of the comorbidities of hypertension, hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, diabetes, and fibromyalgia were classified in the comorbidity group. ***$p < 0.001$

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Table 4. Migraine incidences and HRs among individuals with various types of CS and those without CS

| Variable | N | Events | PYs | Rate# | Crude HR (95% CI) | Adjusted HR& 95% CI) |
|---|---|---|---|---|---|---|
| Without cervical spondylosis | 111720 | 1414 | 677913 | 2.09 | 1.00 | 1.00 |
| Type of Cervical spondylosis | | | | | | |
| Cervical spondylosis without myelopathy | 24287 | 771 | 150298 | 5.13 | 2.47(2.26, 2.69)*** | 2.01(1.83, 2.20)*** |
| Cervical spondylosis with myelopathy | 3643 | 112 | 20880 | 5.36 | 2.55(2.10, 3.09)*** | 2.19(1.80, 2.66)*** |

Rate#: incidence rate per 1,000 people per year; Crude HR: relative hazard ratio; Adjusted HR&: crude HR mutually adjusted for age, sex, and the comorbidities of hypertension, hyperlipidemia, depression, coronary artery disease, anxiety, sleep disorders, irritable bowel syndrome, and fibromyalgia by using Cox proportional hazards regression.
***$p < 0.001$