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# Increased risk of strokes in patients with chronic low back pain (CLBP): A nationwide population-based cohort study

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ABSTRACT

*Objectives:* There have not been any longitudinal studies reported that chronic low back pain (CLBP) patients are at risk for stroke. Thus, in this study, we explored the association between CLBP and strokes.
*Patients and methods:* Data (2000～2010) from the Taiwan National Health Insurance database were analyzed. We matched 10,308 CLBP patients with 20,616 propensity score-matched non-low back pain (NLBP) patients according to age, gender, index year and comorbidities. Covariates of age, gender, comorbidities, and usage of non-steroidal anti-inflammatory drugs (NSAIDs) were adjusted and analyzed.
*Results:* The mean follow-up duration was 8 years. CLBP patients had higher risks of all stroke, hemorrhagic stroke, and ischemic stroke. The adjusted hazard ratios (aHRs) were 2.35 (95 % confidence interval (CI): 2.14–2.57, $p < 0.001$), 1.55 (95 % CI: 1.16–2.06, $p = 0.003$), and 2.41 (95 % CI: 2.18–2.66, $p < 0.001$), respectively. After adjusting and analyzing the NSAIDs used for the varied duration in the CLBP patients, we did not observe any impacts of such NSAIDs used on the association of CLBP with strokes. The association between CLBP and ischemic stroke was most prominent in the patients less than 50 years old with aHR: 3.56 (CI: 2.74～4.61, $p < 0.001$).
*Conclusion:* CLBP was associated with increased risk of strokes, especially ischemic stroke, and the association was most prominent in patients less than 50 years old. Further large prospective studies on detailed lifestyle-related factors and qualitative pain assessment are needed to clarify the causal relationship between CLBP and stroke.

## 1. Introduction

Low back pain (LBP) defined as pain originated from the costal margin and above the inferior gluteal folds with or without sciatica is mostly due to mechanical causes contributing to musculoskeletal strains and neuropathic pain syndromes. [1] Its incidence was highest in the working age (middle-age), and was recognized as the greatest contributor to disability worldwide in the 2013 global burden of disease study [2]. If people suffered from on-and-off or persistent LBP for 12 weeks or more (chronic LBP, CLBP), they might further be hindered by loss of productivity, and prolongation of disability [1,3]. There has not been much progress in management of CLBP in respects of satisfied pain reduction and functional gain, despite improving understanding of pathogenesis and advances in surgeries or interventions for it. Failed back surgery syndrome is the toughest condition of CLBP, characterized as persistent or recurrent LBP with or without sciatica after receiving repeated spinal surgeries [4]. Therefore, it is reasonable that CLBP may lead considerable impacts on the patients and the health care system.

Besides well-known modifiable atherosclerosis risk factors (e.g., hypertension, diabetes, hyperlipidemia), cardiovascular diseases had been associated with multiple risk factors such as chronic pain conditions, e.g., fibromyalgia [5], psychiatric disorders, e.g., depression, anxiety [6,7], sleep disturbances, e.g., insomnia [8] and inactivity [9,10]. Patients with chronic pain, possibly in a stress status, were

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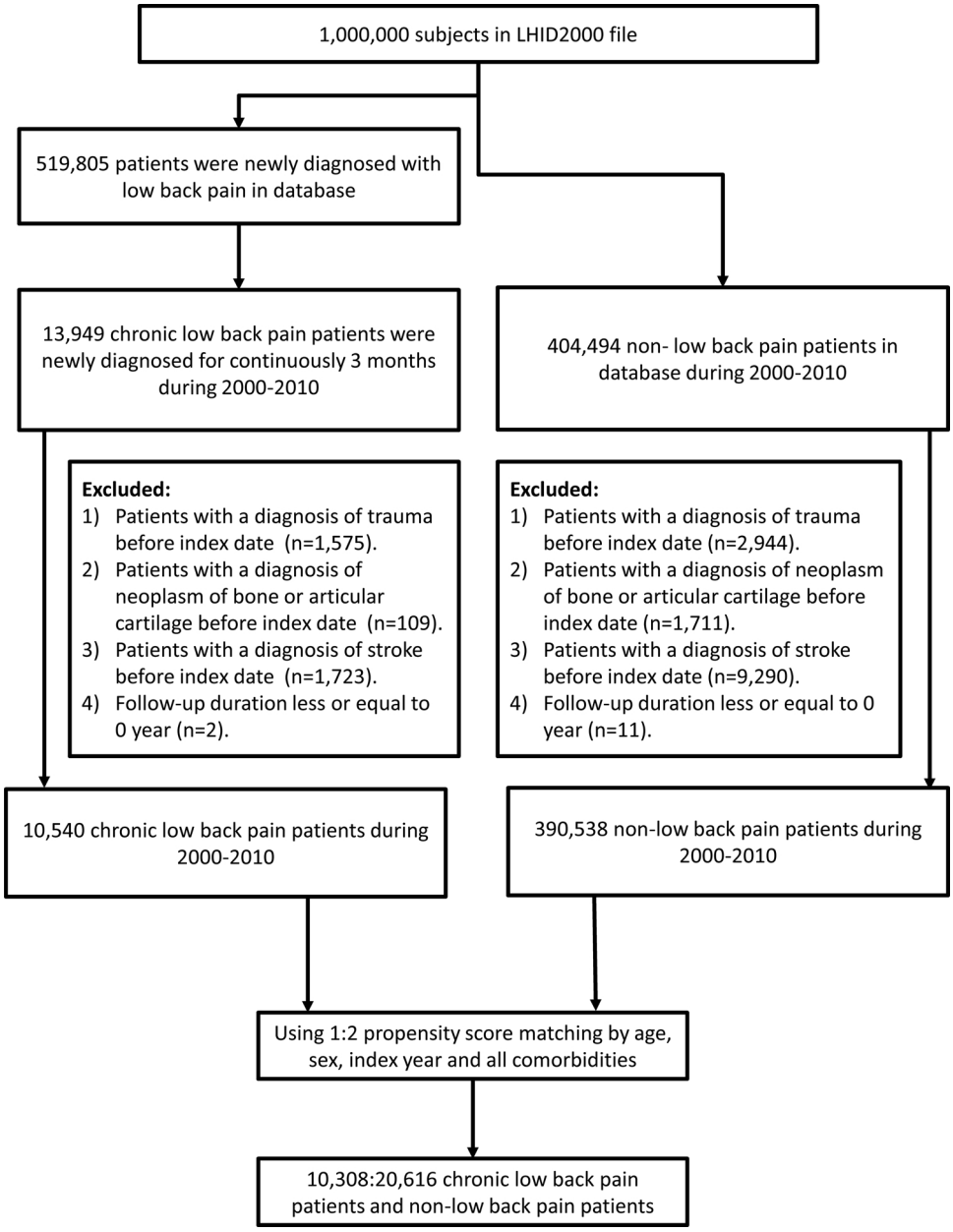



**Fig. 1.** Flow of participants.

associated with depression; and up to 85 % of patients of them were accompanied with severe depression [11]. Additionally, coexistence of socioeconomic conditions like conflicting relationships at work and insurance issues might make the CLBP patients more vulnerable to having psychiatric disorders and sleep disturbances [4]. Taken together, CLBP patients were more likely facing difficult conditions as chronic pain, emotional stress or psychiatric disorders, sleep disturbances, and aggravated inactivity. Thus, we supposed that the CLBP patients may be at risk for stroke. If the association will exist, it will be an important issue since the incidence of LBP was highest in the middle-age population and could further magnify the socioeconomic burden.

To the best of our knowledge, there have not been any longitudinal studies revealing that CLBP patients are at risk of stroke. Only one cross-sectional study showed that chronic musculoskeletal pain was associated with cardiovascular disease. [12] Therefore, we conducted this large longitudinal study to explore the association between CLBP and stroke.

## 2. Materials and methods

### 2.1. Ethical review

Ethical approval for this study (CMUH104-REC2-115) was provided by the Institutional Review Board of China Medical University Hospital, Taichung, Taiwan.

This retrospective study used anonymous data from the Taiwan National Health Insurance Research Database (NHIRD). All personal information that could be used to identify the patients was encrypted before entry into the NHIRD and was further encrypted before releasing to the public for research purposes. Therefore, patient consents are not required to access the NHIRD.

### 2.2. Data source

The National Health Insurance (NHI) program in Taiwan offers nearly full medical services to 99 % of 23 million residents in Taiwan

**Table 1**
Distribution of population characteristics of the chronic low back pain and the compared cohort.(2000 ~ 2010).

| Variables | Chronic low back pain | | | | p-value[a] |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | (n = 20616) | | (n = 10308) | | |
| | n | % | n | % | |
| **Gender** | | | | | 0.16 |
| Female | 9683 | 47.0 | 4929 | 47.8 | |
| Male | 10933 | 53.0 | 5379 | 52.2 | |
| **Age, years** | | | | | 0.41 |
| Less than 50 years | 10741 | 52.1 | 5387 | 52.3 | |
| 50-65 years | 5628 | 27.3 | 2860 | 27.8 | |
| More than 65 years | 4247 | 20.6 | 2061 | 20.0 | |
| Mean (SD) | 43.80 (23.83) | | 49.15 (17.14) | | < 0.001[b] |
| **Baseline comorbidity** | | | | | |
| Depression | 773 | 3.75 | 376 | 3.65 | 0.66 |
| Hypertensive disease | 5870 | 28.5 | 2864 | 27.8 | 0.20 |
| Diabetes mellitus | 1554 | 7.54 | 774 | 7.51 | 0.93 |
| Coronary heart disease | 1673 | 8.12 | 846 | 8.21 | 0.78 |
| Congestive heart failure | 395 | 1.92 | 213 | 2.07 | 0.37 |
| Hyperlipidemia | 3979 | 19.3 | 1951 | 18.9 | 0.43 |
| Peripheral artery disease | 116 | 0.56 | 71 | 0.69 | 0.18 |
| Atrial fibrillation | 113 | 0.55 | 70 | 0.68 | 0.16 |
| Chronic kidney disease | 556 | 2.7 | 279 | 2.71 | 0.96 |
| **Drug** | | | | | |
| NSAIDs | 16542 | 80.2 | 9945 | 96.5 | < 0.001 |

Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Chi-square test.
[b] Two sample t-test.

and provides universal coverage and access to any medical institutions of the individual patient's choice. We used the Longitudinal Health Insurance Database (LHID 2000), a subset of NHIRD consisting of all medical records of 1 million randomly selected insured people from the 23 million NHI beneficiaries between 1996 and 2013, including dates, primary, secondary diagnostic codes, and prescription orders during hospitalizations as well during outpatient visits.

### 2.3. Study population

We identified patients diagnosed with low back pain (LBP) by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 336.8, 721.3, 721.4, 721.9, 722.10, 722.5, 722.73, 724.XX, 738.4, 738.5, 756.1 between 2000 and 2010 from the LHID 2000 as the study group. These ICD-9-CM codes included diagnosis of lumbago, lumbosacral spondylosis with or without myelopathy, displacement of lumbar intervertebral disc with or without myelopathy, acquired spondylolisthesis, spinal stenosis, sciatica and lumbosacral neuritis or radiculitis. The index date was defined as the first diagnosis date of LBP. Patients who had at least one diagnosis of LBP per month for continuously 3 months from the outpatient visits were included in the chronic low back pain (CLBP) cohort (Fig. 1). We identified the non-low back pain (NLBP) cohort by 1:2 propensity-matching with age, sex, index year and cardiovascular-related comorbidities (Fig. 1). The study objective was to estimate the risk of strokes (ICD-9-CM 430–438, A290-A293, A299), including hemorrhagic stroke and ischemic stroke in the two cohorts. Therefore, individuals who were diagnosed of the stroke before index date were excluded. Patients with diagnosis of neoplasm of bone or articular cartilage (ICD-9-CM: 170, 213), or trauma (ICD-9-CM: 721.7, 8054, 8055, 8056, 8057, 8058, 8059, 8066, 8067, 8068, 8069, 8394, 8395) before index date were also excluded. The follow-up duration was calculated from the index date to the date of the stroke, withdrawal from the NHI, or December 31, 2013.

### 2.4. Comorbidities and non-steroidal anti-inflammatory drugs (NSAIDs) usage

The potential cardiovascular-related comorbidities considered for covariates were depressions (ICD-9-CM 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 311), hypertensive diseases (ICD-9-CM 401–405; A-code A260, A269), diabetes mellitus (ICD-9-CM 250; A-code A181), coronary heart diseases (ICD-9-CM 410–413, 414.01–414.05, 414.8, 414.9), congestive heart failures (ICD-9-CM 428), hyperlipidemias (ICD-9-CM 272; A-code A182), peripheral artery diseases (ICD-9-CM 440.2, 440.3, 443.9), atrial fibrillations (ICD-9-CM 427.3) and chronic kidney diseases (ICD-9-CM 250.4, 403.XX, 404.XX, 585, 586). All comorbidities had to be diagnosed at least twice before the index date in this study. We also included NSAIDs usage as a covariate, defined as cumulative days of NSAIDs usage within follow-up duration. All patients were divided into three groups according to their cumulative days of NSAIDs usage. Patients with the cumulative days of NSAIDs usage < 18 days, between 18 and 132 days, and > 132 days were defined as low, medium, and high usage groups in this study, respectively."

### 2.5. Statistical analysis

The SAS V.9.4 statistical package (SAS Institute, Cary, North Carolina, USA) was used for the statistical analysis. A 2-tailed $P < 0.05$ was considered significant. For the distribution of variables in CLBP and NLBP cohorts, we used a Chi-square test for categorical variables and a Student *t*-test for continuous variables. Adjusted hazard ratios (aHRs) with 95 % confidence interval (95 % CI) were calculated by multivariable Cox proportional regression model. The incidence rates of ischemic stroke in both groups were calculated after stratifying each variable. Kaplan-Meier analysis with a log-rank test was done for estimation of the difference between the 2 cumulative incidence curves of the stroke from the CLBP and NLBP cohorts. The frequency of outpatient visits for CLBP by the CLBP population was defined as the cumulative times of visits divided by the follow-up period (years). All CLBP patients were divided into three groups according to their frequency of outpatient visits (< 2, 2 ~ 3, and ≥ 4 times/ per year).

## 3. Results

### 3.1. Characteristics of the study population

The flow of participants is summarized in Fig. 1. The baseline characteristics of the CLBP and NLBP cohorts are listed in Table 1. There were 10,308 CLBP patients and 20,616 propensity score-matched NLBP patients. The mean follow-up periods were 8.40 and 8.28 years for the CLBP and the NLBP cohort, respectively. The distribution of gender, age group, and comorbidities between the two cohorts did not differ significantly under matching.

### 3.2. Risk of strokes of CLBP patients

At the end of the follow-up period, the cumulative incidences of all stroke, and ischemic stroke were significantly higher in the CLBP than in the NLBP cohort ($p < 0.0001$) (Fig. 2). Compared with the NLBP patients, the adjusted hazard ratios (aHRs) of all stroke, hemorrhagic stroke and ischemic stroke of the CLBP patients were 2.35 (95 % confidence interval (CI): 2.14–2.57, $p < 0.001$), 1.55 (95 % CI: 1.16–2.06, $p = 0.003$), and 2.41 (95 % CI: 2.18–2.66, $p < 0.001$), respectively (Table 2).

The NSAIDs used for varied duration in cumulative manner (< 18 days, between 18 and 132 days, and > 132 days) was not an independent predictor for stroke in this study population (Table 2).

Fig. 3 shows the incidence rates, crude hazard ratios, and aHRs of ischemic stroke of the CLBP cohort, and stratification analysis of each considered variable (including age, gender, cardiovascular-related

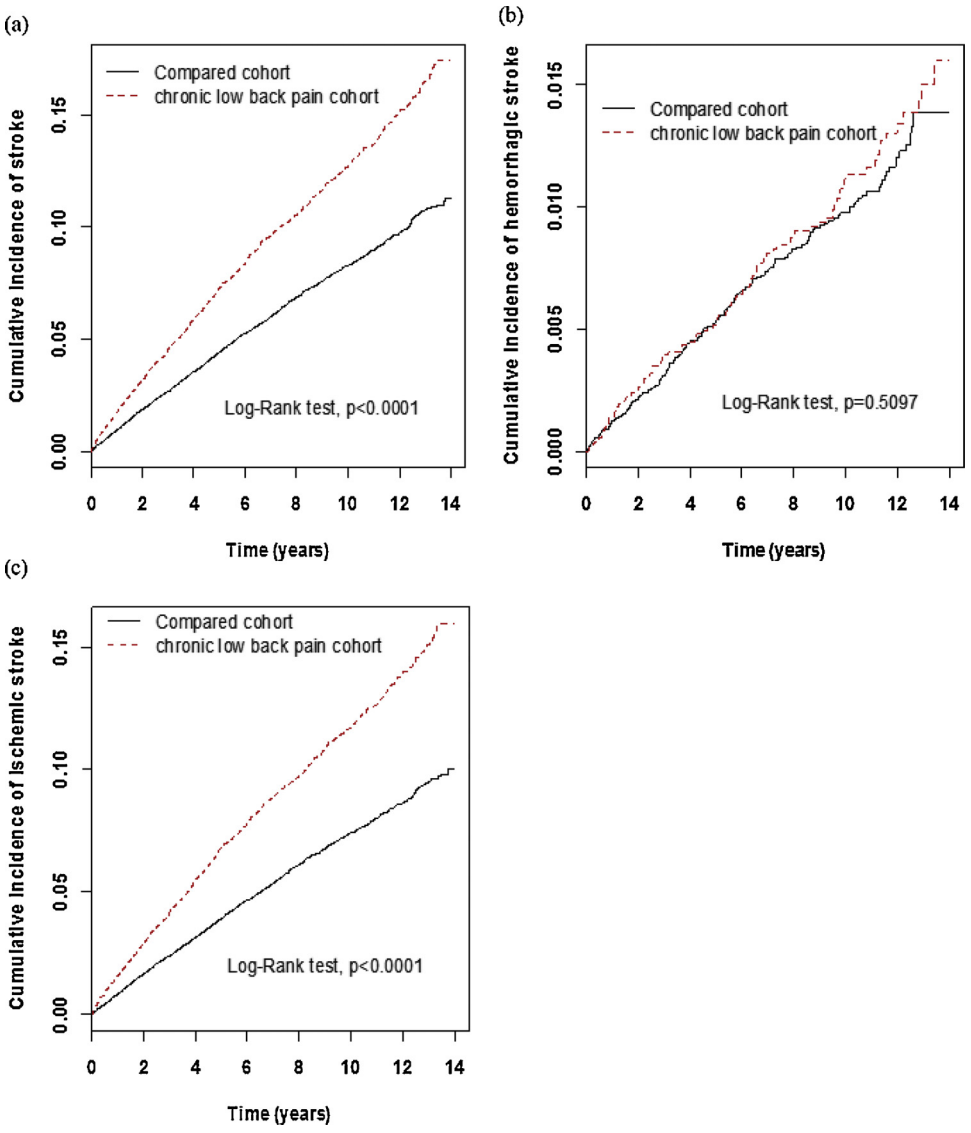



**Fig. 2.** The Kaplan-Meier curves.
The cumulative incidence of all stroke, hemorrhagic stroke, and ischemic stroke of the chronic low back pain and the compared cohort.

comorbidities and usage of NSAIDs). The incidence rates of ischemic stroke for the CLBP and NLBP cohorts were 11.94 per 1000 person-years and 7.97 per 1000 person-years, respectively. The association of CLBP with ischemic stroke was most prominent in the patients less than 50 years old with aHR:3.56 (CI:2.74 ~ 4.61, $p < 0.001$) among the three age groups. There were also greater risks of ischemic stroke for the CLBP patients with or without comorbidities or NSAIDs used compared with the control subjects, except the population having peripheral artery disease, and atrial fibrillation.

Table 3 shows the risk of strokes stratified by the frequency of outpatient visits by the CLBP patients during the follow-up period. The highest frequency of visits (≥4 times/ per year) during the follow-period was associated with higher risks of all stroke, hemorrhagic stroke and ischemic stroke. The aHRs were 4.84 (95 % CI: 4.34–5.40, $p < 0.001$), 3.37 (95 % CI: 2.36–4.82, $p < 0.001$), and 4.92 (95 % CI: 4.38–5.51, $p < 0.001$), respectively.

## 4. Discussion

This is the first longitudinal study to elucidate whether chronic low back pain (CLBP) patients are at risk of strokes, by comparison of the CLBP with NLBP (matched) cohorts under comprehensive adjustments. As a result, CLBP patients had obviously increased risk of strokes. Besides, stratified analysis by age showed that the association was greatest in the patients less than 50 years old among the three age groups. Additionally, CLBP patients are at risk of ischemic stroke in almost all subgroup analysis in our survey, except those having peripheral artery disease and atrial fibrillation. The above-mentioned exceptions could be due to the small sample size of patients having those two comorbidities (those patients were less than 1 % of the respective cohort) (Table 1).

NSAIDs usage might increase cardiovascular risk in the patients already having atherosclerosis disease. [13] Recently, review articles and meta-analysis indicated that that Rofecoxib was the only drug with adverse cardiovascular outcomes among those NSAIDs, otherwise no definite evidence was seen regarding NSAIDs and stroke risk [14,15]. Since the CLBP patients might take NSAIDs more frequently than the non-low back pain (NLBP) patients, we concerned that NSAIDs might lead CLBP patients more vulnerable to having strokes. Therefore, we adjusted the NSAIDs used with different cumulative usage days in our investigation. Consequently, we did not observe any impacts of such NSAIDs use on the association of CLBP with stroke (Table 2 and Fig. 3).

Our study was not primarily designed to explore the effects of NSAIDs on stroke, thus we did not consider different types of NSAIDs

**Table 2**
Independent predictors of all stroke, hemorrhagic stroke, and ischemic stroke in this study population. (2000 ~ 2010).

| Variables | All stroke | | | | Hemorrhagic stroke | | | | Ischemic stroke | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | event no. (%) | aHR | (95 % CI) | P-value | event no. (%) | aHR | (95 % CI) | P-value | event no. (%) | aHR | (95 % CI) | P-value |
| **Chronic low back pain** | | | | | | | | | | | | |
| No | 1531 (57.5) | 1.00 | reference | | 182 (64.8) | 1.00 | reference | | 1364 (56.8) | 1.00 | reference | |
| Yes | 1130 (42.5) | 2.35 | (2.14–2.57) | < 0.001 | 99 (35.2) | 1.55 | (1.16–2.06) | 0.003 | 1037 (43.2) | 2.41 | (2.18–2.66) | < 0.001 |
| **Gender** | | | | | | | | | | | | |
| Female | 1106 (41.6) | 1.00 | reference | | 105 (37.4) | 1.00 | reference | | 1011 (42.1) | 1.00 | reference | |
| Male | 1555 (58.4) | 1.26 | (1.16–1.36) | < 0.001 | 176 (62.6) | 1.44 | (1.13–1.83) | 0.003 | 1390 (57.9) | 1.23 | (1.14–1.34) | < 0.001 |
| **Age, years** | | | | | | | | | | | | |
| Less than 50 years | 347 (13.0) | 1.00 | reference | | 67 (23.8) | 1.00 | reference | | 287 (12.0) | 1.00 | reference | |
| 50-65 years | 996 (37.4) | 4.32 | (3.81–4.91) | < 0.001 | 95 (33.8) | 2.03 | (1.45–2.83) | < 0.001 | 907 (37.8) | 4.75 | (4.14–5.46) | < 0.001 |
| More than 65 years | 1318 (49.5) | 8.09 | (7.1–9.22) | < 0.001 | 119 (42.4) | 3.2 | (2.26–4.53) | < 0.001 | 1207 (50.3) | 8.99 | (7.8–10.35) | < 0.001 |
| **Baseline comorbidity** | | | | | | | | | | | | |
| Depression | | | | | | | | | | | | |
| No | 2567 (96.5) | 1.00 | reference | | 273 (97.2) | 1.00 | reference | | 2314 (96.4) | 1.00 | reference | |
| Yes | 94 (3.53) | 1.1 | (0.9–1.35) | 0.36 | 8 (2.85) | 0.89 | (0.44–1.81) | 0.76 | 87 (3.62) | 1.14 | (0.92–1.41) | 0.25 |
| Hypertensive disease | | | | | | | | | | | | |
| No | 1108 (41.6) | 1.00 | reference | | 122 (43.4) | 1.00 | reference | | 996 (41.5) | 1.00 | reference | |
| Yes | 1553 (58.4) | 1.92 | (1.76–2.1) | < 0.001 | 159 (56.6) | 2.62 | (1.98–3.47) | < 0.001 | 1405 (58.5) | 1.84 | (1.68–2.02) | < 0.001 |
| Diabetes mellitus | | | | | | | | | | | | |
| No | 2067 (77.7) | 1.00 | reference | | 238 (84.7) | 1.00 | reference | | 1846 (76.9) | 1.00 | reference | |
| Yes | 594 (22.3) | 2.16 | (1.95–2.38) | < 0.001 | 43 (15.3) | 1.41 | (1–2.01) | 0.05 | 555 (23.1) | 2.21 | (1.99–2.45) | < 0.001 |
| Coronary heart disease | | | | | | | | | | | | |
| No | 2224 (83.6) | 1.00 | reference | | 249 (88.6) | 1.00 | reference | | 1998 (83.2) | 1.00 | reference | |
| Yes | 437 (16.4) | 1.07 | (0.96–1.19) | 0.25 | 32 (11.4) | 0.76 | (0.51–1.13) | 0.18 | 403 (16.8) | 1.08 | (0.96–1.21) | 0.21 |
| Congestive heart failure | | | | | | | | | | | | |
| No | 2546 (95.7) | 1.00 | reference | | 268 (95.4) | 1.00 | reference | | 2297 (95.7) | 1.00 | reference | |
| Yes | 115 (4.32) | 1.09 | (0.89–1.33) | 0.40 | 13 (4.63) | 1.46 | (0.8–2.66) | 0.21 | 104 (4.33) | 1.08 | (0.88–1.33) | 0.47 |
| Hyperlipidemia | | | | | | | | | | | | |
| No | 1806 (67.9) | 1.00 | reference | | 220 (78.3) | 1.00 | reference | | 1603 (66.8) | 1.00 | reference | |
| Yes | 855 (32.1) | 1.11 | (1.02–1.22) | 0.02 | 61 (21.7) | 0.71 | (0.52-0.97) | 0.03 | 798 (33.2) | 1.16 | (1.05–1.27) | 0.002 |
| Peripheral artery disease | | | | | | | | | | | | |
| No | 2632 (98.9) | 1.00 | reference | | 278 (98.9) | 1.00 | reference | | 2373 (98.8) | 1.00 | reference | |
| Yes | 29 (1.09) | 1.2 | (0.83–1.74) | 0.33 | 3 (1.07) | 1.44 | (0.46–4.52) | 0.53 | 28 (1.17) | 1.27 | (0.87–1.84) | 0.22 |
| Atrial fibrillation | | | | | | | | | | | | |
| No | 2620 (98.5) | 1.00 | reference | | 277 (98.6) | 1.00 | reference | | 2363 (98.4) | 1.00 | reference | |
| Yes | 41 (1.54) | 1.18 | (0.85–1.62) | 0.32 | 4 (1.42) | 1.21 | (0.43–3.39) | 0.72 | 38 (1.58) | 1.16 | (0.83–1.62) | 0.38 |
| Chronic kidney disease | | | | | | | | | | | | |
| No | 2525 (94.9) | 1.00 | reference | | 269 (95.7) | 1.00 | reference | | 2276 (94.8) | 1.00 | reference | |
| Yes | 136 (5.11) | 0.85 | (0.71–1.02) | 0.07 | 12 (4.27) | 1.01 | (0.55–1.84) | 0.99 | 125 (5.21) | 0.84 | (0.7–1.02) | 0.08 |
| **Drug** | | | | | | | | | | | | |
| NSAIDs | | | | | | | | | | | | |
| Non-user | 626 (23.5) | 1.00 | reference | | 73 (26.0) | 1.00 | reference | | 561 (23.4) | 1.00 | reference | |
| Low | 536 (20.1) | 0.55 | (0.49-0.62) | < 0.001 | 64 (22.8) | 0.62 | (0.44-0.87) | 0.01 | 479 (20.0) | 0.55 | (0.49-0.62) | < 0.001 |
| Medium | 825 (31.0 | 0.34 | (0.31-0.38) | < 0.001 | 85 (30.3) | 0.36 | (0.26-0.5) | < 0.001 | 741 (30.9) | 0.34 | (0.31-0.39) | < 0.001 |
| High | 674 (25.3) | 0.24 | (0.21-0.27) | < 0.001 | 59 (21.0) | 0.28 | (0.19-0.42) | < 0.001 | 620 (25.8) | 0.24 | (0.21-0.27) | < 0.001 |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs;
Low, use NSAIDs less than 18 days; Medium, use NSAIDs between 18 and 132 days; High, use NSAIDs over 132 days.
Adjusted HR: adjusted for chronic low back pain, gender, age, depression, hypertensive disease, diabetes mellitus, coronary heart disease, congestive heart failure, hyperlipidemia, peripheral artery disease, atrial fibrillation, chronic kidney disease and NSAIDs in multi-variable Cox proportional regression model.

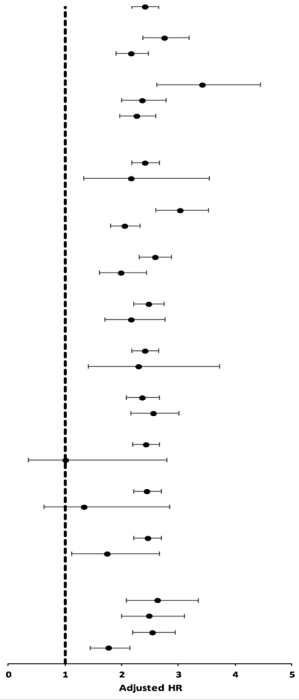
for covariates in this study. There has not been any evidence on the association between NSAIDs and stroke on the study population like ours. Therefore, possible effects of NSAIDs used on the association between chronic low back pain and stroke remain unknown and more studies are needed before further conclusions can be drawn.

Older age (over 65 years) was the most significant risk factor for ischemic stroke with aHR of 8.99 in our study (Table 2), which was compatible with previous ones. [16,17] Interestingly, the association of CLBP with stroke was most prominent in the patients less than 50 years old among the three age groups (Fig. 3). The earlier cross-sectional survey, however, revealed that the association of chronic musculoskeletal pain with cardiovascular disease was stronger in older adults (over 65 years old). [12] It is likely that the differences in study design, pain type, and population might contribute to the discrepancies in ages for the associations. Our study results are particularly interesting that might shed more light in stroke prevention, since there are still about one third of young stroke patients (less than 50 years old) did not have definite etiology [10]. Potential underlying mechanisms, like premature atherosclerosis change attributed to CLBP, warrant further investigations.

While an in-depth analysis of the relevant characteristics of chronic pain (qualitative assessment of pain) would be more helpful and provide more information to elucidate the relationship between chronic pain and stroke, the dataset obtained from NHIRD databank did not contain such clinical information (e.g., evaluation of chronic pain in chronicity and objective pain scales). Thus, in this study, it is beyond our scope to explore those potential impacts on the relation between CLBP and strokes.

Instead, to reinforce this weakness of the study design, we conducted a stratified analysis of the relation between strokes and CLBP by looking at different frequency of outpatient visits made by the CLBP patients during their follow-up periods (Table 3). Our assumption was: the more frequent OPD visits, the more severe the CLBP. The data shown in the Table 3, therefore, was an alternative solution to this issue (as a surrogate indicator to pain scale). The data showed that the more frequent visits made by the CLBP cohort was associated with the higher

| Variables | Chronic low back pain | | | | | | Forest plot of adjusted HR | Crude HR | Adjusted HR |
|---|---|---|---|---|---|---|---|---|---|
| | No (n=20616) | | | Yes (n=10308) | | | | | |
| | Event | Person years | IR | Event | Person years | IR | | (95%CI) | (95%CI) |
| **Total** | 1364 | 171236 | 7.97 | 1037 | 86861 | 11.94 | | 1.5(1.38-1.63)*** | 2.41(2.18-2.66)*** |
| **Gender** | | | | | | | | | |
| Female | 533 | 82673 | 6.45 | 478 | 42531 | 11.24 | | 1.75(1.54-1.98)*** | 2.76(2.38-3.2)*** |
| Male | 831 | 88562 | 9.38 | 559 | 44330 | 12.61 | | 1.34(1.21-1.5)*** | 2.17(1.91-2.47)*** |
| **Age, years** | | | | | | | | | |
| Less than 50 years | 139 | 98451 | 1.41 | 148 | 49245 | 3.01 | | 2.13(1.69-2.68)*** | 3.42(2.62-4.45)*** |
| 50-65 years | 521 | 46875 | 11.11 | 386 | 24132 | 16 | | 1.44(1.26-1.64)*** | 2.37(2.01-2.79)*** |
| More than 65 years | 704 | 25910 | 27.17 | 503 | 13484 | 37.3 | | 1.38(1.23-1.55)*** | 2.27(1.97-2.61)*** |
| **Baseline comorbidity** | | | | | | | | | |
| Depression | | | | | | | | | |
| No | 1310 | 165749 | 7.9 | 1004 | 84119 | 11.94 | | 1.51(1.39-1.64)*** | 2.42(2.19-2.67)*** |
| Yes | 54 | 5487 | 9.84 | 33 | 2742 | 12.03 | | 1.22(0.79-1.89) | 2.17(1.33-3.56)** |
| Hypertensive disease | | | | | | | | | |
| No | 510 | 130076 | 3.92 | 486 | 65447 | 7.43 | | 1.89(1.67-2.14)*** | 3.03(2.6-3.53)*** |
| Yes | 854 | 41159 | 20.75 | 551 | 21414 | 25.73 | | 1.25(1.12-1.39)*** | 2.05(1.8-2.33)*** |
| Diabetes mellitus | | | | | | | | | |
| No | 1008 | 161955 | 6.22 | 838 | 81729 | 10.25 | | 1.65(1.5-1.81)*** | 2.58(2.31-2.89)*** |
| Yes | 356 | 9280 | 38.36 | 199 | 5131 | 38.78 | | 1.02(0.86-1.22) | 1.98(1.61-2.44)*** |
| Coronary heart disease | | | | | | | | | |
| No | 1139 | 160568 | 7.09 | 859 | 80994 | 10.61 | | 1.5(1.37-1.63)*** | 2.47(2.22-2.75)*** |
| Yes | 225 | 10668 | 21.09 | 178 | 5867 | 30.34 | | 1.46(1.2-1.78)*** | 2.17(1.7-2.76)*** |
| Congestive heart failure | | | | | | | | | |
| No | 1306 | 169241 | 7.72 | 991 | 85588 | 11.58 | | 1.5(1.38-1.63)*** | 2.41(2.18-2.66)*** |
| Yes | 58 | 1994 | 29.07 | 46 | 1273 | 36.12 | | 1.28(0.87-1.89) | 2.3(1.42-3.74)*** |
| Hyperlipidemia | | | | | | | | | |
| No | 900 | 141647 | 6.35 | 703 | 71797 | 9.79 | | 1.54(1.4-1.7)*** | 2.36(2.09-2.66)*** |
| Yes | 464 | 29589 | 15.68 | 334 | 15064 | 22.17 | | 1.42(1.23-1.63)*** | 2.55(2.16-3.02)*** |
| Peripheral artery disease | | | | | | | | | |
| No | 1345 | 170600 | 7.88 | 1028 | 86376 | 11.9 | | 1.51(1.39-1.64)*** | 2.43(2.2-2.68)*** |
| Yes | 19 | 636 | 29.87 | 9 | 485 | 18.55 | | 0.62(0.28-1.37) | 1(0.36-2.81) |
| Atrial fibrillation | | | | | | | | | |
| No | 1342 | 170739 | 7.86 | 1021 | 86498 | 11.8 | | 1.5(1.39-1.63)*** | 2.45(2.22-2.7)*** |
| Yes | 22 | 496 | 44.3 | 16 | 363 | 44 | | 1.07(0.56-2.03) | 1.34(0.63-2.85) |
| Chronic kidney disease | | | | | | | | | |
| No | 1290 | 168044 | 7.68 | 986 | 85129 | 11.58 | | 1.51(1.39-1.64)*** | 2.45(2.22-2.71)*** |
| Yes | 74 | 3191 | 23.18 | 51 | 1732 | 29.44 | | 1.27(0.89-1.82) | 1.73(1.13-2.67)* |
| **Drug** | | | | | | | | | |
| NSAIDs | | | | | | | | | |
| Non-user | 481 | 25120 | 19.2 | 80 | 1732 | 46.2 | | 2.19(1.72-2.77)*** | 2.64(2.08-3.36)*** |
| Low | 375 | 43869 | 8.55 | 104 | 6146 | 16.9 | | 1.94(1.56-2.42)*** | 2.5(2-3.11)*** |
| Medium | 379 | 82853 | 4.57 | 362 | 35504 | 10.2 | | 2.22(1.92-2.57)*** | 2.54(2.2-2.95)*** |
| High | 129 | 19395 | 6.65 | 491 | 43481 | 11.3 | | 1.71(1.41-2.08)*** | 1.77(1.45-2.15)*** |




Abbreviations: IR, incidence rates, per 1,000 person-years; HR, hazard ratio; CI, confidence interval; Low, use NSAIDs less than 18 days; Medium, use NSAIDs between 18 and 132 days; High, use NSAIDs over 132 days.

Adjusted HR: adjusted for chronic low back pain, gender, age, depression, hypertensive disease, diabetes mellitus, coronary heart disease, congestive heart failure, hyperlipidemia, peripheral artery disease, atrial fibrillation, chronic kidney disease and NSAIDs in Cox proportional hazards regression.

*;<0.05; **;<0.01; *** p<0.001

**Fig. 3.** Stratification analysis of ischemic stroke associated with chronic low back pain.

**Table 3**
The risk of stroke stratified by chronic low back pain (CLBP) with different frequency of outpatient visits during the follow-up period. (2000 ~ 2010).

| Frequency, times/ per year | All stroke | | | | Hemorrhagic stroke | | | | Ischemic stroke | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | event no. (%) | aHR | (95% CI) | P-value | event no. (%) | aHR | (95% CI) | P-value | event no. (%) | aHR | (95% CI) | P-value |
| Control group | 1531 (57.5) | 1.00 | reference | | 182 (64.8) | 1.00 | reference | | 1364 (56.8) | 1.00 | reference | |
| Chronic low back pain | 186 (6.99) | 0.96 | (0.82–1.13) | 0.62 | 18 (6.41) | 0.64 | (0.39–1.06) | 0.08 | 169 (7.04) | 0.99 | (0.83–1.16) | 0.86 |
| group < 2 | | | | | | | | | | | | |
| 2-3 | 280 (10.5) | 2.26 | (1.97–2.60) | < 0.001 | 26 (9.25) | 1.67 | (1.08–2.58) | 0.02 | 256 (10.7) | 2.32 | (2.01–2.67) | < 0.001 |
| ≥4 | 664 (25) | 4.84 | (4.34–5.40) | < 0.001 | 55 (19.6) | 3.37 | (2.36–4.82) | < 0.001 | 612 (25.5) | 4.92 | (4.38–5.51) | < 0.001 |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

Adjusted HR: adjusted for chronic low back pain, gender, age, depression, hypertensive disease, diabetes mellitus, coronary heart disease, congestive heart failure, hyperlipidemia, peripheral artery disease, atrial fibrillation, chronic kidney disease and NSAIDs in Cox proportional hazards regression.

The mean follow-up periods were 8.40 and 8.28 years for the CLBP and the compared cohort, respectively.

risks of strokes, compared with the NLBP cohort.

In our study, CLBP was associated with increased risk for stroke in all age groups and subgroups without cardiovascular-related comorbidities. Exposure of chronic pain could induce elevated cortisol levels [18], and sympathetic-parasympathetic imbalances might promote atherosclerotic process [19]. Additionally, central sensitization from pro-inflammatory cytokines induced by CLBP might also play a role for further atherosclerotic change [20,21]. Strong association between chronic pain and depression has been reported [11,22,23]. Both chronic pain and depression were related with perspectives of brain regions for mood management like insular cortex, anterior cingulate, thalamus, hippocampus, and amygdala, etc. Therefore, chronic pain with related chronic neuroplasticity changes may play an important role leading to depression [11]. Besides, pain mediated by inflammatory response may correlate with depression more strongly [24,25]. Taken together, chronic pain, inflammation, emotional stress and depression often coexist on the CLBP patients. Therefore, our results in the higher risk for stroke in the CLBP patients could be clinically meaningful.

### 4.1. Study limitations and strengths

There are several limitations in this study owing to the features of NHIRD. Firstly, lifestyle-related risk factors for stroke as alcohol consumption, smoking status, obesity, sleeping disturbances and inactivity were unavailable from diagnostic codes, therefore the potential effects were not known. Interestingly, a cross-sectional survey revealed that neither objectively and subjectively measured physical activity nor sedentary behavior contributed to the association of chronic musculoskeletal pain with cardiovascular disease [12], which was in contrast with the earlier study [26]. Further prospective studies considering detailed lifestyle-related factors as alcohol consumption, smoking

status, obesity, sleeping disturbances and activity are in need.

This is the first large longitudinal study to explore whether CLBP patients are at risk for stroke. Key strengths of this survey are listed as below. Firstly, our strict criteria for identifying CLBP cohort would enhance the objectivity of the patient selection. Furthermore, the validation study of the NHIRD with ischemic stroke cases in Taiwan showed the accuracy rate of 94.51%–97.85%, which could confirm the reliability of the recognition of our study outcome well. [27] Secondly, we compared the CLBP cohort with propensity score-matched NLBP cohort, and investigated rigorously by considering extensive covariates. Thus, the results should be reliable and reproducible. Thirdly, the large sample size allowed us to have enough power to perform the subgroups stratification analysis (e.g., age, gender, comorbidities, and NSAIDs usage), therefore it increased the generalizability of the findings.

## 5. Conclusion

In conclusion, CLBP was associated with increased risk of strokes, especially ischemic stroke, and the association was most prominent in patients less than 50 years old. The severity of chronic pain in the CLBP patients was related to the higher risks of strokes. Further large prospective studies on detailed lifestyle-related factors and qualitative pain assessment are needed to clarify the causal relationship between CLBP and stroke.

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## Declaration of Competing Interest

All the authors have no conflicts of interest to disclose.

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