BMJ Open Association between benzodiazepine use and risks of chronic-onset poststroke pneumonia: a population-based cohort study

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ABSTRACT

Objectives To investigate the association between benzodiazepine (BZD) use and the risk of chronic-onset poststroke pneumonia.

Design Population-based propensity-matched retrospective cohort study.

Setting Taiwan’s National Health Insurance Research Database.

Participants Patients newly diagnosed with stroke between 2000 and 2012 were identified and, after propensity score matching, 7516 patients were enrolled. Among these, 3758 patients received BZDs after stroke while 3758 did not.

Outcome measures HRs for developing pneumonia over 1 month after stroke according to BZD use were assessed using Cox proportional hazards regression models. Analyses according to cumulative defined daily doses (cDDDs) of BZDs and stratification for age and sex were also performed.

Results During a mean follow-up time of 4.4 years, 1027 patients in the BZD cohort and 478 patients in the non-BZD cohort developed pneumonia over 1 month after stroke. Patients using BZDs after stroke had a higher pneumonia risk than did those not using BZDs (52.2 vs 32.6). The aHRs for developing pneumonia within 1 month of stroke according to BZD use were assessed using Cox proportional hazards regression models.

Conclusion BZD use is associated with an increased risk of chronic-onset poststroke pneumonia.

INTRODUCTION

Pneumonia is one of the most common serious medical complications that occurs after stroke, affecting up to one-third of patients with stroke. Previous studies have indicated that poststroke pneumonia is independently associated with poor prognoses, including higher morbidity and mortality, and decreased functional outcomes. Poststroke pneumonia can be divided into two types according to the time of occurrence: acute-onset refers to pneumonia developed within 1 month of the stroke event, while chronic onset was referred to as pneumonia developed after 1 month of stroke. Poststroke pneumonia is also a considerable financial burden to healthcare systems. Thus, developing strategies to prevent poststroke pneumonia is an important clinical issue.

As modulators of the γ-aminobutyric acid type A receptor (GABA_A), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm and epilepsy. Previous studies have postulated that BZDs may increase the risk of pneumonia, possibly on account of nocturnal and daytime sedation, an increased risk of aspiration and the possible depression of immune cells. However, the link between BZD use and increased risk of pneumonia has been disputed by other studies, and thus the association between these factors remains unclear.

Strengths and limitations of this study

- This retrospective cohort study was performed based on a nationwide population database, which contained one million subjects randomly sampled from Taiwan’s population.
- This is the first large-scale study to demonstrate an association between benzodiazepine use and pneumonia risk in patients who had a stroke over a long-term follow-up period.
- The claim-based data did not allow for the retrieval of certain clinical information (eg, patient lifestyle and physical, psychiatric or laboratory examination data), and thus we could not control or adjust for these potential confounders in our analyses.

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A considerable proportion of stroke survivors are prescribed BZDs, owing to the high prevalence of post-stroke psychological problems, such as insomnia, depression and anxiety. Although pneumonia is a serious medical complication that can lead to a poor prognosis, to our knowledge, only one prior study has addressed the association between BZD use and the risk of pneumonia in patients poststroke; moreover, that study used a short follow-up period. Indeed, investigations into chronic-onset poststroke pneumonia over long-term follow-up periods in stroke survivors are still lacking. Therefore, we conducted a population-based retrospective cohort study to evaluate the association between BZD use and the risk of chronic-onset poststroke pneumonia in a large sample of stroke survivors over a long study period.

METHODS

Data sources
We conducted a population-based retrospective cohort study by analysing claims data obtained from Taiwan’s National Health Insurance Research Database (NHIRD). The national health insurance (NHI) programme of Taiwan, which was launched in March 1995 and is administered by the government, is a mandatory single-payer NHI system that covers more than 99% of Taiwan’s residents and has contracts with 97% of the hospitals and clinics in Taiwan. Data in the current study were obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the NHIRD that contains a representative database of one million people from NHI beneficiaries registered in Taiwan in the year 2000. For research purposes, the LHID2000 was systemically and randomly sampled by the National Health Research Institute from the Taiwanese population. The database included medical claims of all inpatient, outpatient, emergency department and home care services. Before releasing the database, information related to personal identification was encrypted to protect patient privacy and data security. National Health Research Institute approval was obtained prior to using the LHID2000 in this study. Diagnostic disease codes were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This coding is considered highly reliable in the NHIRD, as insurance claims have been investigated by medical reimbursement specialists and the coding system has undergone peer review.

Study population
The same database used in our previous study was employed here. The database comprised adult patients (aged ≥20 years) with new-onset stroke occurring between 2000 and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM codes 430–437). The ‘index date’ was defined as the date of the new-onset stroke diagnosis, while ‘index hospitalisation’ was defined as concurrent hospitalisation for stroke. Exclusion criteria for this study were as follows: (1) history of stroke before the 2000–2012 study period, (2) history of pneumonia 1 year preceding the index date, (3) concurrent diagnosis of pneumonia during the index hospitalisation and/or (4) death during the index hospitalisation.

Exposure to BZDs
In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only obtain such drugs through a doctor’s prescription. We identified BZD prescriptions written after the index hospitalisation using the prescription database in the LHID. The study population was then divided into BZD and non-BZD cohorts. The BZD cohort included patients who had used any BZDs after stroke during the follow-up period, while the non-BZD cohort comprised patients who were not prescribed BZDs poststroke. To evaluate the effects of different BZD doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD) methodology—a WHO-recommended unit of measure employed to evaluate the prescribed amount of a drug for its main indication in an adult. Note that DDD methodology is widely used for the investigation of administrative pharmacy claim data. Using this approach, we calculated the cumulative DDD (cDDD) by determining the sum of the dispensed DDD of all BZDs. This value was then employed to quantify BZD use during the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365 and >365 cDDD subgroups.

Outcome measures and sensitivity analysis
The main outcome of this study was defined as the occurrence of chronic-onset poststroke pneumonia after index hospitalisation, as identified by a discharge diagnosis of pneumonia (ICD-9-CM codes of 480–486). In order to increase the accuracy of this outcome, only patients with pneumonia who required hospitalisation were considered. According to previous research, chronic-onset poststroke pneumonia is defined as pneumonia developing over 1 month after the incidence of stroke. As the present study evaluated chronic-onset poststroke pneumonia, cases of pneumonia diagnosed within 30 days of the stroke event were excluded. The identification of patients with pneumonia using ICD-9-CM coding in inpatient service has been previously validated and shows high accuracy. All subjects were followed up from the index date until the first occurrence of pneumonia, death or until 31 December 2013. Death was defined as a patient withdrawn from the NHI programme, as previous studies have indicated that this is an accurate and reliable proxy for date of death. Analyses stratified by age and sex were also performed.

In addition, to examine whether a diagnosis of pneumonia rendered in an outpatient service would influence our results, we performed a sensitivity analysis. For this analysis, pneumonia events were defined as those diagnosed during the follow-up period regardless of whether
the diagnosis was rendered in an inpatient or outpatient service.

**Covariates and propensity score matching**

Baseline characteristics, such as demographic data, socio-economic status, comorbidities and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and procedure codes. A pre-existing comorbidity was defined as a disease diagnosed at least one time during inpatient service or two times during outpatient visits within the year prior to the index date. The Charlson Comorbidity Index was calculated according to information related to pre-existing comorbidities. Baseline medication use was defined as any medication taken for at least 30 days over the course of the year preceding the index date. Information related to stroke severity proxies was obtained based on the indicated clinical condition during the index hospitalisation. Such information included diagnosis codes for hemiplegia and aphasia, operation/procedural codes for head surgery, mechanical ventilation and utilisation of the intensive care unit, as mentioned in our previous studies. In addition, estimated National Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of neurological deficits, converting scores from a claims-based Stroke Severity Index (SSI)—a measure specifically developed for use with Taiwan’s NHIRD claims-based data—with a formula developed by Hsieh et al (estimated NIHSS=1.1722 × SSI − 0.7533). The SSI has been validated in previous studies and is highly correlated with the NIHSS and consequent functional outcomes after stroke. Additionally, some comorbidities may occur after stroke and also possibly cause a confounding effect. We therefore calculated an additional Charlson Comorbidity Index at the end point of follow-up, using the data on comorbidities from the year prior to the end-point date. Socioeconomic status was determined according to patient income and dwelling urbanisation levels. Income, which was accessed based on NHI premiums, was classified into four levels (New Taiwan dollars ≥ 40,000, 20,000–39,999, 1–19,999 and financially dependent). Urbanisation was classified into five levels, with level-1 corresponding to the most urbanised areas. Detailed descriptions of income and urbanisation levels have been described in our previous studies.

In order to decrease the selection bias between groups, propensity score matching was performed to balance patient baseline characteristics, including age, sex, income level, urbanisation level, comorbidities, Charlson Comorbidity Index, stroke severity proxies and medication use (table 1). A logistic regression model was used to calculate a propensity score which estimated the probability of BZD use based on all baseline covariates for each BZD user and non-user. Using the method of nearest-neighbour matching without replacement (with a calliper width equal to 0.2 SD of the propensity score logit), we matched each BZD user with a non-BZD user.

| Table 1 | Baseline characteristics of patients poststroke in the BZD and non-BZD cohorts after propensity score matching |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | **BZD use** | **Yes (n=3758)** | **No (n=3758)** | **P value** |
| Age (years) | 66.2±14.9 | 66.3±14.7 | 0.941 |
| Sex | | | | 0.267 |
| Male | 2455 | 65.3 | 2409 | 64.1 |
| Female | 1303 | 34.7 | 1349 | 35.9 |
| Income level (NTD) | | | | 0.816 |
| Financially dependent | 1123 | 29.9 | 1125 | 29.9 |
| 1–19,999 | 1801 | 47.9 | 1826 | 48.6 |
| 20,000–39,999 | 522 | 13.9 | 516 | 13.7 |
| ≥40,000 | 312 | 8.3 | 291 | 7.7 |
| Urbanisation level | | | | 0.732 |
| 1 (most urbanised) | 974 | 25.9 | 985 | 26.2 |
| 2 | 993 | 26.4 | 1010 | 26.9 |
| 3 | 791 | 21.0 | 744 | 19.8 |
| 4 | 579 | 15.4 | 580 | 15.4 |
| 5 (least urbanised) | 421 | 11.2 | 439 | 11.7 |
| Comorbidities | | | | |
| Charlson Comorbidity Index | 2.26±1.50 | 2.27±1.63 | 0.837 |
| Hypertension | 2666 | 70.9 | 2666 | 70.9 | 1.000 |
| Diabetes mellitus | 1263 | 33.6 | 1256 | 33.4 | 0.864 |
| COPD | 247 | 6.6 | 265 | 7.1 | 0.410 |
| Asthma | 114 | 3.0 | 112 | 3.0 | 0.893 |
| Chronic kidney disease | 180 | 4.8 | 198 | 5.3 | 0.342 |
| Cirrhosis | 200 | 5.3 | 207 | 5.5 | 0.721 |
| Coronary artery disease | 491 | 13.1 | 528 | 14.1 | 0.213 |
| Congestive heart failure | 192 | 5.1 | 202 | 5.4 | 0.605 |
| Hypoventilation | 6 | 0.2 | 7 | 0.2 | 0.781 |
| Hyperlipidaemia | 1096 | 29.2 | 1080 | 28.7 | 0.684 |
| Malignancy | 188 | 5.0 | 176 | 4.7 | 0.519 |
| Dementia | 207 | 5.5 | 208 | 5.5 | 0.960 |
| Depression | 34 | 0.9 | 50 | 1.3 | 0.079 |
| Parkinsonism | 107 | 2.8 | 106 | 2.8 | 0.945 |
| Epilepsy | 24 | 0.6 | 26 | 0.7 | 0.777 |
| Bipolar disorders | 3 | 0.1 | 3 | 0.1 | 1.000 |
| Alcohol-related disorders | 14 | 0.4 | 19 | 0.5 | 0.383 |
| Substance use disorders | 18 | 0.5 | 18 | 0.5 | 1.000 |
| Schizophrenia | 18 | 0.5 | 16 | 0.4 | 0.731 |

Continued
Continuous statistical analysis
Continuous variables between the BZD and non-BZD cohort were compared using independent t-tests, while categorical variables were compared using $\chi^2$ tests. The Kaplan-Meier method was performed to estimate the risk of developing pneumonia, and the log-rank test was used to compare differences between cumulative incidence curves. Univariate and multivariate Cox proportional hazards regression models were used to compute the HRs and corresponding 95% CIs for developing pneumonia after stroke; all baseline characteristics listed in table 1 were adjusted for when conducting the multivariate Cox proportional hazards regression models. To eliminate possible bias caused by competing mortality, modified Cox proportional hazards regression models were used with adjustment for competing risk events. Differences were considered statistically significant at a two-sided probability value of <0.05. All statistical analyses were performed using Stata V.13.

**Patient and public involvement**
Due to the present study having used deidentified secondary data, the patients and public were not directly involved in this study, and the need for consent was waived.

**RESULTS**

**Demographic characteristics**

After propensity score matching according to the baseline characteristics listed in table 1, a total of 7516 patients with newly onset stroke were included in our study. Among these patients, 3758 received BZDs and were classified into the BZD cohort, while 3758 did not receive BZDs and were classified into the non-BZD cohort. Although most baseline characteristics were well-balanced after propensity score matching, significant differences were found regarding the baseline prevalence of sleep disorders and the proportion of patients using antihypertensive agents and anxiolytics; however, the actual between-group differences were minor (table 1).

**Risk of chronic-onset poststroke pneumonia according to BZD use**

During a mean follow-up of 4.4 years, 1027 patients in the BZD cohort (52.2/1000 person-years), compared with 478 patients in the non-BZD cohort (32.6/1000 person-years), developed pneumonia. A Kaplan-Meier analysis revealed a significantly higher cumulative incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, p<0.0001) (figure 1). Cox proportional hazards regression models.

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**Table 1** Continued

|                  | BZD use (n=3758) | No (n=3758) | P value |
|------------------|------------------|-------------|---------|
| Anxiety          | 90 2.4           | 104 2.8     | 0.309   |
| Sleep disorders  | 170 4.5          | 186 4.9     | 0.385   |
| Charlson Comorbidity Index at the end point of follow-up | 2.03±1.79 2.13±2.06 | 0.022 |
| Estimated NIHSS  | 8.0±6.0          | 7.7±5.8     | 0.061   |
| ICU utilisation  | 937 24.9         | 871 23.2    | 0.075   |
| Mechanical ventilation | 308 8.2       | 299 8.0    | 0.703   |
| Hemiplegia       | 562 15.0         | 530 14.1    | 0.295   |
| Aphasia          | 69 1.8           | 63 1.7      | 0.598   |
| Neurosurgery     | 202 5.4          | 210 5.6     | 0.685   |
| Use of medication |                |             |         |
| Steroids         | 109 2.9          | 116 3.1     | 0.636   |
| Antidiabetic agents | 795 21.2     | 821 21.8    | 0.465   |
| Antihypertensive agents | 1676 44.6 | 1715 45.6  | 0.366   |
| Statins          | 319 8.5          | 332 8.8     | 0.594   |
| Proton pump inhibitors | 89 2.4   | 97 2.6     | 0.553   |
| Antiepileptics   | 70 1.9           | 82 2.2      | 0.325   |
| Antiparkinsonian | 92 2.4           | 90 2.4      | 0.881   |
| Antipsychotics   | 76 2.0           | 85 2.3      | 0.473   |
| Anxiolytics      | 246 6.5          | 286 7.6     | 0.072   |
| Hypnotics and sedatives | 156 4.2  | 180 4.8    | 0.180   |
| Antidepressants  | 79 2.1           | 97 2.6      | 0.170   |

Continuous data expressed as means±SD and categorical data expressed as number and percentage.

BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NIHSS, National Institutes of Health Stroke Scale.; NTD, New Taiwan dollars.

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**Figure 1** Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use poststroke. BZD, benzodiazepine.
hazards regression models revealed that BZD use after stroke was associated with an increased risk of pneumonia in both the univariate (crude HR=1.95, 95% CI=1.75 to 2.17, \(p<0.001\)) and multivariate models (adjusted HR (aHR)=2.21, 95% CI=1.97 to 2.48, \(p<0.001\)) (table 2).

### Analyses according to different cumulative BZD doses

Patients in all three cDDD subgroups had a higher risk of developing pneumonia than did the non-BZD cohort. The aHRs for the 1–90, 91–365 and >365 cDDD subgroups were 2.28 (95% CI=2.01 to 2.58; \(p<0.001\)), 2.09 (95% CI=1.77 to 2.47; \(p<0.001\)) and 2.08 (95% CI=1.72 to 2.52; \(p<0.001\)), respectively (table 3).

### Analyses after stratification for age and sex

The association between BZD use and the risk of pneumonia development in patients who had a stroke was further analysed after stratification for age and sex (table 4). Using this approach, we found a significantly greater risk of pneumonia in BZD users than in non-users in both age subgroups (<65 years old: aHR=2.42, 95% CI=1.84 to 3.17, \(p<0.001\); \geq 65 years old: aHR=2.11, 95% CI=1.76 to 2.49, \(p<0.001\)). Additionally, BZD users had an increased risk of pneumonia in both male (aHR=2.46, 95% CI=2.13 to 2.84, \(p<0.001\)) and female (aHR=1.83, 95% CI=1.50 to 2.22, \(p<0.001\)) subgroups (table 4). Together, these results reveal that BZD use after stroke was associated with an increased risk of pneumonia regardless of age and sex.

### Results of sensitivity analysis

In the sensitivity analysis, which considered the pneumonia event regardless of diagnosis in inpatient or outpatient service, BZD use was independently associated with increased risk of developing pneumonia (adjusted

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**Table 2** Risk of pneumonia after stroke among patients in the BZD and non-BZD cohorts

| BZD use | Yes | No |
|---------|-----|----|
| Patient numbers | 3758 | 3758 |
| Pneumonia cases | 1027 | 478 |
| Person-years | 19680.1 | 14663.8 |
| Incidence rate* | 52.2 | 32.6 |

**Univariate model**

- Crude HR (95% CI) | 1.95 (1.75 to 2.17) | 1 (ref) |
- P value | \(<0.001\) |

**Multivariate model†**

- Adjusted HR (95% CI) | 2.21 (1.97 to 2.48) | 1 (ref) |
- P value | \(<0.001\) |

*Per 1000 person-years.
†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in table 1) and competing mortality.

**Table 3** Risk of pneumonia after stroke according to different cumulative BZD doses

| Cumulative BZD doses | n | Person-years | Pneumonia cases | Incidence rate* |
|----------------------|---|--------------|-----------------|-----------------|
| Non-user             | 3758 | 19680.1 | 1027 | 52.2 |
| 1–90 cDDDs           | 2507 | 7602.2 | 702 | 59.7 |
| 91–365 cDDDs         | 728 | 4036.6 | 198 | 47.0 |
| >365 cDDDs           | 523 | 3703.4 | 127 | 34.3 |

**Univariate model**

- Crude HR (95% CI) | 2.10 (1.87 to 2.36) | 1 (ref) |
- Adjusted HR (95% CI) | 2.28 (2.01 to 2.58) | 1 (ref) |
- P value | \(<0.001\) |

**Multivariate model†**

- Adjusted HR (95% CI) | 2.09 (1.77 to 2.47) | 1 (ref) |
- P value | \(<0.001\) |

*Per 1000 person-years.
†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in table 1) and competing mortality.

BZD, benzodiazepine.
HR=1.94, 95% CI=1.77 to 2.14, p<0.001). The results for different cumulative doses of BZDs also revealed a pattern to our primary analyses. The detailed statistical values are shown in the online supplementary materials (online supplementary table S1).

**Table 4 Risk of pneumonia after stroke in the BZD and non-BZD cohorts after stratification for age and sex**

|                | BZD use | Non-BZD use | Univariate model | Multivariate model* |
|----------------|---------|-------------|------------------|---------------------|
|                | n       | Pneumonia cases | Person-years | Incidence rate† | n | Pneumonia cases | Person-years | Incidence rate† | Crude HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
| Age            |         |              |                 |                   |              |              |                 |                   |                     |         |                       |         |
| <65            | 1599    | 221         | 10,438.4       | 21.2              | 1626         | 77           | 7,568.1       | 10.2              | 2.32 (1.79 to 3.00) | <0.001  | 2.42 (1.84 to 3.17) | <0.001  |
| ≥65            | 2159    | 806         | 9,241.7        | 87.2              | 2132         | 401          | 7,095.7       | 56.5              | 1.94 (1.72 to 2.18) | <0.001  | 2.11 (1.86 to 2.40) | <0.001  |
| Sex            |         |              |                 |                   |              |              |                 |                   |                     |         |                       |         |
| Male           | 2455    | 721         | 12,709.5       | 56.7              | 2409         | 278          | 9,945.3       | 28.0              | 2.35 (2.04 to 2.69) | <0.001  | 2.46 (2.13 to 2.84) | <0.001  |
| Female         | 1303    | 306         | 6,970.6        | 43.9              | 1349         | 200          | 4,718.5       | 42.4              | 1.39 (1.16 to 1.66) | <0.001  | 1.83 (1.50 to 2.22) | <0.001  |

*Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in table 1) and competing mortality.
†Per 1000 person-years.
BZD, benzodiazepine.

**DISCUSSION**

This population-based propensity-matched retrospective cohort study investigated the association between BZD use and the risk of chronic-onset poststroke pneumonia. We observed that patients prescribed BZDs poststroke had a risk of developing pneumonia that was 2.21 times higher than that for patients who had not been prescribed BZDs. To the best of our knowledge, this is the first large-scale study to demonstrate an association between BZD use and the risk of chronic-onset poststroke pneumonia over a long-term follow-up period.

Our results are consistent with those previously reported from studies that focused on the general population. For example, previous observational studies found a 17% increase in the risk of pneumonia development in BZD users when compared with non-BZD users (relative risk of 1.18). However, other observational studies have reported conflicting results showing negative or non-significant relationships between BZD use and the risk of pneumonia. For instance, a previous case–control study on participants aged ≥65 years old did not find a significant association between BZD use and the risk of pneumonia (relative risk of 1.05). Nevertheless, the results of our study add to the increasing body of evidence suggesting that BZD use may be associated with an increased risk of pneumonia in stroke patients.

Pneumonia is a significant complication in stroke patients owing to the increased risk of apparent aspiration and dysphagia-associated microaspiration, as well as stroke-induced immunodepression. Acute-onset poststroke pneumonia, which develops within 1 month of the stroke event, is mainly associated with apparent aspiration and stroke-induced immunodepression. However, chronic-onset poststroke pneumonia, which develops over a relatively short study period and focused on the general population, may be associated with the increased risk of aspiration and depression of immune cells by BZDs. Therefore, it is important to further investigate the long-term effects of BZD use on the risk of pneumonia development in stroke patients.

Table 4 shows the risk of pneumonia after stroke in the BZD and non-BZD cohorts after stratification for age and sex. The results indicate that BZD users had a statistically significant higher risk of pneumonia compared to non-BZD users, with an adjusted hazard ratio of 2.11 (95% CI: 1.86 to 2.40) for patients aged ≥65 years. These findings are consistent with previous studies that have reported an increased risk of pneumonia in BZD users compared to non-BZD users.

In conclusion, our study provides further evidence for the association between BZD use and the risk of chronic-onset poststroke pneumonia. However, more research is needed to fully understand the underlying mechanisms and to develop strategies to mitigate this risk.

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**Conflicts of interest**

The authors declare no conflicts of interest.

**Ethical approval**

This study was approved by the institutional review board of the participating hospitals.

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contrast, the current study, which specifically focused on the chronic phase of poststroke to evaluate pneumonia developed over 1 month after the stroke,7 included a large sample size and long-term follow-up period (mean follow-up time, 4.4 years). The present study revealed a significantly increased risk of chronic-onset pneumonia in stroke survivors using BZDs (aHR=2.21), even after carefully controlling for socioeconomic status, important comorbidities, stroke severity proxies and concomitant medications. In addition, the subgroup analyses, which were performed according to cumulative BZD doses and stratified for age and sex, also revealed a similar pattern of results, further strengthening our findings. As pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burdens, we believe that our study addresses a knowledge gap regarding the clinical management of patients after stroke.

Although the exact biological mechanisms underlying the influence of BZDs on pneumonia remain unclear, some hypotheses have been reported. One previous animal study suggested that BZDs may negatively influence immune function via the activation of GABA<sub>A</sub> receptors on immune cells, thus interfering with macrophages/monocytes and impairing cytokine release, phagocytosis and bacterial killing capabilities.12 In addition, BZDs may increase the risk of aspiration by decreasing lower oesophageal sphincter pressure, inducing the relaxation of muscles in the upper respiratory tract, and depressing the swallowing reflex, ultimately leading to pharyngeal dysfunction.11 13 40 Further research is necessary to explore these postulated mechanisms.

The strengths of the present study include its large sample size, use of a nationwide population database and the provision of sufficient power to evaluate the effect of BZDs on the risk of pneumonia development after stroke over a long-term follow-up period. The study design also provided better evidence in terms of epidemiology than previous studies that used case–control or cross-sectional designs. Moreover, performing propensity score matching before our analyses and then using multivariate Cox proportional hazard regression models with adjustment for competing mortality allowed us to rule out several important sources of bias and ensure that confounding factors were carefully controlled.

The following limitations of the present study should also be acknowledged. First, the claim-based database did not allow for the retrieval of certain clinical information (eg, patient lifestyle and physical, psychiatric or laboratory examination data). Although our study design ensured the control of several variables, unknown or unmeasured confounders could still exist. Second, by using deidentified claims, we could not obtain the patient details to analyse the medical history and identify exact mechanism of pneumonia; thus, we could not determine whether the pneumonia was caused by aspiration or not. Third, our analyses performed according to different cumulative BZD doses did not reveal an obvious dose–effect relationship. It is difficult to completely avoid an indication bias in observational studies that evaluate the effect of medication or intervention. Hence, the existence of unidentified residual confounders (ie, the effect of the underlying aetiologies needing BDZ prescription, other exposures, etc) cannot be completely ruled out from the present study. Thus, further prospective clinical trials are necessary to address these possible biases and to determine the cause-and-effect relationship between poststroke BDZ use and the pneumonia risk. Finally, the accuracy of the diagnostic coding could not be directly confirmed due to the anonymity policy enforced in the NHIRD. However, only patients who were hospitalised under a primary diagnosis of stroke were included in our study population. The identification of stroke and pneumonia using ICD-9-CM coding in inpatient services has been previously validated and shows high accuracy.24 41 42 Additionally, the claims were routinely and randomly reviewed by the NHI Bureau to confirm the diagnostic accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the inclusion of stroke and pneumonia cases in this study.

CONCLUSIONS

In summary, this population-based propensity-matched retrospective cohort study indicated an association between BDZ use and an increased risk of chronic-onset poststroke pneumonia. However, further large-scale prospective studies are needed to determine possible cause–effect relationships.

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