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The association between benzodiazepine use and pneumonia risk among patients with stroke: A population-based cohort study

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Manuscripts

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3 **The association between benzodiazepine use and pneumonia risk among**
4 **patients with stroke: A population-based cohort study**
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Abstract

Objectives

To investigate the association between benzodiazepine (BZD) use and the risk of pneumonia after stroke.

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, 7602 patients were enrolled. Among these, 3801 patients received BZDs after stroke while 3801 did not.

Outcome measures

Hazard ratios (HRs) for developing pneumonia after stroke according to BZD use were assessed using Cox proportional hazards regression models. Analyses according to cumulative defined daily doses (cDDD) of BZDs and stratification for age and sex were also performed.

Results

During a mean follow-up time of 4.4 years, 1218 patients in the BZD cohort and 526 patients in the non-BZD cohort developed pneumonia post-stroke. Patients using BZDs after stroke had a higher pneumonia risk than did those not using BZDs (63.9 vs. 35.9 per 1000 person-years, adjusted HR [aHR] = 2.33, 95% confidence interval [CI] = 2.09–2.59, $p < 0.001$). Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated with a higher risk of post-stroke pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDDs of BZDs were 2.26 (95% CI = 2.01–2.53; $p < 0.001$), 2.47 (95% CI = 2.12–2.87; $p < 0.001$), and 2.52 (95% CI = 2.13–2.99; $p < 0.001$), respectively. The significant association between BZD use and increased pneumonia risk persisted even after

1
2
3 stratifying subgroups by age and sex.

4 5 **Conclusions**

6
7 BZD use is associated with an increased risk of post-stroke pneumonia.

10 11 **Strengths and limitations of this study**

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

Pneumonia is one of the most common serious medical complications that occurs after stroke,¹ affecting up to one third of patients with stroke.^{2,3} Previous studies have indicated that post-stroke pneumonia is independently associated with poor prognoses, including higher morbidity and mortality, and decreased functional outcomes.^{1,4-6} Post-stroke pneumonia is also a considerable financial burden to health-care systems.⁷ Thus, developing strategies to prevent post-stroke pneumonia is an important clinical issue.

As modulators of the γ -amino butyric 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.⁸ Previous studies have postulated that BZDs may increase the risk of pneumonia, suggesting the cause may be related to nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells.⁸⁻¹² However, the link between BZD use and increased risk of pneumonia has been disputed by other studies,¹³⁻¹⁷ and thus the association between these factors remains unclear.

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.^{16,18,19} Although post-stroke 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 development in patients post-stroke; moreover, that study utilized a short follow-up period.¹⁶ Indeed, investigations 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 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 analyzing claims data obtained from Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and is administered by the government, is a mandatory single-payer national health insurance 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.^{20 21} 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.²² The study protocol we applied was approved by the Institutional Review Board of Tzu Chi Medical Center. The requirement for patient consent was waived owing to the retrospective nature of this study using de-identified secondary data.

Study population

The same database used in our previous study was employed here.²¹ The database is comprised of adult patients (aged ≥ 20 years) with new-onset stroke occurring between 2000

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3 and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM
4 codes 430–437). The “index date” was defined as the date of the new-onset stroke diagnosis,
5 while “index hospitalization” was defined as concurrent hospitalization for stroke. Exclusion
6 criteria for this study were as follows: 1) history of stroke before the 2000–2012 study period;
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11 2) history of pneumonia 1 year preceding the index date; 3) concurrent diagnosis of
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13 pneumonia during the index hospitalization; and/or 4) death during the index hospitalization.
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16 17 **Exposure to benzodiazepines**

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19 In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only
20 obtain such drugs through a doctor’s prescription. We identified BZD prescriptions written
21 after the index hospitalization using the prescription database in the LHID. The study
22 population was then divided into BZD and non-BZD cohorts. The BZD cohort included
23 patients who had used any BZDs after stroke, while the non-BZD cohort was comprised of
24 patients who were not prescribed BZDs post-stroke. To evaluate the effects of different BZD
25 doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD)
26 methodology—a World Health Organization-recommended unit of measure employed to
27 evaluate the prescribed amount of a drug for its main indication in an adult. Note that DDD
28 methodology is widely used for the investigation of administrative pharmacy claim data.^{20 22}
29 Using this approach, we calculated the cumulative DDD (cDDD) by determining the sum of
30 the dispensed DDD of all BZDs. This value was then employed to quantify BZD use during
31 the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365, and
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>365 cDDD subgroups.

51 **Outcome measures**

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53 The main outcome of this study was defined as the occurrence of pneumonia after index
54 hospitalization, as identified by a discharge diagnosis of pneumonia (ICD-9-CM codes of
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3 480–486). In order to increase the accuracy of this outcome, only pneumonia patients that
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5 required hospitalization were considered. To focus on the long-term prognosis, cases of
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7 pneumonia that were diagnosed during index hospitalization for stroke were excluded. The
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9 identification of patients with pneumonia using ICD-9-CM coding in inpatient service has
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11 been previously validated and shows high accuracy.²³ All subjects were followed-up on, from
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13 the index date until the first occurrence of pneumonia, death, or until December 31, 2013.
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15 Death was defined as a patient withdrawn from the NHI program,²⁴ as previous studies have
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17 indicated that this is an accurate and reliable proxy for date of death.^{25 26} Analyses stratified
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19 by age and sex were also performed.
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24 **Covariates and propensity score matching**

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26 Baseline characteristics, such as demographic data, socioeconomic status, comorbidities,
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28 and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and
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30 procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one
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32 time during inpatient service or two times during outpatient visits within the year prior to the
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34 index date. Charlson comorbidity index scores were calculated according to information
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36 related to preexisting comorbidities.²⁷ Baseline medication use was defined as any medication
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38 taken for at least 30 days over the course of the year preceding the index date. Information
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40 related to stroke severity proxies was obtained based on the indicated clinical condition during
41
42 the index hospitalization. Such information included diagnosis codes for hemiplegia and
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44 aphasia, operation/procedural codes for head surgery, mechanical ventilation, and utilization
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46 of the intensive care unit, as mentioned in our previous studies.^{21 28} In addition, estimated
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48 National Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the
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50 severity of neurologic deficits, converting scores from a claims-based stroke severity index
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52 (SSI)—a measure specifically developed for use with Taiwan’s NHIRD claims-based
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54 data—with a formula developed by Hsieh et al. (estimated NIHSS = 1.1722 × SSI –
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3 0.7533).^{29 30} The SSI has been validated in previous studies and is highly correlated with the
4
5 NIHSS and consequent functional outcomes after stroke.³⁰⁻³²
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7 Socioeconomic status was determined according to patient income and dwelling
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9 urbanization levels. Income, which was accessed based on NHI premiums, was classified into
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11 four levels (New Taiwan dollars $\geq 40,000$, 20,000–39,999, 1–19,999, and financially
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13 dependent). Urbanization was classified into five levels, with level 1 corresponding to the
14
15 most urbanized areas.³³ Detailed descriptions of income and urbanization levels have been
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17 described in our previous studies.^{21 28}
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20 In order to decrease the selection bias between groups, propensity score matching was
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22 performed to balance patient baseline characteristics, including age, sex, income level,
23
24 urbanization level, comorbidities, stroke severity proxies, and medication use (Table 1). A
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26 logistic regression model was used to calculate a propensity score, which estimated the
27
28 probability of BZD use based on all baseline covariates for each BZD user and non-user.
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30 Using the method of nearest-neighbor matching without replacement (with a caliper width
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32 equal to 0.2 standard deviations of the propensity score logit), we matched each BZD user
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34 with a non-BZD user.^{21 34 35}
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39 **Statistical analysis**

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41 Continuous variables between the BZD and non-BZD cohort were compared using
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43 independent *t*-tests, while categorical variables were compared using chi-squared tests. The
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45 Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the
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47 log-rank test was used to compare differences between cumulative incidence curves.
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49 Univariate and multivariate Cox proportional hazards regression models were used to
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51 compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for
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53 developing pneumonia after stroke; all baseline characteristics listed in Table 1 were adjusted
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55 for when conducting the multivariate Cox proportional hazards regression models. To
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3 eliminate possible bias caused by competing mortality, modified Cox proportional hazards
4 regression models were used with adjustment for competing risk events.^{24 36} Differences were
5 considered statistically significant at a two-sided probability value of <0.05. All statistical
6 analyses were performed using Stata version 13 (Stata Corporation, College Station, TX,
7 USA).
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Results

Demographic characteristics

After propensity score matching according to the baseline characteristics listed in Table 1, a total of 7602 patients with newly onset stroke were included in our study. Among these patients, 3801 received BZDs and were classified into the BZD cohort, while 3801 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 anti-hypertensive agents and anxiolytics; however, the actual between-group differences were minor (Table 1).

Risk of post-stroke pneumonia according to BZD use

During a mean follow-up of 4.4 years, 1218 patients in the BZD cohort (63.9/1000 person-years), compared to 526 patients in the non-BZD cohort (35.9/1000 person-years), developed pneumonia post-stroke. 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 revealed that BZD use after stroke was associated with an increased risk of pneumonia in both the univariate (crude HR = 2.15, 95% CI = 1.94–2.38, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.33, 95% CI = 2.09–2.59, $p < 0.001$) (Table 2).

Analyses according to different cumulative BZD doses

Patients in all three cDDD subgroups had a higher risk of developing post-stroke pneumonia than did the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were 2.26 (95% CI = 2.01–2.53; $p < 0.001$), 2.47 (95% CI = 2.12–2.87; $p < 0.001$), and 2.52 (95% CI = 2.13–2.99; $p < 0.001$), respectively (Table 3).

Analyses after stratification for age and sex

The association between BZD use and the risk of post-stroke pneumonia development was further analyzed 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 = 2.99, 95% CI = 2.33–3.84, $p < 0.001$; ≥ 65 years old: aHR = 2.16, 95% CI = 1.92–2.43, $p < 0.001$). Additionally, BZD users had an increased risk of pneumonia in both male (aHR = 2.46, 95% CI = 2.15–2.82, $p < 0.001$) and female (aHR = 2.09, 95% CI = 1.74–2.50, $p < 0.001$) 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.

Discussion

This population-based propensity-matched retrospective cohort study investigated the association between BZD use and the risk of post-stroke pneumonia. We observed that patients prescribed BZDs post-stroke had a risk of developing pneumonia that was 2.33 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 pneumonia risk in patients post-stroke over a long-term follow-up period.

Our results are consistent with those previously reported by studies that focused on the general population.⁸⁻¹⁰ For example, previous observational studies found a 54 to 176% increase in the risk of pneumonia development in BZD users when compared to non-BZD users (relative risk or odds ratio: 1.54,⁸ 1.86,⁹ and 2.76¹⁰). However, other observational studies have reported conflicting results, showing negative or nonsignificant relationships between BZD use and the risk of pneumonia.¹³⁻¹⁵⁻¹⁷ For instance, a previous case-control study on participants aged ≥ 65 years old did not find a significant association between BZD use and pneumonia risk; however, only 87 BZD users were found among all of the pneumonia cases included in that study.¹³ Another cross-sectional study using 30-, 60-, and 90-day windows revealed protective effects of BZDs on the risk of pneumonia, but was conducted over a relatively short study period and focused on the general population.¹⁷

To our knowledge, the only previous study to focus on the association between BZDs and pneumonia in stroke patients did not reveal a significant association between BZD use and the risk of pneumonia post-stroke; however, in that study, the follow-up period for identifying pneumonia was only 90 days post-stroke.¹⁶ In contrast, the current study, which specifically focused on patients with stroke and included a large sample size and long-term follow-up period (mean follow-up time, 4.4 years), revealed a significantly increased risk of pneumonia in stroke survivors using BZDs (aHR = 2.33), even after carefully controlling for socioeconomic status, important comorbidities, stroke severity proxies, and concomitant

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3 medications. In addition, the subgroup analyses, which were performed according to
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5 cumulative BZD doses and stratified for age and sex, also revealed a similar pattern of results,
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7 further strengthening our findings. As pneumonia is one of the most common serious medical
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9 complications following stroke and can cause not only poor functional outcomes but also high
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11 mortality and financial burdens, we believe that our study addresses a knowledge gap
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13 regarding the clinical management of patients after stroke.
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16 Although the exact biological mechanisms underlying the influence of BZDs on
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18 pneumonia remain unclear, some hypotheses have been reported. One previous animal study
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20 suggested that BZDs may negatively influence immune function via the activation of GABA_A
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22 receptors on immune cells, thus interfering with macrophages/monocytes and impairing
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24 cytokine release, phagocytosis, and bacterial killing capabilities.¹¹ In addition, BZDs may
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26 increase the risk of aspiration by decreasing lower esophageal sphincter pressure, inducing the
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28 relaxation of muscles in the upper respiratory tract, and depressing the swallowing reflex,
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30 ultimately leading to pharyngeal dysfunction.^{10 12 37} Further research is necessary to explore
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32 these postulated mechanisms.
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35 The strengths of the present study include its large sample size, use of a nationwide
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37 population database, and the provision of sufficient power to evaluate the effect of BZDs on
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39 the risk of pneumonia development after stroke over a long-term follow-up period. The study
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41 design also provided better evidence in terms of epidemiology than previous studies that used
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43 case-control or cross-sectional designs. Moreover, performing propensity score matching
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45 before our analyses and then using multivariate Cox proportional hazard regression models
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47 with adjustment for competing mortality allowed us to rule out several important sources of
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49 bias and ensured that confounding factors were carefully controlled.
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52 The following limitations of the present study should also be acknowledged. First, the
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54 claim-based database did not allow for the retrieval of certain clinical information (e.g.,
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56 patient lifestyle and physical, psychiatric, or laboratory examination data). Although our study
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3 design ensured the control of several variables, unknown or unmeasured confounders could
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5 still exist. Second, the accuracy of the diagnostic coding could not be directly confirmed due
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7 to the anonymity policy enforced in the NHIRD. However, only patients who were
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9 hospitalized under a primary diagnosis of stroke were included in our study population. The
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11 identification of stroke and pneumonia using ICD-9-CM coding in inpatient services has been
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13 previously validated and shows high accuracy.^{23 38 39} Additionally, the claims were routinely
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15 and randomly reviewed by the National Health Insurance Bureau to confirm the diagnostic
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17 accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of
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19 misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the
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21 inclusion of stroke and pneumonia cases in this study.
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26 **Conclusions**

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28 In summary, this population-based propensity-matched retrospective cohort study
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30 indicated an association between BZD use and an increased risk of pneumonia in patients
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32 following stroke. However, further large-scale prospective studies are needed to determine
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34 possible cause-effect relationships.
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6
7 Loh; drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man
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9 Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.
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23 **Ethics approval:** The study was approved by the Institutional Review Board of Tzu Chi
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25 Medical Center (REC No. IRB104-131C).
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29 **Data sharing statement:** All relevant data are within the paper. No additional data are
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31 available.
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Figure legends

Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

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Table 1. Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts after propensity score matching

	BZD use				p value
	Yes (n = 3801)		No (n = 3801)		
	n	%	n	%	
Age (years)	66.2 ± 15.1		66.4 ± 14.7		0.605
Sex					0.102
Male	2510	66.0	2442	64.2	
Female	1291	34.0	1359	35.8	
Income level (NTD)					0.486
Financially dependent	1165	30.6	1146	30.1	
1–19,999	1794	47.2	1845	48.5	
20,000–39,999	520	13.7	519	13.7	
≥40,000	322	8.5	291	7.7	
Urbanization level					0.913
1 (Most urbanized)	999	26.3	990	26.0	
2	1006	26.5	1022	26.9	
3	777	20.4	748	19.7	
4	576	15.2	592	15.6	
5 (Least urbanized)	443	11.7	449	11.8	
Comorbidities					
Charlson comorbidity index	2.27 ± 1.52		2.27 ± 1.64		0.948
Hypertension	2642	69.5	2691	70.8	0.219
Diabetes mellitus	1296	34.1	1271	33.4	0.544
COPD	233	6.1	273	7.2	0.066
Asthma	110	2.9	114	3.0	0.786
Chronic kidney disease	175	4.6	198	5.2	0.222
Cirrhosis	215	5.7	212	5.6	0.881
Coronary artery disease	513	13.5	541	14.2	0.353
Congestive heart failure	196	5.2	207	5.4	0.573
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1128	29.7	1085	28.5	0.278
Malignancy	201	5.3	181	4.8	0.294
Dementia	219	5.8	207	5.4	0.550
Depression	38	1.0	50	1.3	0.198
Parkinsonism	95	2.5	109	2.9	0.320

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3	Epilepsy	23	0.6	26	0.7	0.667
4	Bipolar disorders	3	0.1	3	0.1	1.000
5	Alcohol related disorders	19	0.5	19	0.5	1.000
6	Substance use disorders	14	0.4	18	0.5	0.479
7	Schizophrenia	13	0.3	16	0.4	0.577
8	Anxiety	87	2.3	106	2.8	0.166
9	Sleep disorders	151	4.0	191	5.0	0.027
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12	Stroke severity proxies					
13						
14	Estimated NIHSS	8.0 ± 6.1		7.8 ± 5.9		0.096
15	ICU utilization	929	24.4	891	23.4	0.307
16	Mechanical ventilation	319	8.4	306	8.1	0.587
17	Hemiplegia	534	14.0	536	14.1	0.947
18	Aphasia	65	1.7	62	1.6	0.788
19	Neurosurgery	222	5.8	212	5.6	0.621
20						
21	Use of medication					
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24	Steroids	112	2.9	120	3.2	0.594
25	Anti-diabetic agents	841	22.1	833	21.9	0.825
26	Anti-hypertensive agents	1636	43.0	1739	45.8	0.017
27	Statins	335	8.8	336	8.8	0.968
28	Proton pump inhibitors	94	2.5	99	2.6	0.715
29	Anti-epileptics	65	1.7	83	2.2	0.135
30	Antiparkinsonian	86	2.3	91	2.4	0.704
31	Antipsychotics	90	2.4	84	2.2	0.645
32	Anxiolytics	229	6.0	297	7.8	0.002
33	Hypnotics and sedatives	164	4.3	184	4.8	0.272
34	Antidepressants	96	2.5	100	2.6	0.772
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40 Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and
 41 percentage.

42 Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars;
 43 NIHSS, National Institutes of Health Stroke Scale.
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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	3801	3801
Pneumonia cases	1218	526
Person-years	19064.7	14659.8
Incidence rate*	63.9	35.9
Univariate model		
Crude HR (95% CI)	2.15 (1.94–2.38)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.33 (2.09–2.59)	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.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

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

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3801	526	14659.8	35.9	1 (ref.)		1 (ref.)	
1–90 cDDD	2572	816	11690.1	69.8	2.21 (1.98–2.46)	<0.001	2.26 (2.01–2.53)	<0.001
91–365 cDDD	734	247	4040.9	61.1	2.18 (1.88–2.52)	<0.001	2.47 (2.12–2.87)	<0.001
>365 cDDD	495	155	3333.7	46.5	1.84 (1.55–2.19)	<0.001	2.52 (2.13–2.99)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily doses

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

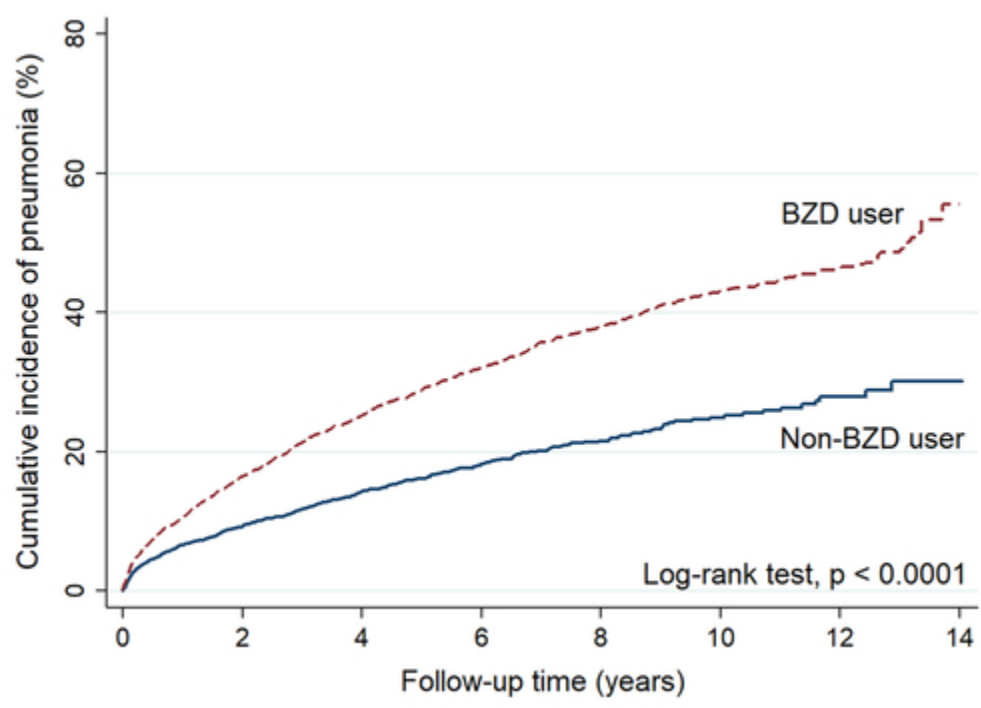
	BZD use				Non-BZD use				Univariate model		Multivariate model†	
	n	Pneumonia cases	Person-years	Incidence rate*	n	Pneumonia cases	Person-years	Incidence rate*	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age												
<65	1590	278	10122.3	27.5	1632	83	7568.4	11.0	2.87 (2.25–3.67)	<0.001	2.99 (2.33–3.84)	<0.001
≥65	2211	940	8942.4	105.1	2169	443	7091.4	62.5	2.06 (1.84–2.30)	<0.001	2.16 (1.92–2.43)	<0.001
Sex												
Male	2510	848	12580.0	67.4	2442	313	9944.7	31.5	2.46 (2.16–2.80)	<0.001	2.46 (2.15–2.82)	<0.001
Female	1291	370	6484.6	57.1	1359	213	4715.1	45.2	1.68 (1.42–1.98)	<0.001	2.09 (1.74–2.50)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

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Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

42x29mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number in manuscript
✓ Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	8-10
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4

p.11-12

✓ Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

The association between benzodiazepine use and pneumonia risk among patients with stroke: A population-based cohort study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Infectious diseases
Keywords:	Benzodiazepines, Stroke < NEUROLOGY, Pneumonia, Cohort study

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Manuscripts

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3 1 **The association between benzodiazepine use and pneumonia risk among**
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9 4 Shu-Man Lin¹, Shih-Hsien Yang^{1,2}, Chung-Chao Liang¹, Huei-Kai Huang^{3¶}, Ching-Hui Loh^{4¶}
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11 28

12 29 **Keywords:** Benzodiazepines; Stroke; Pneumonia; Cohort study
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31 **Abstract**

32 **Objectives**

33 To investigate the association between benzodiazepine (BZD) use and the risk of chronic-onset
34 post-stroke pneumonia.

35 **Design**

36 Population-based propensity-matched retrospective cohort study.

37 **Setting**

38 Taiwan's National Health Insurance Research Database.

39 **Participants**

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

43 **Outcome measures**

44 Hazard ratios (HRs) for developing pneumonia over 1 month after stroke according to BZD use
45 were assessed using Cox proportional hazards regression models. Analyses according to
46 cumulative defined daily doses (cDDD) of BZDs and stratification for age and sex were also
47 performed.

48 **Results**

49 During a mean follow-up time of 4.4 years, 1027 patients in the BZD cohort and 478 patients in
50 the non-BZD cohort developed pneumonia over 1 month after stroke. Patients using BZDs after
51 stroke had a higher pneumonia risk than did those not using BZDs (52.2 vs. 32.6 per 1000
52 person-years, adjusted HR [aHR] = 2.21, 95% confidence interval [CI] = 1.97–2.48, $p < 0.001$).
53 Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated
54 with a higher risk of pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDD

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3 55 of BZDs were 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and
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5 56 2.08 (95% CI = 1.72–2.52; $p < 0.001$), respectively. The significant association between BZD use
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7 57 and increased pneumonia risk persisted even after stratifying subgroups by age and sex.
8

9 58 **Conclusions**

10
11 59 BZD use is associated with an increased risk of chronic-onset post-stroke pneumonia.
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16 61 **Strengths and limitations of this study**

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19 62 • This retrospective cohort study was performed based on a nationwide population database,
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21 63 which contained one million subjects randomly sampled from Taiwan's population.
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23 64 • This is the first large-scale study to demonstrate an association between benzodiazepine use
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25 65 and pneumonia risk in stroke patients over a long-term follow-up period.
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27 66 • The claim-based data did not allow for the retrieval of certain clinical information (e.g.,
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29 67 patient lifestyle and physical, psychiatric, or laboratory examination data), and thus we
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31 68 could not control or adjust for these potential confounders in our analyses.
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69 Introduction

70 Pneumonia is one of the most common serious medical complications that occurs after
71 stroke,¹ affecting up to one third of patients with stroke.^{2,3} Previous studies have indicated that
72 post-stroke pneumonia is independently associated with poor prognoses, including higher
73 morbidity and mortality, and decreased functional outcomes.^{1,4-6} Post-stroke pneumonia can be
74 divided into two types according to the time of occurrence: acute-onset refers to pneumonia
75 developed within 1 month of the stroke event, while chronic onset was referred as pneumonia
76 developed after 1 month of stroke.⁷ Post-stroke pneumonia is also a considerable financial burden
77 to health-care systems.⁸ Thus, developing strategies to prevent post-stroke pneumonia is an
78 important clinical issue.

79 As modulators of the γ -amino butyric acid type A receptor (GABA_A), benzodiazepines
80 (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle
81 spasm, and epilepsy.⁹ Previous studies have postulated that BZDs may increase the risk of
82 pneumonia, possibly on account of nocturnal and daytime sedation, an increased risk of
83 aspiration, and the possible depression of immune cells.⁹⁻¹³ However, the link between BZD use
84 and increased risk of pneumonia has been disputed by other studies,¹⁴⁻¹⁸ and thus the association
85 between these factors remains unclear.

86 A considerable proportion of stroke survivors are prescribed BZDs, owing to the high
87 prevalence of post-stroke psychological problems, such as insomnia, depression, and anxiety.^{17,19}
88 ²⁰ Although pneumonia is a serious medical complication that can lead to a poor prognosis, to our
89 knowledge, only one prior study has addressed the association between BZD use and the risk of
90 pneumonia development in patients post-stroke; moreover, that study utilized a short follow-up
91 period.¹⁷ Indeed, investigations into chronic-onset post-stroke pneumonia over long-term
92 follow-up periods in stroke survivors are still lacking. Therefore, we conducted a

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3 93 population-based retrospective cohort study to evaluate the association between BZD use and the
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5 94 risk of chronic-onset post-stroke pneumonia in a large sample of stroke survivors over a long
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7 95 study period.
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11 97 **Methods**

13 98 **Data sources**

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16 99 We conducted a population-based retrospective cohort study by analyzing claims data
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18 100 obtained from Taiwan's National Health Insurance Research Database (NHIRD). The National
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20 101 Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and is
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22 102 administered by the government, is a mandatory single-payer national health insurance system
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24 103 that covers more than 99% of Taiwan's residents and has contracts with 97% of the hospitals and
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26 104 clinics in Taiwan. Data in the current study were obtained from the Longitudinal Health Insurance
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28 105 Database 2000 (LHID2000), a subset of the NHIRD that contains a representative database of
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30 106 one million people from NHI beneficiaries registered in Taiwan in the year 2000. For research
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32 107 purposes, the LHID2000 was systemically and randomly sampled by the National Health
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34 108 Research Institute from the Taiwanese population. The database included medical claims of all
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36 109 inpatient, outpatient, emergency department, and home care services. Before releasing the
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38 110 database, information related to personal identification was encrypted to protect patient privacy
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40 111 and data security.^{21 22} National Health Research Institute approval was obtained prior to using the
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42 112 LHID2000 in this study. Diagnostic disease codes were derived using the International
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44 113 Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This coding is
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46 114 considered highly reliable in the NHIRD, as insurance claims have been investigated by medical
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48 115 reimbursement specialists and the coding system has undergone peer review.²³ The study
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50 116 protocol we applied was approved by the Institutional Review Board of Tzu Chi Medical Center.
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3 117 The requirement for patient consent was waived owing to the retrospective nature of this study
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5 118 using de-identified secondary data.
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9 120 **Study population**

11 121 The same database used in our previous study was employed here.²² The database is
12
13 122 comprised of adult patients (aged ≥ 20 years) with new-onset stroke occurring between 2000 and
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15 123 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM codes 430–
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17 124 437). The “index date” was defined as the date of the new-onset stroke diagnosis, while “index
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19 125 hospitalization” was defined as concurrent hospitalization for stroke. Exclusion criteria for this
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21 126 study were as follows: 1) history of stroke before the 2000–2012 study period; 2) history of
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23 127 pneumonia 1 year preceding the index date; 3) concurrent diagnosis of pneumonia during the
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25 128 index hospitalization; and/or 4) death during the index hospitalization.
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31 130 **Exposure to benzodiazepines**

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34 131 In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can only
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36 132 obtain such drugs through a doctor’s prescription. We identified BZD prescriptions written after
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38 133 the index hospitalization using the prescription database in the LHID. The study population was
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40 134 then divided into BZD and non-BZD cohorts. The BZD cohort included patients who had used
41
42 135 any BZDs after stroke during the follow-up period, while the non-BZD cohort was comprised of
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44 136 patients who were not prescribed BZDs post-stroke. To evaluate the effects of different BZD
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46 137 doses, we divided the BZD cohort into three subgroups using defined daily dose (DDD)
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48 138 methodology—a World Health Organization-recommended unit of measure employed to evaluate
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50 139 the prescribed amount of a drug for its main indication in an adult. Note that DDD methodology
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52 140 is widely used for the investigation of administrative pharmacy claim data.^{21 23} Using this
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3 141 approach, we calculated the cumulative DDD (cDDD) by determining the sum of the dispensed
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5 142 DDD of all BZDs. This value was then employed to quantify BZD use during the study follow-up
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7 143 period. As such, the BZD cohort was divided into 1–90, 91–365, and >365 cDDD subgroups.
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11 145 **Outcome measures and sensitivity analysis**

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14 146 The main outcome of this study was defined as the occurrence of chronic-onset post-stroke
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16 147 pneumonia after index hospitalization, as identified by a discharge diagnosis of pneumonia
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18 148 (ICD-9-CM codes of 480–486). In order to increase the accuracy of this outcome, only
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20 149 pneumonia patients that required hospitalization were considered. According to previous
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22 150 research, chronic-onset post-stroke pneumonia is defined as pneumonia developing over 1 month
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24 151 after the incidence of stroke.⁷ As the present study evaluated chronic-onset post-stroke
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26 152 pneumonia, cases of pneumonia diagnosed within 30 days of the stroke event were excluded. The
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28 153 identification of patients with pneumonia using ICD-9-CM coding in inpatient service has been
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30 154 previously validated and shows high accuracy.²⁴ All subjects were followed-up on, from the
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32 155 index date until the first occurrence of pneumonia, death, or until December 31, 2013. Death was
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34 156 defined as a patient withdrawn from the NHI program,²⁵ as previous studies have indicated that
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36 157 this is an accurate and reliable proxy for date of death.^{26 27} Analyses stratified by age and sex
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38 158 were also performed.
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43 159 In addition, to examine whether a diagnosis of pneumonia rendered in an outpatient service
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45 160 would influence our results, we performed a sensitivity analysis. For this analysis, pneumonia
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47 161 events were defined as those diagnosed during the follow-up period regardless of whether the
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49 162 diagnosis was rendered in an inpatient or outpatient service.
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54 164 **Covariates and propensity score matching**

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3 165 Baseline characteristics, such as demographic data, socioeconomic status, comorbidities, and
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5 166 clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and
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7 167 procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one time
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9 168 during inpatient service or two times during outpatient visits within the year prior to the index
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11 169 date. The Charlson comorbidity index was calculated according to information related to
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13 170 preexisting comorbidities.²⁸ Baseline medication use was defined as any medication taken for at
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15 171 least 30 days over the course of the year preceding the index date. Information related to stroke
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17 172 severity proxies was obtained based on the indicated clinical condition during the index
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19 173 hospitalization. Such information included diagnosis codes for hemiplegia and aphasia,
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21 174 operation/procedural codes for head surgery, mechanical ventilation, and utilization of the
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23 175 intensive care unit, as mentioned in our previous studies.²²⁻²⁹ In addition, estimated National
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25 176 Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of
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27 177 neurologic deficits, converting scores from a claims-based stroke severity index (SSI)—a
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29 178 measure specifically developed for use with Taiwan's NHIRD claims-based data—with a
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31 179 formula developed by Hsieh et al. (estimated NIHSS = $1.1722 \times \text{SSI} - 0.7533$).³⁰⁻³¹ The SSI has
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33 180 been validated in previous studies and is highly correlated with the NIHSS and consequent
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35 181 functional outcomes after stroke.³¹⁻³³ Additionally, some comorbidities may occur after stroke
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37 182 and also possibly cause a confounding effect. We therefore calculated an additional Charlson
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39 183 comorbidity index at the end point of follow-up, using the data on comorbidities from the year
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41 184 prior to the end-point date. Socioeconomic status was determined according to patient income
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43 185 and dwelling urbanization levels. Income, which was accessed based on NHI premiums, was
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45 186 classified into four levels (New Taiwan dollars $\geq 40,000$, 20,000–39,999, 1–19,999, and
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47 187 financially dependent). Urbanization was classified into five levels, with level 1 corresponding to
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49 188 the most urbanized areas.³⁴ Detailed descriptions of income and urbanization levels have been
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3 189 described in our previous studies.^{22 29}

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5 190 In order to decrease the selection bias between groups, propensity score matching was
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7 191 performed to balance patient baseline characteristics, including age, sex, income level,
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9 192 urbanization level, comorbidities, Charlson comorbidity index, stroke severity proxies, and
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11 193 medication use (Table 1). A logistic regression model was used to calculate a propensity score,
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14 194 which estimated the probability of BZD use based on all baseline covariates for each BZD user
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16 195 and non-user. Using the method of nearest-neighbor matching without replacement (with a
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18 196 caliper width equal to 0.2 standard deviations of the propensity score logit), we matched each
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20 197 BZD user with a non-BZD user.^{22 35 36}

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24 25 199 **Statistical analysis**

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27 200 Continuous variables between the BZD and non-BZD cohort were compared using
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29 201 independent *t*-tests, while categorical variables were compared using chi-squared tests. The
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31 202 Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the
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33 203 log-rank test was used to compare differences between cumulative incidence curves. Univariate
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35 204 and multivariate Cox proportional hazards regression models were used to compute the hazard
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37 205 ratios (HRs) and corresponding 95% confidence intervals (CIs) for developing pneumonia after
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39 206 stroke; all baseline characteristics listed in Table 1 were adjusted for when conducting the
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41 207 multivariate Cox proportional hazards regression models. To eliminate possible bias caused by
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43 208 competing mortality, modified Cox proportional hazards regression models were used with
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45 209 adjustment for competing risk events.^{25 37} Differences were considered statistically significant at
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47 210 a two-sided probability value of <0.05. All statistical analyses were performed using Stata
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50 211 version 13 (Stata Corporation, College Station, TX, USA).

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3 **213 Patient and public involvement**

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5 **214** Due to the present study having used de-identified secondary data, the patients and public

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7 **215** were not directly involved in this study and the need for consent was waived.
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216 **Results**

217 **Demographic characteristics**

218 After propensity score matching according to the baseline characteristics listed in Table 1, a
219 total of 7516 patients with newly onset stroke were included in our study. Among these patients,
220 3758 received BZDs and were classified into the BZD cohort, while 3758 did not receive BZDs
221 and were classified into the non-BZD cohort. Although most baseline characteristics were
222 well-balanced after propensity score matching, significant differences were found regarding the
223 baseline prevalence of sleep disorders and the proportion of patients using anti-hypertensive
224 agents and anxiolytics; however, the actual between-group differences were minor (Table 1).

226 **Risk of chronic-onset post-stroke pneumonia according to BZD use**

227 During a mean follow-up of 4.4 years, 1027 patients in the BZD cohort (52.2/1000
228 person-years), compared to 478 patients in the non-BZD cohort (32.6/1000 person-years),
229 developed pneumonia. A Kaplan-Meier analysis revealed a significantly higher cumulative
230 incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, $p < 0.0001$)
231 (Figure 1). Cox proportional hazards regression models revealed that BZD use after stroke was
232 associated with an increased risk of pneumonia in both the univariate (crude HR = 1.95, 95% CI
233 = 1.75–2.17, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.21, 95% CI = 1.97–
234 2.48, $p < 0.001$) (Table 2).

236 **Analyses according to different cumulative BZD doses**

237 Patients in all three cDDD subgroups had a higher risk of developing pneumonia than did
238 the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were 2.28
239 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95% CI =

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3 240 1.72–2.52; $p < 0.001$), respectively (Table 3).

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6 7 242 **Analyses after stratification for age and sex**

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9 243 The association between BZD use and the risk of pneumonia development in stroke patients
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11 244 was further analyzed after stratification for age and sex (Table 4). Using this approach, we found
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13 245 a significantly greater risk of pneumonia in BZD users than in non-users in both age subgroups
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15 246 (<65 years old: aHR = 2.42, 95% CI = 1.84–3.17, $p < 0.001$; ≥ 65 years old: aHR = 2.11, 95% CI
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17 = 1.86–2.40, $p < 0.001$). Additionally, BZD users had an increased risk of pneumonia in both
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19 247 male (aHR = 2.46, 95% CI = 2.13–2.84, $p < 0.001$) and female (aHR = 1.83, 95% CI = 1.50–
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21 248 2.22, $p < 0.001$) subgroups (Table 4). Together, these results reveal that BZD use after stroke was
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23 249 associated with an increased risk of pneumonia regardless of age and sex.
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28 29 252 **Results of sensitivity analysis**

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31 253 In the sensitivity analysis, which considered the pneumonia event regardless of diagnosis in
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33 254 inpatient or outpatient service, BZD use was independently associated with increased risk of
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35 255 developing pneumonia (adjusted HR = 1.94, 95% CI = 1.77–2.14, $p < 0.001$). The results for
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37 256 different cumulative doses of BZDs also revealed a pattern to our primary analyses. The detailed
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39 257 statistical values are shown in the Supplementary materials (Supplementary Table S1).
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258 Discussion

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

265 Our results are consistent with those previously reported by studies that focused on the
266 general population.⁹⁻¹¹ For example, previous observational studies found a 54 to 176% increase
267 in the risk of pneumonia development in BZD users when compared to non-BZD users (relative
268 risk or odds ratio: 1.54,⁹ 1.86,¹⁰ and 2.76¹¹). However, other observational studies have reported
269 conflicting results, showing negative or nonsignificant relationships between BZD use and the
270 risk of pneumonia.^{14 16-18} For instance, a previous case-control study on participants aged ≥ 65
271 years old did not find a significant association between BZD use and pneumonia risk; however,
272 only 87 BZD users were found among all of the pneumonia cases included in that study.¹⁴
273 Another cross-sectional study using 30-, 60-, and 90-day windows revealed protective effects of
274 BZDs on the risk of pneumonia, but was conducted over a relatively short study period and
275 focused on the general population.¹⁸

276 Pneumonia is a significant complication in stroke patients owing to the increased risk of
277 apparent aspiration and dysphagia-associated microaspiration, as well as stroke-induced
278 immunodepression.^{6 7 38} Acute-onset post-stroke pneumonia, which develops within 1 month of
279 the stroke event, is mainly associated with apparent aspiration and stroke-induced
280 immunodepression.^{6 7} However, although apparent aspiration and immunodepression gradually
281 attenuate following stroke recovery, the silent aspiration or microaspiration into the lower

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3 282 airways may still occur and cause chronic-onset post-stroke pneumonia.^{7 39} BZDs are commonly
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5 283 used in stroke patients on account of the high prevalence of psychological problems in stroke
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7 284 patients;^{17 19 20} previous studies have indicated that BZDs may be associated with the increased
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9 285 risk of aspiration and depression of immune cells.⁹⁻¹³ To the best of our knowledge, the only
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11 286 previous study to focus on the association between BZDs and pneumonia in stroke patients did
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13 287 not reveal a significant association between BZD use and the risk of pneumonia post-stroke;
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15 288 however, in that study, the follow-up period for identifying pneumonia was only 90 days
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17 289 post-stroke.¹⁷ In contrast, the current study, which specifically focused on the chronic phase of
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19 290 post-stroke to evaluate pneumonia developed over 1 month after the stroke,⁷ included a large
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21 291 sample size and long-term follow-up period (mean follow-up time, 4.4 years). The present study
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23 292 revealed a significantly increased risk of chronic-onset pneumonia in stroke survivors using
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25 293 BZDs (aHR = 2.21), even after carefully controlling for socioeconomic status, important
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27 294 comorbidities, stroke severity proxies, and concomitant medications. In addition, the subgroup
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29 295 analyses, which were performed according to cumulative BZD doses and stratified for age and
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31 296 sex, also revealed a similar pattern of results, further strengthening our findings. As pneumonia is
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33 297 one of the most common serious medical complications following stroke and can cause not only
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35 298 poor functional outcomes but also high mortality and financial burdens, we believe that our study
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37 299 addresses a knowledge gap regarding the clinical management of patients after stroke.
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43 300 Although the exact biological mechanisms underlying the influence of BZDs on pneumonia
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45 301 remain unclear, some hypotheses have been reported. One previous animal study suggested that
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47 302 BZDs may negatively influence immune function via the activation of GABA_A receptors on
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49 303 immune cells, thus interfering with macrophages/monocytes and impairing cytokine release,
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51 304 phagocytosis, and bacterial killing capabilities.¹² In addition, BZDs may increase the risk of
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53 305 aspiration by decreasing lower esophageal sphincter pressure, inducing the relaxation of muscles
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3 306 in the upper respiratory tract, and depressing the swallowing reflex, ultimately leading to
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5 307 pharyngeal dysfunction.^{11 13 40} Further research is necessary to explore these postulated
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7 308 mechanisms.

8
9 309 The strengths of the present study include its large sample size, use of a nationwide
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11 310 population database, and the provision of sufficient power to evaluate the effect of BZDs on the
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13 311 risk of pneumonia development after stroke over a long-term follow-up period. The study design
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15 312 also provided better evidence in terms of epidemiology than previous studies that used
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17 313 case-control or cross-sectional designs. Moreover, performing propensity score matching before
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19 314 our analyses and then using multivariate Cox proportional hazard regression models with
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21 315 adjustment for competing mortality allowed us to rule out several important sources of bias and
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23 316 ensured that confounding factors were carefully controlled.

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27 317 The following limitations of the present study should also be acknowledged. First, the
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29 318 claim-based database did not allow for the retrieval of certain clinical information (e.g., patient
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31 319 lifestyle and physical, psychiatric, or laboratory examination data). Although our study design
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33 320 ensured the control of several variables, unknown or unmeasured confounders could still exist.
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35 321 Second, by using de-identified claims, we could not obtain the patient details to analyze the
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37 322 medical history and identify exact mechanism of pneumonia; thus, we could not determine
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39 323 whether the pneumonia was caused by aspiration or not. Third, our analyses performed according
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41 324 to different cumulative BZD doses did not reveal an obvious dose-effect relationship. It is
42
43 325 difficult to completely avoid an indication bias in observational studies that evaluate the effect of
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45 326 medication or intervention. Hence, the existence of unidentified residual confounders cannot be
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47 327 completely ruled out from the present study. Thus, further prospective clinical trials are necessary
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49 328 to determine the cause-and-effect relationship between post-stroke BZD use and the pneumonia
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51 329 risk. Finally, the accuracy of the diagnostic coding could not be directly confirmed due to the
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3 330 anonymity policy enforced in the NHIRD. However, only patients who were hospitalized under a
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5 331 primary diagnosis of stroke were included in our study population. The identification of stroke
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7 332 and pneumonia using ICD-9-CM coding in inpatient services has been previously validated and
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9 333 shows high accuracy.^{24 41 42} Additionally, the claims were routinely and randomly reviewed by
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11 334 the National Health Insurance Bureau to confirm the diagnostic accuracy. Given that hospitals
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13 335 and doctors in Taiwan are heavily fined in instances of misdiagnosis and coding errors, we feel
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15 336 confident in the validity of the criteria used for the inclusion of stroke and pneumonia cases in
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17 337 this study.
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22 339 **Conclusions**

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25 340 In summary, this population-based propensity-matched retrospective cohort study indicated
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27 341 an association between BZD use and an increased risk of chronic-onset post-stroke pneumonia.
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29 342 However, further large-scale prospective studies are needed to determine possible cause-effect
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31 343 relationships.
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38 346 **Contributors:** Study conception and design: Shu-Man Lin, Huei-Kai Huang, and Ching-Hui
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40 347 Loh; acquisition of data: Shih-Hsien Yang and Huei-Kai Huang; analysis and interpretation of
41
42 348 data: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh;
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44 349 drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man Lin,
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46 350 Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.

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50 352 **Competing interests:** The authors declare that no competing interests exist.
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3 353 **Ethics approval:** The study was approved by the Institutional Review Board of Tzu Chi Medical
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5 354 Center (REC No. IRB104-131C).
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7 355 **Data sharing statement:** All relevant data are within the paper. No additional data are available.
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For peer review only

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3 505 **Figure legends**

4
5 506 **Figure 1.** Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with
6
7 507 and without BZD use post-stroke.
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508 **Table 1.** Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts after
 509 propensity score matching

	BZD use				p value
	Yes (n = 3,758)		No (n = 3,758)		
	n	%	n	%	
Age (years)	66.2 ± 14.9		66.3 ± 14.7		0.941
Sex					0.267
Male	2,455	65.3	2,409	64.1	
Female	1,303	34.7	1,349	35.9	
Income level (NTD)					0.816
Financially dependent	1,123	29.9	1,125	29.9	
1–19,999	1,801	47.9	1,826	48.6	
20,000–39,999	522	13.9	516	13.7	
≥40,000	312	8.3	291	7.7	
Urbanization level					0.732
1 (Most urbanized)	974	25.9	985	26.2	
2	993	26.4	1,010	26.9	
3	791	21.0	744	19.8	
4	579	15.4	580	15.4	
5 (Least urbanized)	421	11.2	439	11.7	
Comorbidities					
Charlson comorbidity index	2.26 ± 1.50		2.27 ± 1.63		0.837
Hypertension	2,666	70.9	2,666	70.9	1.000
Diabetes mellitus	1,263	33.6	1,256	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
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1,096	29.2	1,080	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
Anxiety	90	2.4	104	2.8	0.309
Sleep disorders	170	4.5	186	4.9	0.385
Charlson comorbidity index	2.03 ± 1.79		2.13 ± 2.06		0.022
at the end point of follow-up					
Stroke severity proxies					
Estimated NIHSS	8.0 ± 6.0		7.7 ± 5.8		0.061
ICU utilization	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
Anti-diabetic agents	795	21.2	821	21.8	0.465
Anti-hypertensive agents	1,676	44.6	1,715	45.6	0.366
Statins	319	8.5	332	8.8	0.594
Proton pump inhibitors	89	2.4	97	2.6	0.553
Anti-epileptics	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

510 Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and
 511 percentage.

512 Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan dollars;
 513 NIHSS, National Institutes of Health Stroke Scale.

514 **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 (1.75–2.17)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.21 (1.97–2.48)	1 (ref.)
p value	<0.001	

515 *Per 1000 person-years.

516 †Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics
517 (listed in Table 1) and competing mortality.

518 Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

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

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3758	478	14663.8	32.6	1 (ref.)		1 (ref.)	
1–90 cDDD	2507	702	11760.2	59.7	2.10 (1.87–2.36)	<0.001	2.28 (2.01–2.58)	<0.001
91–365 cDDD	728	198	4216.6	47.0	1.84 (1.56–2.16)	<0.001	2.09 (1.77–2.47)	<0.001
>365 cDDD	523	127	3703.4	34.3	1.47 (1.21–1.77)	<0.001	2.08 (1.72–2.52)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily doses

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	10438.4	21.2	1626	77	7568.1	10.2	2.32 (1.79–3.00)	<0.001	2.42 (1.84–3.17)	<0.001
≥65	2159	806	9241.7	87.2	2132	401	7095.7	56.5	1.94 (1.72–2.18)	<0.001	2.11 (1.86–2.40)	<0.001
Sex												
Male	2455	721	12709.5	56.7	2409	278	9945.3	28.0	2.35 (2.04–2.69)	<0.001	2.46 (2.13–2.84)	<0.001
Female	1303	306	6970.6	43.9	1349	200	4718.5	42.4	1.39 (1.16–1.66)	<0.001	1.83 (1.50–2.22)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

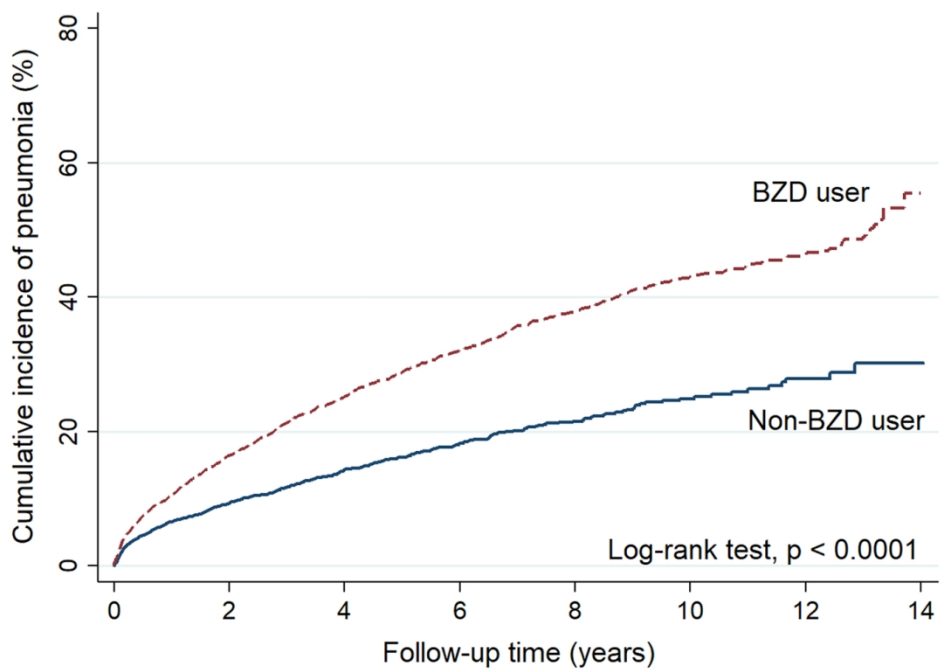


Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

127x92mm (300 x 300 DPI)

Supplementary Materials

Table S1. Sensitivity analysis of risk of contracting pneumonia after stroke according to BZD-use status

Cumulative BZD doses	Univariate model		Multivariate model†	
	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	1 (ref.)		1 (ref.)	
All BZD user	1.75 (1.60–1.91)	<0.001	1.94 (1.77–2.14)	<0.001
1–90 cDDD	1.83 (1.66–2.02)	<0.001	1.96 (1.77–2.18)	<0.001
91–365 cDDD	1.72 (1.50–1.98)	<0.001	1.89 (1.64–2.18)	<0.001
>365 cDDD	1.45 (1.24–1.70)	<0.001	1.92 (1.63–2.25)	<0.001

For the sensitivity 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.

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily doses

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number in manuscript
✓ Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	8-10
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	8
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each	N/A

		variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4 p.11-12
✓ Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

The association between benzodiazepine use and risks of chronic-onset post-stroke pneumonia: A population-based cohort study

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Primary Subject Heading:	Neurology
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Keywords:	Benzodiazepines, Stroke < NEUROLOGY, Pneumonia, Cohort study

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3 1 **The association between benzodiazepine use and risks of chronic-onset**
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9 4 Shu-Man Lin¹, Shih-Hsien Yang^{1,2}, Chung-Chao Liang¹, Huei-Kai Huang^{3¶}, Ching-Hui Loh^{4¶}
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For peer review only

Abstract**Objectives**

To investigate the association between benzodiazepine (BZD) use and the risk of chronic-onset post-stroke 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

Hazard ratios (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 (cDDD) 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 per 1000 person-years, adjusted HR [aHR] = 2.21, 95% confidence interval [CI] = 1.97–2.48, $p < 0.001$). Analyses based on cumulative BZD dose revealed that all BZD user subgroups were associated with a higher risk of pneumonia. The aHRs for patients taking 1–90, 91–365, and >365 cDDD of BZDs were 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95% CI = 1.72–2.52; $p < 0.001$), respectively. The significant

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3 57 association between BZD use and increased pneumonia risk persisted even after stratifying
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5 58 subgroups by age and sex.
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7 59 **Conclusions**

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9 60 BZD use is associated with an increased risk of chronic-onset post-stroke pneumonia.
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14 62 **Strengths and limitations of this study**

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17 63 • This retrospective cohort study was performed based on a nationwide population
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19 64 database, which contained one million subjects randomly sampled from Taiwan's
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21 65 population.
22
23 66 • This is the first large-scale study to demonstrate an association between benzodiazepine
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25 67 use and pneumonia risk in stroke patients over a long-term follow-up period.
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27 68 • The claim-based data did not allow for the retrieval of certain clinical information (e.g.,
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29 69 patient lifestyle and physical, psychiatric, or laboratory examination data), and thus we
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31 70 could not control or adjust for these potential confounders in our analyses.
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71 Introduction

72 Pneumonia is one of the most common serious medical complications that occurs after
73 stroke,¹ affecting up to one third of patients with stroke.^{2,3} Previous studies have indicated that
74 post-stroke pneumonia is independently associated with poor prognoses, including higher
75 morbidity and mortality, and decreased functional outcomes.^{1,4-6} Post-stroke pneumonia can
76 be divided into two types according to the time of occurrence: acute-onset refers to
77 pneumonia developed within 1 month of the stroke event, while chronic onset was referred as
78 pneumonia developed after 1 month of stroke.⁷ Post-stroke pneumonia is also a considerable
79 financial burden to health-care systems.⁸ Thus, developing strategies to prevent post-stroke
80 pneumonia is an important clinical issue.

81 As modulators of the γ -amino butyric acid type A receptor (GABA_A), benzodiazepines
82 (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle
83 spasm, and epilepsy.⁹ Previous studies have postulated that BZDs may increase the risk of
84 pneumonia, possibly on account of nocturnal and daytime sedation, an increased risk of
85 aspiration, and the possible depression of immune cells.⁹⁻¹³ However, the link between BZD
86 use and increased risk of pneumonia has been disputed by other studies,¹⁴⁻¹⁸ and thus the
87 association between these factors remains unclear.

88 A considerable proportion of stroke survivors are prescribed BZDs, owing to the high
89 prevalence of post-stroke psychological problems, such as insomnia, depression, and
90 anxiety.^{17,19,20} Although pneumonia is a serious medical complication that can lead to a poor
91 prognosis, to our knowledge, only one prior study has addressed the association between BZD
92 use and the risk of pneumonia development in patients post-stroke; moreover, that study
93 utilized a short follow-up period.¹⁷ Indeed, investigations into chronic-onset post-stroke
94 pneumonia over long-term follow-up periods in stroke survivors are still lacking. Therefore,
95 we conducted a population-based retrospective cohort study to evaluate the association
96 between BZD use and the risk of chronic-onset post-stroke pneumonia in a large sample of

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2 97 stroke survivors over a long study period.
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7 99 **Methods**

9 100 **Data sources**

11 101 We conducted a population-based retrospective cohort study by analyzing claims data
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13 102 obtained from Taiwan's National Health Insurance Research Database (NHIRD). The
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15 103 National Health Insurance (NHI) program of Taiwan, which was launched in March 1995 and
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17 104 is administered by the government, is a mandatory single-payer national health insurance
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19 105 system that covers more than 99% of Taiwan's residents and has contracts with 97% of the
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21 106 hospitals and clinics in Taiwan. Data in the current study were obtained from the Longitudinal
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23 107 Health Insurance Database 2000 (LHID2000), a subset of the NHIRD that contains a
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25 108 representative database of one million people from NHI beneficiaries registered in Taiwan in
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27 109 the year 2000. For research purposes, the LHID2000 was systemically and randomly sampled
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29 110 by the National Health Research Institute from the Taiwanese population. The database
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31 111 included medical claims of all inpatient, outpatient, emergency department, and home care
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33 112 services. Before releasing the database, information related to personal identification was
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35 113 encrypted to protect patient privacy and data security.^{21 22} National Health Research Institute
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37 114 approval was obtained prior to using the LHID2000 in this study. Diagnostic disease codes
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39 115 were derived using the International Classification of Diseases, Ninth Revision, Clinical
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41 116 Modification (ICD-9-CM). This coding is considered highly reliable in the NHIRD, as
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43 117 insurance claims have been investigated by medical reimbursement specialists and the coding
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45 118 system has undergone peer review.²³ The study protocol we applied was approved by the
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47 119 Institutional Review Board of Tzu Chi Medical Center. The requirement for patient consent
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49 120 was waived owing to the retrospective nature of this study using de-identified secondary data.
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58 122 **Study population**

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3 123 The same database used in our previous study was employed here.²² The database is
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5 124 comprised of adult patients (aged ≥ 20 years) with new-onset stroke occurring between 2000
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7 125 and 2012; patients were identified by a primary discharge diagnosis of stroke (ICD-9-CM
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9 126 codes 430–437). The “index date” was defined as the date of the new-onset stroke diagnosis,
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11 127 while “index hospitalization” was defined as concurrent hospitalization for stroke. Exclusion
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13 128 criteria for this study were as follows: 1) history of stroke before the 2000–2012 study period;
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15 129 2) history of pneumonia 1 year preceding the index date; 3) concurrent diagnosis of
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17 130 pneumonia during the index hospitalization; and/or 4) death during the index hospitalization.
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22 132 **Exposure to benzodiazepines**

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25 133 In Taiwan, BZDs are controlled by the Bureau of Controlled Drugs, and patients can
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27 134 only obtain such drugs through a doctor’s prescription. We identified BZD prescriptions
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29 135 written after the index hospitalization using the prescription database in the LHID. The study
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31 136 population was then divided into BZD and non-BZD cohorts. The BZD cohort included
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33 137 patients who had used any BZDs after stroke during the follow-up period, while the non-BZD
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35 138 cohort was comprised of patients who were not prescribed BZDs post-stroke. To evaluate the
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37 139 effects of different BZD doses, we divided the BZD cohort into three subgroups using defined
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39 140 daily dose (DDD) methodology—a World Health Organization-recommended unit of measure
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41 141 employed to evaluate the prescribed amount of a drug for its main indication in an adult. Note
42
43 142 that DDD methodology is widely used for the investigation of administrative pharmacy claim
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45 143 data.^{21 23} Using this approach, we calculated the cumulative DDD (cDDD) by determining the
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47 144 sum of the dispensed DDD of all BZDs. This value was then employed to quantify BZD use
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49 145 during the study follow-up period. As such, the BZD cohort was divided into 1–90, 91–365,
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51 146 and >365 cDDD subgroups.
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148 **Outcome measures and sensitivity analysis**

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3 149 The main outcome of this study was defined as the occurrence of chronic-onset
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5 150 post-stroke pneumonia after index hospitalization, as identified by a discharge diagnosis of
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7 151 pneumonia (ICD-9-CM codes of 480–486). In order to increase the accuracy of this outcome,
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9 152 only pneumonia patients that required hospitalization were considered. According to previous
10
11 153 research, chronic-onset post-stroke pneumonia is defined as pneumonia developing over 1
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13 154 month after the incidence of stroke.⁷ As the present study evaluated chronic-onset post-stroke
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15 155 pneumonia, cases of pneumonia diagnosed within 30 days of the stroke event were excluded.
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17 156 The identification of patients with pneumonia using ICD-9-CM coding in inpatient service
18
19 157 has been previously validated and shows high accuracy.²⁴ All subjects were followed-up on,
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21 158 from the index date until the first occurrence of pneumonia, death, or until December 31,
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23 159 2013. Death was defined as a patient withdrawn from the NHI program,²⁵ as previous studies
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25 160 have indicated that this is an accurate and reliable proxy for date of death.^{26 27} Analyses
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27 161 stratified by age and sex were also performed.
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32 162 In addition, to examine whether a diagnosis of pneumonia rendered in an outpatient
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34 163 service would influence our results, we performed a sensitivity analysis. For this analysis,
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36 164 pneumonia events were defined as those diagnosed during the follow-up period regardless of
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38 165 whether the diagnosis was rendered in an inpatient or outpatient service.
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43 167 **Covariates and propensity score matching**

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45 168 Baseline characteristics, such as demographic data, socioeconomic status, comorbidities,
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47 169 and clinical conditions, were obtained using reimbursement claims data and ICD-9-CM and
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49 170 procedure codes. A preexisting comorbidity was defined as a disease diagnosed at least one
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51 171 time during inpatient service or two times during outpatient visits within the year prior to the
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53 172 index date. The Charlson comorbidity index was calculated according to information related
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55 173 to preexisting comorbidities.²⁸ Baseline medication use was defined as any medication taken
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57 174 for at least 30 days over the course of the year preceding the index date. Information related to
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2 175 stroke severity proxies was obtained based on the indicated clinical condition during the index
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4 176 hospitalization. Such information included diagnosis codes for hemiplegia and aphasia,
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6 177 operation/procedural codes for head surgery, mechanical ventilation, and utilization of the
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8 178 intensive care unit, as mentioned in our previous studies.^{22 29} In addition, estimated National
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10 179 Institutes of Health Stroke Scale (NIHSS) scores were calculated to represent the severity of
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12 180 neurologic deficits, converting scores from a claims-based stroke severity index (SSI)—a
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14 181 measure specifically developed for use with Taiwan’s NHIRD claims-based data—with a
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16 182 formula developed by Hsieh et al. (estimated NIHSS = $1.1722 \times \text{SSI} - 0.7533$).^{30 31} The SSI
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18 183 has been validated in previous studies and is highly correlated with the NIHSS and
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20 184 consequent functional outcomes after stroke.³¹⁻³³ Additionally, some comorbidities may occur
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22 185 after stroke and also possibly cause a confounding effect. We therefore calculated an
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24 186 additional Charlson comorbidity index at the end point of follow-up, using the data on
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26 187 comorbidities from the year prior to the end-point date. Socioeconomic status was determined
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28 188 according to patient income and dwelling urbanization levels. Income, which was accessed
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30 189 based on NHI premiums, was classified into four levels (New Taiwan dollars $\geq 40,000$,
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32 190 20,000–39,999, 1–19,999, and financially dependent). Urbanization was classified into five
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34 191 levels, with level 1 corresponding to the most urbanized areas.³⁴ Detailed descriptions of
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36 192 income and urbanization levels have been described in our previous studies.^{22 29}

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43 193 In order to decrease the selection bias between groups, propensity score matching was
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45 194 performed to balance patient baseline characteristics, including age, sex, income level,
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47 195 urbanization level, comorbidities, Charlson comorbidity index, stroke severity proxies, and
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49 196 medication use (Table 1). A logistic regression model was used to calculate a propensity
50
51 197 score, which estimated the probability of BZD use based on all baseline covariates for each
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53 198 BZD user and non-user. Using the method of nearest-neighbor matching without replacement
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55 199 (with a caliper width equal to 0.2 standard deviations of the propensity score logit), we
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57 200 matched each BZD user with a non-BZD user.^{22 35 36}

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202 Statistical analysis

203 Continuous variables between the BZD and non-BZD cohort were compared using
204 independent *t*-tests, while categorical variables were compared using chi-squared tests. The
205 Kaplan-Meier method was performed to estimate the risk of developing pneumonia and the
206 log-rank test was used to compare differences between cumulative incidence curves.
207 Univariate and multivariate Cox proportional hazards regression models were used to
208 compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for
209 developing pneumonia after stroke; all baseline characteristics listed in Table 1 were adjusted
210 for when conducting the multivariate Cox proportional hazards regression models. To
211 eliminate possible bias caused by competing mortality, modified Cox proportional hazards
212 regression models were used with adjustment for competing risk events.^{25 37} Differences were
213 considered statistically significant at a two-sided probability value of <0.05. All statistical
214 analyses were performed using Stata version 13 (Stata Corporation, College Station, TX,
215 USA).

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217 Patient and public involvement

218 Due to the present study having used de-identified secondary data, the patients and
219 public were not directly involved in this study and the need for consent was waived.

220 **Results**

221 **Demographic characteristics**

222 After propensity score matching according to the baseline characteristics listed in Table
223 1, a total of 7516 patients with newly onset stroke were included in our study. Among these
224 patients, 3758 received BZDs and were classified into the BZD cohort, while 3758 did not
225 receive BZDs and were classified into the non-BZD cohort. Although most baseline
226 characteristics were well-balanced after propensity score matching, significant differences
227 were found regarding the baseline prevalence of sleep disorders and the proportion of patients
228 using anti-hypertensive agents and anxiolytics; however, the actual between-group differences
229 were minor (Table 1).

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231 **Risk of chronic-onset post-stroke pneumonia according to BZD use**

232 During a mean follow-up of 4.4 years, 1027 patients in the BZD cohort (52.2/1000
233 person-years), compared to 478 patients in the non-BZD cohort (32.6/1000 person-years),
234 developed pneumonia. A Kaplan-Meier analysis revealed a significantly higher cumulative
235 incidence of pneumonia in the BZD than in the non-BZD cohort (log-rank test, $p < 0.0001$)
236 (Figure 1). Cox proportional hazards regression models revealed that BZD use after stroke
237 was associated with an increased risk of pneumonia in both the univariate (crude HR = 1.95,
238 95% CI = 1.75–2.17, $p < 0.001$) and multivariate models (adjusted HR [aHR] = 2.21, 95% CI
239 = 1.97–2.48, $p < 0.001$) (Table 2).

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241 **Analyses according to different cumulative BZD doses**

242 Patients in all three cDDD subgroups had a higher risk of developing pneumonia than
243 did the non-BZD cohort. The aHRs for the 1–90, 91–365, and >365 cDDD subgroups were
244 2.28 (95% CI = 2.01–2.58; $p < 0.001$), 2.09 (95% CI = 1.77–2.47; $p < 0.001$), and 2.08 (95%
245 CI = 1.72–2.52; $p < 0.001$), respectively (Table 3).

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5 247 **Analyses after stratification for age and sex**

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7 248 The association between BZD use and the risk of pneumonia development in stroke
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9 249 patients was further analyzed after stratification for age and sex (Table 4). Using this
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11 250 approach, we found a significantly greater risk of pneumonia in BZD users than in non-users
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13 251 in both age subgroups (<65 years old: aHR = 2.42, 95% CI = 1.84–3.17, $p < 0.001$; ≥ 65 years
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15 252 old: aHR = 2.11, 95% CI = 1.86–2.40, $p < 0.001$). Additionally, BZD users had an increased
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17 253 risk of pneumonia in both male (aHR = 2.46, 95% CI = 2.13–2.84, $p < 0.001$) and female
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19 254 (aHR = 1.83, 95% CI = 1.50–2.22, $p < 0.001$) subgroups (Table 4). Together, these results
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21 255 reveal that BZD use after stroke was associated with an increased risk of pneumonia
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23 256 regardless of age and sex.
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30 258 **Results of sensitivity analysis**

31 259 In the sensitivity analysis, which considered the pneumonia event regardless of diagnosis
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33 260 in inpatient or outpatient service, BZD use was independently associated with increased risk
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35 261 of developing pneumonia (adjusted HR = 1.94, 95% CI = 1.77–2.14, $p < 0.001$). The results
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37 262 for different cumulative doses of BZDs also revealed a pattern to our primary analyses. The
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39 263 detailed statistical values are shown in the Supplementary materials (Supplementary Table
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265 Discussion

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

272 Our results are consistent with those previously reported by studies that focused on the
273 general population.⁹⁻¹¹ For example, previous observational studies found a 54 to 176%
274 increase in the risk of pneumonia development in BZD users when compared to non-BZD
275 users (relative risk or odds ratio: 1.54,⁹ 1.86,¹⁰ and 2.76¹¹). However, other observational
276 studies have reported conflicting results, showing negative or nonsignificant relationships
277 between BZD use and the risk of pneumonia.^{14 16-18} For instance, a previous case-control
278 study on participants aged ≥ 65 years old did not find a significant association between BZD
279 use and pneumonia risk; however, only 87 BZD users were found among all of the pneumonia
280 cases included in that study.¹⁴ Another cross-sectional study using 30-, 60-, and 90-day
281 windows revealed protective effects of BZDs on the risk of pneumonia, but was conducted
282 over a relatively short study period and focused on the general population.¹⁸

283 Pneumonia is a significant complication in stroke patients owing to the increased risk of
284 apparent aspiration and dysphagia-associated microaspiration, as well as stroke-induced
285 immunodepression.^{6 7 38} Acute-onset post-stroke pneumonia, which develops within 1 month
286 of the stroke event, is mainly associated with apparent aspiration and stroke-induced
287 immunodepression.^{6 7} However, although apparent aspiration and immunodepression
288 gradually attenuate following stroke recovery, the silent aspiration or microaspiration into the
289 lower airways may still occur and cause chronic-onset post-stroke pneumonia.^{7 39} BZDs are
290 commonly used in stroke patients on account of the high prevalence of psychological

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3 291 problems in stroke patients;^{17 19 20} previous studies have indicated that BZDs may be
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5 292 associated with the increased risk of aspiration and depression of immune cells.⁹⁻¹³ To the best
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7 293 of our knowledge, the only previous study to focus on the association between BZDs and
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9 294 pneumonia in stroke patients did not reveal a significant association between BZD use and the
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11 295 risk of pneumonia post-stroke; however, in that study, the follow-up period for identifying
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13 296 pneumonia was only 90 days post-stroke.¹⁷ In contrast, the current study, which specifically
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15 297 focused on the chronic phase of post-stroke to evaluate pneumonia developed over 1 month
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17 298 after the stroke,⁷ included a large sample size and long-term follow-up period (mean
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19 299 follow-up time, 4.4 years). The present study revealed a significantly increased risk of
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21 300 chronic-onset pneumonia in stroke survivors using BZDs (aHR = 2.21), even after carefully
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23 301 controlling for socioeconomic status, important comorbidities, stroke severity proxies, and
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25 302 concomitant medications. In addition, the subgroup analyses, which were performed
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27 303 according to cumulative BZD doses and stratified for age and sex, also revealed a similar
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29 304 pattern of results, further strengthening our findings. As pneumonia is one of the most
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31 305 common serious medical complications following stroke and can cause not only poor
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33 306 functional outcomes but also high mortality and financial burdens, we believe that our study
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35 307 addresses a knowledge gap regarding the clinical management of patients after stroke.

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40 308 Although the exact biological mechanisms underlying the influence of BZDs on
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42 309 pneumonia remain unclear, some hypotheses have been reported. One previous animal study
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44 310 suggested that BZDs may negatively influence immune function via the activation of GABA_A
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46 311 receptors on immune cells, thus interfering with macrophages/monocytes and impairing
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48 312 cytokine release, phagocytosis, and bacterial killing capabilities.¹² In addition, BZDs may
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50 313 increase the risk of aspiration by decreasing lower esophageal sphincter pressure, inducing the
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52 314 relaxation of muscles in the upper respiratory tract, and depressing the swallowing reflex,
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54 315 ultimately leading to pharyngeal dysfunction.^{11 13 40} Further research is necessary to explore
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56 316 these postulated mechanisms.

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3 317 The strengths of the present study include its large sample size, use of a nationwide
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5 318 population database, and the provision of sufficient power to evaluate the effect of BZDs on
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7 319 the risk of pneumonia development after stroke over a long-term follow-up period. The study
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9 320 design also provided better evidence in terms of epidemiology than previous studies that used
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11 321 case-control or cross-sectional designs. Moreover, performing propensity score matching
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13 322 before our analyses and then using multivariate Cox proportional hazard regression models
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15 323 with adjustment for competing mortality allowed us to rule out several important sources of
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17 324 bias and ensured that confounding factors were carefully controlled.

20 325 The following limitations of the present study should also be acknowledged. First, the
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22 326 claim-based database did not allow for the retrieval of certain clinical information (e.g.,
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24 327 patient lifestyle and physical, psychiatric, or laboratory examination data). Although our study
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26 328 design ensured the control of several variables, unknown or unmeasured confounders could
27
28 329 still exist. Second, by using de-identified claims, we could not obtain the patient details to
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30 330 analyze the medical history and identify exact mechanism of pneumonia; thus, we could not
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32 331 determine whether the pneumonia was caused by aspiration or not. Third, our analyses
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34 332 performed according to different cumulative BZD doses did not reveal an obvious dose-effect
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36 333 relationship. It is difficult to completely avoid an indication bias in observational studies that
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38 334 evaluate the effect of medication or intervention. Hence, the existence of unidentified residual
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40 335 confounders (i.e., the effect of the underlying etiologies needing BDZ prescription, other
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42 336 exposures, etc.) cannot be completely ruled out from the present study. Thus, further
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44 337 prospective clinical trials are necessary to address these possible biases and to determine the
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46 338 cause-and-effect relationship between post-stroke BZD use and the pneumonia risk. Finally,
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48 339 the accuracy of the diagnostic coding could not be directly confirmed due to the anonymity
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50 340 policy enforced in the NHIRD. However, only patients who were hospitalized under a
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52 341 primary diagnosis of stroke were included in our study population. The identification of
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54 342 stroke and pneumonia using ICD-9-CM coding in inpatient services has been previously
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3 343 validated and shows high accuracy.^{24 41 42} Additionally, the claims were routinely and
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5 344 randomly reviewed by the National Health Insurance Bureau to confirm the diagnostic
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7 345 accuracy. Given that hospitals and doctors in Taiwan are heavily fined in instances of
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9 346 misdiagnosis and coding errors, we feel confident in the validity of the criteria used for the
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11 347 inclusion of stroke and pneumonia cases in this study.

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15 16 349 **Conclusions**

17
18 350 In summary, this population-based propensity-matched retrospective cohort study
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20 351 indicated an association between BZD use and an increased risk of chronic-onset post-stroke
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22 352 pneumonia. However, further large-scale prospective studies are needed to determine possible
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24 353 cause-effect relationships.

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32 356 **Contributors:** Study conception and design: Shu-Man Lin, Huei-Kai Huang, and Ching-Hui
33
34 357 Loh; acquisition of data: Shih-Hsien Yang and Huei-Kai Huang; analysis and interpretation of
35
36 358 data: Shu-Man Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui
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38 359 Loh; drafting of manuscript: Shu-Man Lin and Huei-Kai Huang; critical revision: Shu-Man
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40 360 Lin, Shih-Hsien Yang, Chung-Chao Liang, Huei-Kai Huang, and Ching-Hui Loh.

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44
45 362 **Competing interests:** The authors declare that no competing interests exist.

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47 363 **Ethics approval:** The study was approved by the Institutional Review Board of Tzu Chi
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49 364 Medical Center (REC No. IRB104-131C).

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52 365 **Data sharing statement:** All relevant data are within the paper. No additional data are
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54 366 available.

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520 **Figure legends**

521 **Figure 1.** Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with
522 and without BZD use post-stroke.

For peer review only

523 **Table 1.** Baseline characteristics of patients post-stroke in the BZD and non-BZD cohorts
 524 after propensity score matching

	BZD use				p value
	Yes (n = 3,758)		No (n = 3,758)		
	n	%	n	%	
Age (years)	66.2 ± 14.9		66.3 ± 14.7		0.941
Sex					0.267
Male	2,455	65.3	2,409	64.1	
Female	1,303	34.7	1,349	35.9	
Income level (NTD)					0.816
Financially dependent	1,123	29.9	1,125	29.9	
1–19,999	1,801	47.9	1,826	48.6	
20,000–39,999	522	13.9	516	13.7	
≥40,000	312	8.3	291	7.7	
Urbanization level					0.732
1 (Most urbanized)	974	25.9	985	26.2	
2	993	26.4	1,010	26.9	
3	791	21.0	744	19.8	
4	579	15.4	580	15.4	
5 (Least urbanized)	421	11.2	439	11.7	
Comorbidities					
Charlson comorbidity index	2.26 ± 1.50		2.27 ± 1.63		0.837
Hypertension	2,666	70.9	2,666	70.9	1.000
Diabetes mellitus	1,263	33.6	1,256	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
Pneumoconiosis	6	0.2	7	0.2	0.781
Hyperlipidemia	1,096	29.2	1,080	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

1								
2	Epilepsy	24	0.6	—	26	0.7	—	0.777
3								
4	Bipolar disorders	3	0.1		3	0.1		1.000
5	Alcohol related disorders	14	0.4		19	0.5		0.383
6								
7	Substance use disorders	18	0.5		18	0.5		1.000
8	Schizophrenia	18	0.5		16	0.4		0.731
9								
10	Anxiety	90	2.4		104	2.8		0.309
11	Sleep disorders	170	4.5		186	4.9		0.385
12								
13	Charlson comorbidity index	2.03 ± 1.79			2.13 ± 2.06			0.022
14	at the end point of follow-up							
15								
16	Stroke severity proxies							
17	Estimated NIHSS	8.0 ± 6.0			7.7 ± 5.8			0.061
18								
19	ICU utilization	937	24.9		871	23.2		0.075
20	Mechanical ventilation	308	8.2		299	8.0		0.703
21								
22	Hemiplegia	562	15.0		530	14.1		0.295
23								
24	Aphasia	69	1.8		63	1.7		0.598
25	Neurosurgery	202	5.4		210	5.6		0.685
26								
27	Use of medication							
28	Steroids	109	2.9		116	3.1		0.636
29								
30	Anti-diabetic agents	795	21.2		821	21.8		0.465
31	Anti-hypertensive agents	1,676	44.6		1,715	45.6		0.366
32								
33	Statins	319	8.5		332	8.8		0.594
34	Proton pump inhibitors	89	2.4		97	2.6		0.553
35								
36	Anti-epileptics	70	1.9		82	2.2		0.325
37	Antiparkinsonian	92	2.4		90	2.4		0.881
38								
39	Antipsychotics	76	2.0		85	2.3		0.473
40	Anxiolytics	246	6.5		286	7.6		0.072
41								
42	Hypnotics and sedatives	156	4.2		180	4.8		0.180
43								
44	Antidepressants	79	2.1		97	2.6		0.170

525 Continuous data expressed as mean ± standard deviation (SD) and categorical data expressed as number and
 526 percentage.

527 Abbreviations: BZD, benzodiazepine; COPD, chronic obstructive pulmonary disease; NTD, New Taiwan
 528 dollars; NIHSS, National Institutes of Health Stroke Scale.

529 **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 (1.75–2.17)	1 (ref.)
p value	<0.001	
Multivariate model†		
Adjusted HR (95% CI)	2.21 (1.97–2.48)	1 (ref.)
p value	<0.001	

530 *Per 1000 person-years.

531 †Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics
532 (listed in Table 1) and competing mortality.

533 Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

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

Cumulative BZD doses	n	Pneumonia cases	Person-years	Incidence rate*	Univariate model		Multivariate model†	
					Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	3758	478	14663.8	32.6	1 (ref.)		1 (ref.)	
1–90 cDDD	2507	702	11760.2	59.7	2.10 (1.87–2.36)	<0.001	2.28 (2.01–2.58)	<0.001
91–365 cDDD	728	198	4216.6	47.0	1.84 (1.56–2.16)	<0.001	2.09 (1.77–2.47)	<0.001
>365 cDDD	523	127	3703.4	34.3	1.47 (1.21–1.77)	<0.001	2.08 (1.72–2.52)	<0.001

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily doses

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	10438.4	21.2	1626	77	7568.1	10.2	2.32 (1.79–3.00)	<0.001	2.42 (1.84–3.17)	<0.001
≥65	2159	806	9241.7	87.2	2132	401	7095.7	56.5	1.94 (1.72–2.18)	<0.001	2.11 (1.86–2.40)	<0.001
Sex												
Male	2455	721	12709.5	56.7	2409	278	9945.3	28.0	2.35 (2.04–2.69)	<0.001	2.46 (2.13–2.84)	<0.001
Female	1303	306	6970.6	43.9	1349	200	4718.5	42.4	1.39 (1.16–1.66)	<0.001	1.83 (1.50–2.22)	<0.001

*Per 1,000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval

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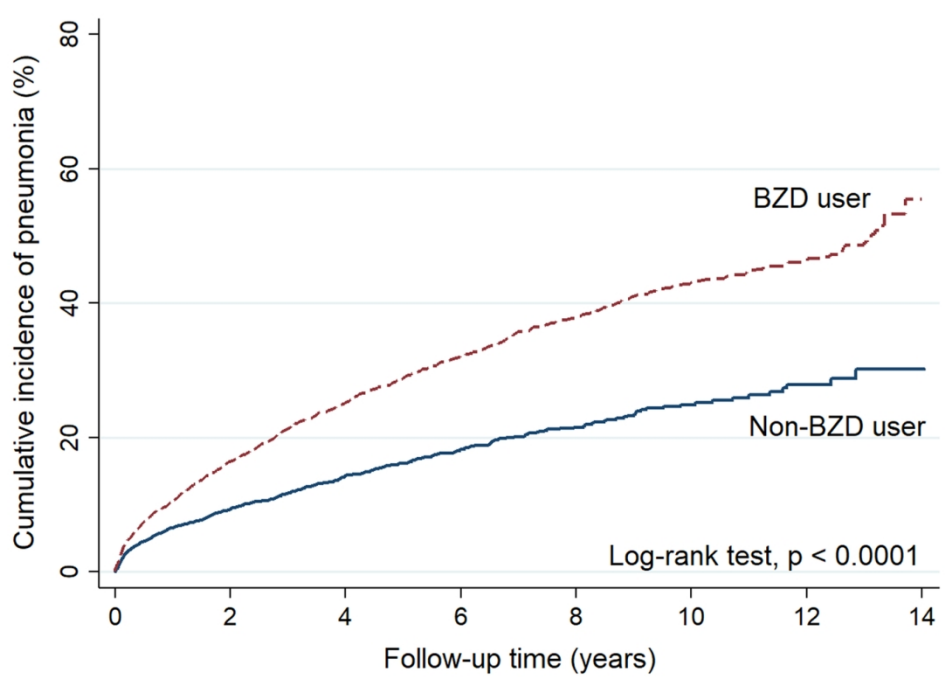


Figure 1. Kaplan-Meier curves showing cumulative incidences of pneumonia in patients with and without BZD use post-stroke.

127x92mm (300 x 300 DPI)

Supplementary Materials

Table S1. Sensitivity analysis of risk of contracting pneumonia after stroke according to BZD-use status

Cumulative BZD doses	Univariate model		Multivariate model†	
	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Non-user	1 (ref.)		1 (ref.)	
All BZD user	1.75 (1.60–1.91)	<0.001	1.94 (1.77–2.14)	<0.001
1–90 cDDD	1.83 (1.66–2.02)	<0.001	1.96 (1.77–2.18)	<0.001
91–365 cDDD	1.72 (1.50–1.98)	<0.001	1.89 (1.64–2.18)	<0.001
>365 cDDD	1.45 (1.24–1.70)	<0.001	1.92 (1.63–2.25)	<0.001

For the sensitivity 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.

*Per 1000 person-years.

†Multivariate Cox proportional hazard regression model, adjusting for all baseline characteristics (listed in Table 1) and competing mortality.

Abbreviations: BZD, benzodiazepine; HR, hazard ratio; CI, confidence interval; cDDD, cumulative defined daily doses

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page number in manuscript
✓ Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
✓ Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
✓ Study design	4	Present key elements of study design early in the paper	6-8
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
✓ Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	8-9 Table 1
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
✓ Bias	9	Describe any efforts to address potential sources of bias	8-10
✓ Study size	10	Explain how the study size was arrived at	6-7
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
✓ Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	8-10
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	8
Results			
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 p.11
		(b) Indicate number of participants with missing data for each	N/A

		variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	11
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2-4 p.11-12
✓ Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12 Table 1
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
✓ Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
✓ Key results	18	Summarise key results with reference to study objectives	13
✓ Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
✓ Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
✓ Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
✓ Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.