Influenza Vaccination and Risk of Stroke in Women With Chronic Obstructive Pulmonary Disease: A Nationwide, Population-Based, Propensity-Matched Cohort Study

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Backgrounds: The risk of stroke is higher among patients with chronic obstructive pulmonary disease (COPD) than among the healthy population. Moreover, women generally have worse long-term stroke outcomes than men.

Methods: The data of 6681 women with COPD (aged ≥ 65 years) registered in Taiwan's National Health Insurance Research Database were retrospectively analyzed from January 1, 2001 to December 31, 2011. After 1:1 propensity score matching, the patients were divided into vaccinated and unvaccinated groups.

Results: In total, 5102 women were enrolled. The vaccinated group had a significantly lower risk of total, hemorrhagic, and ischemic stroke than the unvaccinated group (adjusted hazard ratio [aHR]: 0.60, 95% confidence interval [CI]: 0.54–0.67; aHR: 0.59, 95% CI: 0.43–0.83; and aHR: 0.59, 95% CI: 0.52–0.68, respectively). A lower risk of stroke was observed among the women aged 65–74 and ≥75 years, and the association was dose-dependent in all types of stroke (aHR: 1.08, 95% CI: 0.92–1.26; aHR: 0.70, 95% CI: 0.60–0.82; and aHR: 0.32, 95% CI: 0.26–0.38 for those vaccinated 1, 2 to 3, and ≥4 times, respectively, during the follow-up period). Women with a CHA²DS²-VASc score (conditions and characteristics included congestive heart failure, hypertension, diabetes, stroke, vascular disease, age, and sex) of 2–3 and ≥4 had a significantly lower risk of ischemic stroke while receiving more vaccinations. A smaller significant lower risk of hemorrhagic stroke after more than 4 times of vaccination.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading global cause of death (1). Although COPD is primarily considered a complex respiratory tract disease characterized by irreversible airway pathological changes, it is also strongly associated with cardiovascular disease (2, 3). Common comorbidities of cardiovascular disease include heart failure, ischemic heart disease, obesity, hypertension, hyperlipidemia, and diabetes (4). Furthermore, factors contributing to the development of cardiovascular disease include systemic inflammation, hypoxemia, oxidative stress, and arterial stiffness (5).

Cardiovascular disease risk and stroke prevalence and incidence are all significantly higher in patients with COPD than in the healthy population (6). Stroke is one of the leading causes of functional disability that results in reduced quality of life in patients with COPD and increases caregiver burden. Notably, long-term stroke outcomes are less favorable in women than in men (7).

Studies have identified associations between seasonal influenza infection and an increased risk of cardiovascular mortality (8, 9). A study on influenza vaccination and reduction in hospitalization for cardiac and stroke events among older adults observed that influenza vaccination had a cardioprotective effect on patients with COPD (10). Therefore, high-risk patients should receive annual influenza vaccination (10–12). Although influenza vaccination may reduce the risk of stroke in patients at high risk for thrombogenicity (13, 14), the effect of influenza vaccination on women with COPD remains unclear. Thus, the present study explored the potential cerebroprotective association between influenza vaccination and the risk of stroke among women with COPD.

MATERIALS AND METHODS

Taiwan’s National Health Insurance (NHI) program, launched in 1995, covers 98% of the population of Taiwan, which exceeds 23 million people. The NHI Research Database (NHIRD), which is maintained by the Health and Welfare Data Science Center, has been extensively analyzed and validated (13–16). In Taiwan, influenza vaccination is provided free of charge to adults aged older than 65 years with high-risk comorbidities (i.e., diabetes, chronic liver disease, cirrhosis, cardiovascular disease, and chronic pulmonary disease). All researchers using the NHIRD was noted in the women with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥4. Both interrupted and non-interrupted vaccination was associated with lower risk of stroke occurrence.

Conclusion: Influenza vaccination is associated with a lower risk of total, hemorrhagic, and ischemic stroke among women with COPD, and the association is dose-dependent. However, the findings may be limited by unmeasurable confounders. Further investigations on this subject are warranted.

Keywords: women, COPD, influenza vaccination, ischemic stroke, hemorrhagic stroke

Study Cohort

The patients enrolled in the present study were women recorded as having COPD between January 1, 2001 and December 31, 2011, with all diagnoses corresponding to the codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The patients must have been ≥65 years of age (N = 6681) and have had at least two COPD diagnoses as inpatients or outpatients (17). The positive predictive value of the ICD-9-CM codes in COPD diagnosis was previously validated (16). Vaccination status was identified by code V048 and/or the use of vaccine (confirmed by drug codes).

Data Selection Process

There were 3768 COPD patients who had vaccination and 2913 COPD patients who did not have vaccination. Propensity score matching (1:1) was performed and the patients were divided into vaccinated (n = 2551) and unvaccinated (n = 2551) groups (Figure 1A and Table 1).

Index Date Definition

To avoid immortal time bias (18), the vaccination date of the patients in the vaccinated group was defined as the index or cohort entry date. In the matched pairs, the participants who did and did not receive vaccination were assigned the same index date (i.e., the vaccination date) for follow-up (Figure 1B).

Definition of Interrupted and Non-interrupted Vaccination

Patients who received more than two vaccinations were divided into interrupted and non-interrupted groups. Interrupted vaccination was defined as receiving more than two vaccinations with any interruption during the follow-up period. Non-interrupted vaccination was defined as receiving more than two yearly vaccinations without any interruption during the follow-up period.

Study Endpoint

The study endpoint was the initial diagnosis of hemorrhagic stroke (ICD-9-CM codes 430, 431, or 432), ischemic stroke (ICD-9-CM codes 433 or 434), or undefined stroke (ICD-9-CM code 436). All patients were followed until stroke diagnosis,
FIGURE 1 | (A) Data selection process. (B) Definition of index date and duration between diagnosis date and vaccination date.
*These variables were not adjusted for in the propensity score matching.

The standardized difference is the difference in the mean or proportions divided by the standard error. Imbalance between groups was defined as an absolute value greater than 0.10 (corresponding to a small effect size).

COPD, chronic obstructive pulmonary disease; HF, heart failure; AMI, acute myocardial infarction; AF, atrial fibrillation; SABA, short-acting beta agonists; SAMA, short-acting muscarinic antagonists; LABA, long-acting beta agonists; ICS, inhaled corticosteroids; RAASi, renin–angiotensin–aldosterone system inhibitors.

COPD-related inpatient visits

| Medication | Before matching | After matching |
|------------|----------------|---------------|
| Statin     | 658 22.59 1279 33.94 0.254 | 522 20.46 740 29.01 0.199 |
| Aspirin    | 962 33.02 1829 48.54 0.320 | 795 31.16 1014 39.75 0.180 |

Comorbidities

| Condition                      | Before matching | After matching |
|-------------------------------|----------------|---------------|
| Asthma                        | 1274 43.73 1953 51.83 0.163 | 1187 46.53 1289 50.53 0.080 |
| HF                            | 545 18.71 514 13.64 0.138 | 393 15.41 394 15.44 0.001 |
| AMI                           | 62 2.13 61 1.62 0.038 | 40 1.57 47 1.84 0.021 |
| AF                            | 419 14.38 506 13.43 0.028 | 382 14.97 342 13.41 0.045 |
| Ischemic heart disease        | 1239 42.53 1383 36.70 0.119 | 946 37.08 968 37.95 0.018 |
| Angina                        | 417 14.32 470 12.47 0.054 | 290 11.37 329 12.90 0.047 |
| Peripheral vascular disease   | 357 12.26 367 9.74 0.081 | 250 9.80 257 10.07 0.056 |
| Hypertension                  | 2053 70.48 2477 65.74 0.102 | 1645 64.48 1723 67.54 0.065 |
| Diabetes                      | 929 31.89 1106 29.35 0.055 | 753 29.72 760 29.79 0.006 |
| Depression                    | 148 5.08 135 3.58 0.074 | 103 4.04 102 4.00 0.002 |
| Renal failure                 | 467 16.03 448 11.89 0.120 | 358 14.03 335 13.13 0.026 |
| Chronic liver disease         | 752 25.82 863 22.90 0.068 | 621 24.34 601 23.66 0.018 |
| Dementia                      | 227 7.79 193 5.12 0.109 | 135 5.29 169 6.62 0.056 |
| Urbanization level            | 1844 63.30 2236 59.34 0.081 | 1593 62.45 1485 58.21 0.087 |
| Suburban                      | 665 22.83 910 24.15 0.031 | 609 23.87 654 25.64 0.041 |
| Rural                         | 404 13.87 622 16.51 0.074 | 349 13.68 412 16.15 0.069 |
| Monthly income (NT$)          |                  |               |
| 0                             | 670 23.00 778 20.65 0.057 | 650 25.48 561 21.99 0.082 |
| 1–33 300                      | 2060 70.72 2765 73.38 0.059 | 1795 70.36 1859 72.87 0.056 |
| ≥33 301                       | 183 6.28 225 5.97 0.013 | 106 4.16 131 5.14 0.047 |
| COPD medications              |                  |               |
| SABA                           | 488 16.75 833 22.11 0.136 | 486 19.05 549 21.52 0.061 |
| SABA + SAMA                    | 375 12.87 523 13.88 0.030 | 321 12.58 350 13.72 0.034 |
| LABA (ultra-LABA)             | 34 1.17 46 1.22 0.005 | 20 0.78 22 0.86 0.009 |
| LAMA                           | 50 1.72 92 2.44 0.050 | 47 1.84 57 2.23 0.028 |
| ICS                            | 200 6.87 367 9.74 0.104 | 188 7.37 237 9.29 0.070 |
| ICS + LABA                     | 264 9.06 467 12.39 0.108 | 247 9.68 308 12.07 0.077 |
| Total COPD medications         |                  |               |
| 0                             | 2042 70.10 2420 64.23 0.125 | 1765 69.19 1646 64.52 0.099 |
| 1                             | 539 18.50 757 20.09 0.040 | 457 17.91 523 20.50 0.066 |
| ≥2                            | 332 11.40 591 15.88 0.125 | 329 12.90 382 14.97 0.060 |

Medication use

| Medication | Before matching | After matching |
|------------|----------------|---------------|
| Aspirin    | 962 33.02 1829 48.54 0.320 | 795 31.16 1014 39.75 0.180 |
| Statin     | 658 22.59 1279 33.94 0.254 | 522 20.46 740 29.01 0.038 |
| RAASi      | 1508 51.77 2478 65.76 0.287 | 1223 47.94 1498 58.72 0.217 |
| Metformin  | 541 18.59 906 24.04 0.134 | 464 18.19 545 21.36 0.080 |

The standardized difference is the difference in the mean or proportions divided by the standard error. Imbalance between groups was defined as an absolute value greater than 0.10 (corresponding to a small effect size).

In propensity score matching, adjustments were made for COPD-related inpatient visits, COPD medications, total COPD medications, age, CHA2DS2-VASc score, asthma, HF, AMI, AF, ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, depression, renal failure, chronic liver disease, dementia, urbanization level, and monthly income.

*These variables were not adjusted for in the propensity score matching.
withdrawal from NHI, loss to follow-up, death, or December 31, 2012. Except for those patients diagnosed with stroke, the other data were censored.

Potential Confounders

The potential confounders of the cohort were based on sociodemographic characteristics (age, urbanization level, and monthly income), comorbidities [asthma, heart failure [HF], acute myocardial infarction [AMI], atrial fibrillation [AF], ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, depression, renal failure, chronic liver disease, dementia, and CHA²DS²-VASc score (19)], COPD severity and treatment (COPD-related inpatient visits, COPD medications, total number of COPD medications) and medication use (aspirin, statins, renin–angiotensin–aldosterone system inhibitors [RAASi], and metformin). These confounders have been implicated as possible risk factors in stroke (19–21).

Matching Factors

Propensity score matching, which involves assigning levels of 0 and 1 to a treatment variable, given a set of known variables, is used to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies (22). In the present study, the propensity score of each vaccinated patient was estimated by logistic regression with the following 25 potential confounders associated with vaccine introduction: sociodemographic characteristics (age, urbanization level, and monthly income), comorbidities [asthma, HF, AMI, AF, ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, depression, renal failure, chronic liver disease, dementia, and CHA²DS²-VASc score (19)], and COPD severity and treatment (COPD-related inpatient visits, COPD medications, and total number of COPD medications). The vaccinated and unvaccinated patients were then matched using propensity scores and a 1:1 nearest neighbor algorithm. As previously suggested (23), the caliper width was set as 0.03 of the pooled standard deviation of the logit of the propensity scores. Finally, the patients were divided into vaccinated (n = 2551) and unvaccinated (n = 2551) groups.

Statistical Analysis

In the present study, categorical data are expressed as numbers and percentages, whereas quantitative data are presented as the means ± standard deviations. The balance of characteristics was assessed by estimating the standardized differences (StDiffs) between the vaccinated and unvaccinated groups. Empirically, an absolute value of StDiffs that exceeds 0.1 (10%) represents a meaningful imbalance in a given variable between two groups. A Cox proportional hazards model was used to calculate the hazard ratios (HRs) to determine the differences in the risk of stroke between the groups. The adjusted HRs (aHRs) were HRs that were adjusted according to the confounder propensity score. In addition to the previously mentioned confounders, the duration between the COPD diagnosis date and index date was also included in the Cox proportional hazard model for aHR analysis. Fine and Gray’s (F&G) survival and regression analyses were used to determine the risk of stroke while competing with death. In this way the F&G method models the subdistribution hazards. The effect estimated using the F&G model shows the current and real differences between the treatment groups in terms of subdistribution hazards ratios. The assumption of proportionality of hazards is still a requirement, but of course it refers to the subdistribution hazards. The F&G model can accommodate time dependent coefficients to model the non-proportionality of hazards. This model can be applied to both the event of interest (stroke) or the competing risk (death). Sensitivity analysis can improve the understanding of the effects of drugs and biologics in epidemiologic database studies (24). Thus, in the present sensitivity analysis, the patients were stratified to estimate the association of age, CHA²DS²-VASc score, COPD-related inpatient visits, asthma, HF, AF, ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, renal failure, and chronic liver disease with the incidence of stroke in different models. The cumulative incidence of stroke in the vaccinated and unvaccinated patients with COPD was calculated using the cumulative incidence function. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, United States). A two-tailed P-value of <0.05 was considered significant.

RESULTS

The baseline characteristics of both groups of patients after propensity score matching are presented in Table 1. As mentioned, 6681 patients were enrolled, and after 1:1 propensity score matching, we divided the patients into vaccinated and unvaccinated groups (each group, n = 2551).

The Association Between Influenza Vaccination and Stroke Occurrence in Different Age Groups and Patients With Varying CHA²DS²-VASc Scores

Table 2 shows the association between influenza vaccination and the risk of stroke in the present cohort, stratified by age and CHA²DS²-VASc score. Ischemic stroke was higher in incidence than hemorrhagic stroke during the follow-up period. Overall, the occurrence of all strokes, hemorrhagic, ischemic, and undefined were significantly lower in the vaccinated group (aHR: 0.60, 95% confidence interval [CI]: 0.54–0.67; aHR: 0.59, 95% CI: 0.43–0.83; aHR: 0.59, 95% CI: 0.52–0.68; and aHR: 0.64, 95% CI: 0.50–0.81, respectively) than in the unvaccinated group (Figures 2A–D). In the Fine and Gray competing risk model, the risk of all strokes remained significantly lower in the vaccinated group while competing with death (Table 2). Influenza vaccination was also associated with a lower risk of hemorrhagic, ischemic, and undefined stroke in patients aged 65 to 74 years. Vaccinated patients aged ≥75 years had a lower risk of all strokes and ischemic stroke than their unvaccinated counterparts.

The occurrence of hemorrhagic, ischemic, and undefined stroke was considerably lower in women with COPD and a CHA²DS²-VASc score of 2–3 after they were vaccinated. Compared with that of women with a CHA²DS²-VASc score of 2–3, the risk of ischemic stroke was significantly lower in
vaccinated women with COPD who had higher CHA₂DS₂-VASc scores.

Association Between the Total Number of Influenza Vaccinations and Stroke Risk

In the main model, a higher number of influenza vaccinations over the follow-up period was associated with a lower risk of stroke occurrence in women with COPD overall (aHR: 1.08, 95% CI: 0.92–1.26; aHR: 0.70, 95% CI: 0.60–0.82; and aHR: 0.32, 95% CI: 0.26–0.38 for patients vaccinated 1, 2 to 3, and ≥4 times, respectively; Table 3 and Figure 3A). Patients with a history of asthma, HF, AF, ischemic heart disease, angina, hypertension, diabetes, renal failure, and chronic liver disease had a reduced risk of developing all types of stroke after they received more vaccinations. Notably, a considerably lower risk of all types of stroke was detected in patients without such history after they received more vaccinations. In patients with a CHA₂DS₂-VASc score 2–3, significantly lower risk of stroke occurred after receiving more than four times of vaccination was observed. In patients with a CHA₂DS₂-VASc score ≥4, a substantially lower risk of all types of stroke was observed after more than two vaccinations, and further reductions in risk were noted in subsequent vaccinations, with a significant trend (Table 3). The patients with no COPD-related inpatient visits had a substantially lower risk of all types of strokes after receiving more than two vaccinations. The same results were noted in the patients with one COPD-related inpatient visit. Among patients with two or more COPD-related inpatient visits, the risk of all types of strokes only decreased after they received four or more vaccinations (Table 3). In patients who did not have influenza during the follow-up period, a substantially lower risk of all types of stroke was observed after vaccination. In patients who had influenza infection during the follow-up period, a significant trend of lower risk of all types of stroke was observed after vaccination (Table 3).

Supplementary Tables 1–3 present the sensitivity analysis results of the total number of vaccinations in patients with hemorrhagic, ischemic, and undefined stroke, respectively. The main model analysis revealed that patients who received 2 to 3 and ≥4 vaccinations had a lower risk of developing these types of strokes (Supplementary Tables 1–3 and Figures 3B–D). Among patients with no COPD-related inpatient visits, the risk of hemorrhagic stroke decreased after they received more than 4 vaccinations. Following multiple vaccinations, patients without HF, ischemic heart disease, angina, peripheral vascular disease, diabetes, renal failure, or chronic liver disease were less likely to develop hemorrhagic stroke. After receiving more than four vaccinations, patients with hypertension had a reduced risk of hemorrhagic stroke. All the patients had a reduced risk or developed ischemic stroke after receiving a higher number of vaccinations, regardless of the presence of those comorbidities, except patients with angina. Among women with a CHA₂DS₂-VASc score ≥4, the risk of hemorrhagic stroke decreased following more than 4 times of vaccinations, but the risk of ischemic stroke decreased after receiving more than two times of vaccinations. Among patients with a CHA₂DS₂-VASc score 2–3, the risk of hemorrhagic stroke did not decrease despite receiving more than four times of vaccination. A lower risk of ischemic stroke and undefined stroke occurrence was observed in patients with a CHA₂DS₂-VASc score of 2 to 3, or ≥4 after they received 4 or more vaccinations.

Analysis revealed that both interrupted and non-interrupted influenza vaccinations (Supplementary Tables 4–6) were associated with a lower risk of all strokes. In the sensitivity analysis, the risk of stroke was significantly lower after receiving more vaccination regardless of influenza infection (Table 3 and Supplementary Tables 1–3). In mediator analysis of present study, there were no significant decreasing influenza infection after influenza vaccination (β = −0.129) nor significant occurrence of stroke after influenza infection (β = 0.127). However, there was a significant stroke risk reduction after influenza vaccination (β = −0.567**, p < 0.001). The results of mediator analysis suggested that influenza infection was not a mediator effect in the present study (Supplementary Figure).

DISCUSSION

Main Findings

The main findings of the present nationwide population-based propensity-matched cohort study are as follows: (1) Overall, women with COPD had a potentially lower risk of developing any of the types of stroke after receiving influenza vaccination. A similar association between a lower risk of stroke and influenza vaccination was found in elderly (≥65 years-old) and late elderly (≥75 years-old) women (2). The association between influenza vaccination and a lower risk of stroke in women with COPD...
TABLE 2 | Risk of stroke in the unvaccinated and vaccinated groups.

| Study Cohort (N = 5102) | Unvaccinated (total follow-up duration: 10028.9 person-years) | Vaccinated (total follow-up duration: 12858.0 person-years) | HR (95% CI) | aHR† (95% CI) | Subdistribution HR‡ (95% CI) |
|--------------------------|---------------------------------------------------------------|-------------------------------------------------------------|--------------|----------------|-------------------------------|
| **Death Before Event**   | **Number of Events**                                         | **Incidence Rate (per 10^5 person-years)**                  |              |                |                               |
| **Entire cohort**         |                                                               |                                                             |              |                |                               |
| Stroke                   | 596                                                          | 770                                                         | 7677.8 (7135.5, 8220.1) | 525            | 537                                                         | 4176.4 (3823.1, 4529.6) |
| Hemorrhagic stroke        | 909                                                          | 897.4 (712.0, 1082.8)                                        | 705           | 61             | 474.4 (355.4, 593.5) | 0.57 (0.45, 0.76)***        |
| Ischemic stroke           | 716                                                          | 5145.1 (4701.2, 5589.1)                                      | 606           | 357            | 2776.5 (2488.5, 3064.5) | 0.58 (0.49, 0.64)***        |
| Undefined stroke          | 874                                                          | 1635.3 (1385.0, 1885.6)                                      | 688           | 119            | 925.5 (759.2, 1091.8)    | 0.60 (0.47, 0.76)***        |
| **Death Before Event**   |                                                               |                                                             |              |                |                               |
| **Age, 65–74 years**     |                                                               |                                                             |              |                |                               |
| Stroke                   | 237                                                          | 395                                                         | 6468.6 (5830.7, 7106.5) | 178            | 283                                                         | 3569.2 (3153.4, 3985.1) |
| Hemorrhagic stroke        | 340                                                          | 501.8 (3918.3, 1045.8)                                       | 241           | 31             | 391.0 (253.3, 528.6)     | 0.50 (0.32, 0.78)***        |
| Ischemic stroke           | 287                                                          | 241.8 (2617.3, 4636.3)                                       | 208           | 193            | 2434.1 (2090.7, 2777.6)  | 0.61 (0.50, 0.73)***        |
| Undefined stroke          | 320                                                          | 93                                                           | 1523.0 (1213.5, 1832.5) | 233            | 59             | 744.2 (554.2, 934.0)      | 0.51 (0.37, 0.71)***        |
| **Age, ≥75 years**       |                                                               |                                                             |              |                |                               |
| Stroke                   | 358                                                          | 375                                                         | 9560.2 (8592.6, 10527.9) | 347            | 254             | 5153.1 (4153.9, 5786.8)   | 0.57 (0.48, 0.67)***        |
| Hemorrhagic stroke        | 569                                                          | 40                                                           | 1019.8 (703.7, 1335.8)  | 464            | 30             | 608.6 (390.8, 826.4)      | 0.62 (0.38, 0.99)***        |
| Ischemic stroke           | 429                                                          | 264                                                         | 6730.4 (5918.5, 7542.3) | 398           | 164             | 3327.2 (2818.0, 3836.4)   | 0.52 (0.43, 0.63)***        |
| Undefined stroke          | 554                                                          | 71                                                           | 1810.1 (1389.0, 2231.1) | 453           | 60              | 1217.3 (909.3, 1525.3)    | 0.71 (0.51, 1.01)           |
| **CHA2DS2-VASc = 2–3**   |                                                               |                                                             |              |                |                               |
| Stroke                   | 224                                                          | 262                                                         | 5560.2 (4886.9, 6233.4) | 154           | 159             | 2861.4 (2416.6, 3306.2)   | 0.53 (0.43, 0.64)***        |
| Hemorrhagic stroke        | 287                                                          | 40                                                           | 848.9 (588.5, 1111.9)  | 187           | 21              | 377.9 (216.3, 539.6)      | 0.45 (0.27, 0.77)***        |
| Ischemic stroke           | 255                                                          | 168                                                         | 3565.3 (3028.2, 4104.4) | 168           | 106             | 1907.6 (1544.5, 2270.8)   | 0.55 (0.43, 0.70)***        |
| Undefined stroke          | 294                                                          | 54                                                           | 1146.0 (840.3, 1451.6) | 185           | 32              | 575.9 (376.3, 775.4)      | 0.52 (0.33, 0.80)***        |
| **CHA2DS2-VASc ≥ 4**     |                                                               |                                                             |              |                |                               |
| Stroke                   | 371                                                          | 508                                                         | 9554.6 (8723.7, 10385.5) | 371           | 378             | 5177.2 (4655.2, 5699.1)   | 0.57 (0.50, 0.65)***        |
| Hemorrhagic stroke        | 622                                                          | 50                                                           | 940.4 (679.7, 1201.1)  | 518           | 40              | 547.8 (378.1, 717.6)      | 0.61 (0.40, 0.93)***        |
| Ischemic stroke           | 461                                                          | 348                                                         | 6545.3 (5887.6, 7233.0) | 438           | 251             | 3437.7 (2012.4, 3863.0)   | 0.55 (0.47, 0.65)***        |
| Undefined stroke          | 580                                                          | 110                                                         | 2068.9 (1682.3, 2455.5) | 501           | 87              | 1191.6 (941.2, 1442.0)    | 0.61 (0.46, 0.82)***        |

†Adjusted for COPD-related inpatient visits, COPD medications, total COPD medications, age, CHA2DS2-VASc score, asthma, HF, AMI, AF, ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, depression, renal failure, chronic liver disease, dementia, level of urbanization, monthly income, and the use of aspirin, statins, RAASi, and metformin, duration between the COPD diagnosis date and index date.

‡Subdistribution hazard model was used as a sensitivity analysis to account for death as a competing risk.

*P < 0.05; **P < 0.01; ***P < 0.001.

CI, confidence interval; HR, hazard ratio; aHR, adjusted HR; HF, heart failure; AMI, acute myocardial infarction; AF, atrial fibrillation; RAASi, renin–angiotensin–aldosterone system inhibitors.
### Table 3: Sensitivity analysis of the adjusted hazard ratios of vaccination in stroke risk reduction.

| Subgroup effects | Unvaccinated | Vaccinated | P for Trend |
|------------------|--------------|------------|-------------|
|                  | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) |
|                  | 1            | 2–3        | ≥4          |              |              |
| Unadjusted       | 1.00         | 1.06 (0.90, 1.24) | 0.68 (0.59, 0.79)*** | 0.29 (0.24, 0.35)*** | <0.001 |
| Main model       | 1.00         | 1.08 (0.92, 1.26) | 0.70 (0.60, 0.82)*** | 0.32 (0.26, 0.38)*** | <0.001 |
| Competing Risk model | 1.00       | 0.94 (0.80, 1.12) | 0.73 (0.63, 0.85)*** | 0.39 (0.33, 0.46)*** | <0.001 |

#### Subgroup effects

| Asthma           | No                        | Yes                       | 0.97 (0.81, 1.17) | 0.76 (0.65, 0.90)*** | 0.32 (0.25, 0.42)*** | <0.001 |
| Peripheral vascular disease | No                        | Yes                       | 0.93 (0.75, 1.16) | 0.75 (0.62, 0.91)** | 0.38 (0.31, 0.47)** | <0.001 |
| Hypertension     | No                        | Yes                       | 0.89 (0.74, 1.06) | 0.75 (0.62, 0.87)*** | 0.37 (0.31, 0.45)*** | <0.001 |
| Diabetes         | No                        | Yes                       | 0.95 (0.80, 1.15) | 0.72 (0.62, 0.84)*** | 0.37 (0.31, 0.44)*** | <0.001 |
| Renal failure    | No                        | Yes                       | 1.49 (0.96, 2.30) | 0.65 (0.41, 1.04) | 0.53 (0.32, 0.88)* | 0.005 |
| Chronic liver disease | No                        | Yes                       | 1.00 (0.48, 1.38) | 0.84 (0.53, 1.34) | 0.68 (0.39, 1.18) | 0.153 |
| Influenza infection | No                        | Yes                       | 1.00 (0.80, 1.15) | 0.72 (0.62, 0.84)*** | 0.37 (0.31, 0.44)*** | <0.001 |

**P < 0.05; **P < 0.01; ***P < 0.001.

COPD: chronic obstructive pulmonary disease; CI, confidence interval; aHR, adjusted hazard ratio; HF, heart failure; AMI, acute myocardial infarction; AF, atrial fibrillation; RAASi, renin–angiotensin–aldosterone system inhibitors.

The main model was adjusted for COPD-related inpatient visits, COPD medications, total COPD medications, age, CHA2DS2-VASc score, asthma, HF, AMI, AF, ischemic heart disease, angina, peripheral vascular disease, hypertension, diabetes, depression, renal failure, chronic liver disease, dementia, urbanization level, monthly income, and the use of aspirin, statins, RAASi, and metformin, duration between the COPD diagnosis date and index date.

A subdistribution hazard model was used as a sensitivity analysis to account for death as a competing risk.
not have influenza. An association was observed in both patients who did and did not have influenza after receiving vaccination. In addition, a potential protective effect remained significantly lower among older adults aged ≥75 years after receiving vaccination. Women with COPD and CHA2DS2-VASc scores of ≥4 all had a significantly lower risk of stroke after receiving more than two influenza vaccinations.

**Association Between Influenza Vaccination and Stroke in Women With Chronic Obstructive Pulmonary Disease**

Influenza vaccination is strongly associated with a reduced risk of ischemic and hemorrhagic stroke (10, 13, 14, 25). In a recent nationwide observational study from Spain (26), a significantly higher risk of in-hospital mortality and mechanical ventilation usage was noted among women with COPD who were admitted because of ischemic stroke. Therefore, decreasing the risk of stroke in women with COPD is important. However, few studies have addressed the benefits of influenza vaccination in women with COPD.

The literature indicates the existence of sex differences in stroke. In general, women who have had a stroke are older and have more disabilities (7). Experimental studies have demonstrated the potential cardioprotective effect of estrogen (27). Therefore, postmenopausal women have a higher risk of stroke than premenopausal women (28). In Taiwan, influenza vaccination is provided free of charge to patients aged ≥65 years with high-risk comorbidities, which explains why the majority of the patients in the present study were postmenopausal. After adjustment for comorbidities, medications, urbanization level, monthly income, COPD-related inpatient visits, duration between COPD diagnosis date and vaccination date and age, influenza vaccination remained associated with a lower risk of all types of stroke. Furthermore, the risk of stroke remained significantly lower among older adults aged ≥75 years after receiving vaccination. In addition, a potential protective association was observed in both patients who did and did not have influenza.

Possible explanations are as follows: First, viral infection may trigger the thrombogenic process and induce coagulopathy (29). Influenza vaccination prevents postviral infection thrombus and hemorrhage. In addition, influenza infection may contribute to carotid atherosclerotic plaque inflammation and the eventual development of acute vascular events (30). Furthermore, lowering the risk of influenza infection prevents relevant consequences such as elevated sympathetic tone, hypoxemia, and endothelial dysfunction (31). Second, in a study on apoE knockout mice, influenza vaccination promoted the formation of smaller and more stable atherosclerotic plaques through an immunoresponse (32). Moreover, decreasing levels of interferon gamma, interleukin 2, and tumor necrosis factor alpha, as well as the activation of the bradykinin 2 receptor signaling pathway, constitute potential mechanisms underlying the stabilization of atherosclerotic plaques by influenza vaccination (32, 33).

As mentioned, the association between vaccination and a lower risk of stroke observed in the present study appeared to be dose-dependent and did not differ depending on whether multiple vaccinations were administered consecutively or were interrupted. A higher number of vaccinations was significantly associated with a reduction in all types of stroke, a result in line with that of another study (34). A systematic review and meta-analysis indicated that the protective effects of the influenza vaccine against different types of viruses may be less notable following repeated vaccinations (35). However, annual vaccination is still recommended for the prevention and control of influenza infections (36). The fact that vaccine effectiveness in the United States during the 2017–2018 influenza season was only 38% (37) suggests that receiving vaccination only once may not be sufficient to prevent contracting the virus. With more than one vaccination, the risk of influenza infection may also decrease, as may the risk of further cardiovascular complications, including stroke.

We further investigated the effect of the CHA2DS2-VASc score in women with COPD. Higher CHA2DS2-VASc scores were associated with a higher risk of ischemic stroke in patients with COPD, even those without AF (19). Notably, although the sensitivity analysis yielded significant results for both ischemic and hemorrhagic stroke, vaccination had a stronger risk reduction effect on ischemic stroke in the patients with CHA2DS2-VASc scores of ≥2. Because most hemorrhagic strokes are caused by ruptured cerebral vessels resulting from uncontrolled hypertension and abnormal cerebrovascular
structure, the protective effect of influenza vaccination with plaque stabilization (32, 33) may be diminished in patients with these conditions. However, among female COPD patients with hypertension, the potentially risk reduction of hemorrhagic stroke was observed in the present study. Prospective studies are warranted to confirm these suppositions.

In addition, a significantly lower risk of stroke was observed in the patients with more inpatient visits because of the acute deterioration of their condition after they received four vaccinations, which is a greater number of vaccinations than that required for a protective effect against stroke in the patients with fewer inpatient visits. Thus, acute exacerbation in patients with COPD must be prevented to reduce complications.

In Taiwan, annual influenza vaccination constitutes a preventive strategy against an influenza epidemic. Previous nationwide studies conducted in Taiwan have indicated that influenza vaccination has benefits on cardiovascular and neurological outcomes (10, 14, 38). Overall, the present findings serve as a reference for policy-making with regard to annual influenza vaccination, especially in individuals with high-risk comorbidities.

Limitations
This study has several limitations. First, its retrospective nature limits the generalizability of the findings; prospective randomized controlled trials are required to confirm the present results. Second, the NHIRD does not contain definite information on the severity classification of COPD as indicated by physical activity, smoking status, alcohol intake, body mass index, spirometry test results, and other laboratory data. We performed propensity matching to minimize the impact of this limitation (22). Third, healthy user bias may have been present (39). Therefore, we adjusted for sociodemographic characteristics, such as urbanization and monthly income, as potential confounders. In addition, because influenza vaccination in Taiwan was provided free of charge to the members of our cohort, vaccination refusal caused by the inability to pay for the procedure seems unlikely; as mentioned, the influenza vaccine coverage rate among older adults in Taiwan has reached 49% in recent years (40). Fourth, the data of the present study were collected until the end of 2011, and future studies enrolled more recent data to validate the results of the present study. Moreover, although we controlled for and minimized the bias by propensity score matching and sensitivity analysis, the bias from the residual unmeasured confounders and healthy user bias could still present. Fifth, the patients enrolled in the present study were based on the ICD-9 diagnosis. Although the positive predictive rate and accuracy had been validated before (16, 17), the potential bias from patient selection process remained exist, which could influence the result of the present study.

In conclusion, influenza vaccination was associated with a considerably lower risk of ischemic, hemorrhagic, and undefined stroke in women with COPD, and the association appeared to be dose-dependent. Among women with a CHA2DS2-VASc score of ≥2, the association between vaccination and hemorrhagic stroke risk was not as substantial as ischemic stroke. Further investigations are required to determine the potential mechanism of influenza vaccination against stroke in this patient population.

DATA AVAILABILITY STATEMENT
The data supporting the findings of this research were sourced from NHIRD in Taiwan. Owing to the legal restrictions imposed by the Government of Taiwan related to the Personal Information Protection Act, the database cannot be made publicly available.

ETHICS STATEMENT
The present study protocol was approved by the NHIRD research committee and the Taipei Medical University Joint Institutional Review Board (TMU-JIRB No. N201804043).

AUTHOR CONTRIBUTIONS
W-RH and J-CL are the guarantors of the content of the manuscript and including the data and analysis. C-CCChen conceived and designed the study and drafted the manuscript. Y-AF was responsible for data collection. Y-AF, C-HL, W-RH, C-CChiu, T-YY, M-HH, M-HL, H-TY, and Y-HW analyzed and interpreted the data. All authors reviewed the manuscript and approved its submission.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.811021/full#supplementary-material

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