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The Association between Influenza Vaccination and Stroke Risk in Patients with Hypertension: A Nationwide Population-Based Study

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Abstract: There is evidence of strong association between influenza infections and stroke; however, the influenza vaccination and its effect on strokes is currently unclear. In the present study, Taiwan's National Health Insurance Database was used in obtaining data for study subjects 55 years and older diagnosed with hypertension (n = 59,251; 25,266 vaccinated and 33,985 unvaccinated subjects) from 2001–2012. Propensity scores were calculated using a logistic regression model to determine the effects of vaccination by accounting for covariates that predict receiving the intervention (vaccine). A time-dependent Cox proportional hazard model was used to calculate the hazard ratios (HRs) for stroke in vaccinated and unvaccinated patients. Influenza vaccination was associated with a 42%, 40% and 44% stroke risk reduction in the entire cohort for all seasons, the influenza season and the non-influenza season, respectively (Adjust hazard ratio [aHR]: 0.58, 95% confidence interval [CI]: 0.56–0.61; aHR: 0.60, 95% CI: 0.56–0.63; aHR: 0.56, 95% CI: 0.52–0.60, for all seasons, the influenza season and the non-influenza season, respectively). The effect of risk reduction by vaccination also revealed a trend of dose dependency. Among subjects between 55 to 64 years old with four or more vaccinations during the study period, there is a 73% risk reduction for stroke during the non-influenza season (aHR: 0.27, 95% CI: 0.20–0.34). In conclusion, the influenza vaccination exerts dose-dependent and synergistic protective effects against stroke in individuals 55 years and older with hypertension.

Keywords: influenza vaccination; stroke; hypertension

1. Introduction

Among all cardiovascular diseases (CVD), stroke is the leading cause of death, with 6.7 million each year [1]. Stroke patients encounter high medical expense burdens and also a low quality of life as many of them face long-term disability. Strokes are more common in

elderly individuals and their occurrence will substantially increase as the elderly population is rapidly growing worldwide due to a lower birthrate, higher living standards and better medical care than in the past [2].

For healthcare facilities to cope with future challenges in stroke increases, preventive methods are a suitable solution and could be very efficient. In addition to well-known risk factors, such as diabetes, high blood pressure, sedentary lifestyle and arrhythmia, viral and bacterial infections could also be risk factors [3–6]. Various studies revealed that influenza infections could also increase the risks of acute myocardial infarction (MI) and cardiovascular death [7] as well as the incidence of hemorrhagic strokes [8–10].

It is plausible that by preventing infection, influenza vaccination can also prevent strokes, including ischemic and hemorrhagic strokes, along with cardiovascular diseases as a part of a category called major adverse cardiovascular events (MACEs). Prior studies have demonstrated a decreased risk of primary MACEs after influenza vaccination [11–13].

It is well documented that hypertension is one of the risk factors in stroke occurrence. The risk of stroke increases at blood pressure levels above 115/75 mm Hg and high blood pressure (BP) is the most important modifiable risk factor for stroke, associated with 54% of episodes of stroke worldwide. Hypertensive patients (with BP > 160/95 mm Hg) were shown to have an incidence of stroke five to more than 30 times higher as compared to normotensive persons (<140/90 mm Hg) depending on age and gender. The increased risk was also noted in so-called "borderline hypertensives". Data from subjects 55–84 years old and free from cerebrovascular disease at the time of data collection were used [14] and the probability of stroke was calculated. Initial observations from the Framingham study found casual SBP as a good predictor of stroke as various components of BP, including diastolic and mean arterial pressure, pulse pressure, as well as lability of pressure [15]. Analysis of data from the elderly with isolated systolic hypertension from SHEP (Systolic Hypertension in the Elderly Program) study demonstrated an 11% increase in stroke risk and a 16% increase in risk of all-cause mortality for each 10 mm Hg increase in pulse pressure [16].

Various medications for hypertension and its related effects or conditions have been around for decades; however, the association of various drugs, therapies, vaccinations and other means to reduce the risk of strokes are of particular importance. Moreover, there are several other conditions related to or influencing the risk of strokes, many of which have been shown to have an association with influenza vaccination. A population-based cohort study revealed that the influenza vaccination can also reduce stroke risk in individuals with atrial fibrillation (AF) [17,18]. Antithrombotic therapy is one of the main risk factors for strokes in individuals with AF. A major safety concern regarding the use of antithrombotic agents is the increased risk of bleeding, paagentrticularly major bleeding, which includes events that necessitate hospitalization, transfusion and surgery, as well as situations that involve particularly sensitive anatomical locations [19,20].

Certain risk factors for stroke in individuals with AF are shared by individuals suffering from hypertension which include the following: old age, a high alcohol intake, low cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels, chronic kidney disease and selective serotonin reuptake inhibitor use. Comorbidities (e.g., diabetes, dyslipidemia, AF), anti-hypertension medication (e.g., antihypertensives, diuretics, beta blockers, calcium channel blockers, renin-angiotensin antagonists), co-medications (e.g., statins, metformin, aspirin) and residence (e.g., urban, suburban, rural) are all factors which can influence the risk of stroke in individuals with hypertension. To our knowledge, no study has been carried out on a population-based database previously. Thus, the focus of this article is to investigate the benefits of the influenza vaccination and its association with a reduction in the risk of strokes in hypertension.

2. Methods

In this cohort study, deidentified secondary data released to the public for research purposes were obtained from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD was established in 1995 and provides up to date comprehensive

coverage to 98% of Taiwan's population (>23 million people) [21]. All of the NHIRD data which can be used to identify patients or care providers, including medical institutions and physicians, are encrypted before sending it to the National Health Research Institutes for database construction; records are further scrambled before being released to researchers. Thus, no approval from the institute's review board was necessary as there were no private data of any individual used anywhere in this study. Researchers or anyone using the NHIRD and its data subsets must sign a written agreement declaring that they are not obtaining or using any information that could potentially violate the privacy of patients or care providers [22,23].

2.1. Study Population and Data Collection

This nationwide population-based case–control study used data from patients diagnosed with hypertension from 2001 to 2012 in Taiwan with all diagnoses corresponding to the codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The positive predictive rate of hypertension diagnosis in NHIRD had been validated before [24]. We obtained the data from Taiwan's Longitudinal Health Insurance Database (n = 1,000,000) and selected all patients diagnosed with hypertension (n = 178,315) from January 2001 to December 2012. Those excluded from the initial selection were individuals without a subsequent outpatient or inpatient diagnosis of hypertension or subsequent prescription of any antihypertensives (n = 35,772), individuals younger than 55 years old (n = 72,240), individuals with diagnosis related to stroke before the index date (n = 6374) and individuals already vaccinated within the 6 months prior to index date (n = 4678) (Figure 1).

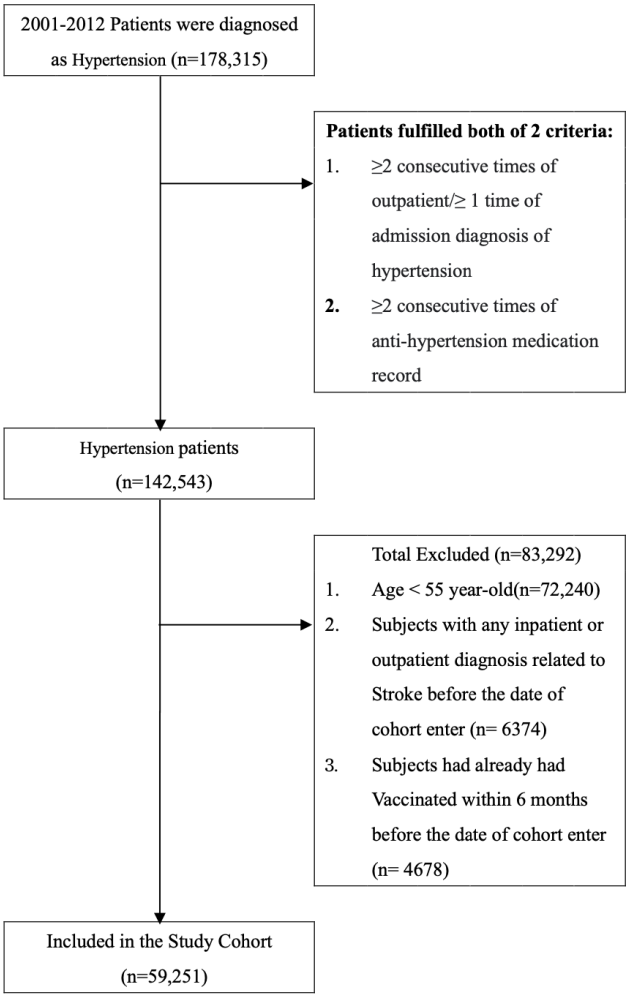

Figure 1. Data selection process.

According to the Taiwan Center for Disease Control, the influenza season is defined as the period between October and March. The influenza vaccine we studied in the present study is a monovalent, unadjuvanted, inactivated, split-virus vaccine. Influenza vaccination is free of charge in Taiwan since 1998 and high-risk individuals (those ≥50 years old, type 2 diabetes, chronic liver infection or cirrhosis, cardiovascular diseases or chronic pulmonary diseases) are encouraged to get the vaccine. Starting in 2001, all adults ≥ 65 years old can obtain the influenza vaccine free of charge. The subjects' vaccination statuses were identified using ICD-9-CM V048 or based on the type of vaccines administered (confirmed via drug codes). The total remaining cohort sample of 59,251 subjects (33,985 unvaccinated and 25,266 vaccinated) with a diagnosis of hypertension over the 12-year study period and their demographics are found in Table 1.

Table 1. Characteristics of the Sample Population.

	Whole Cohort (*n* = 59,521)		**Unvaccinated (*n* = 33,985)**		**Vaccinated (*n* = 25,266)**		***p***
	n	**%**	***n***	**%**	***n***	**%**	
Age, years (Mean ± SD)	66.24 (8.24)		64.08 (8.19)		69.14 (7.37)		<0.001
55–64	30,531	51.53	22,205	65.34	8326	32.95	
65–74	19,122	32.27	7661	22.54	11,461	45.36	<0.001
≥75	9598	16.20	4119	12.12	5479	21.69	
Gender							
Female	30,106	50.81	16,819	49.49	13,287	52.59	<0.001
Male	29,145	49.19	17,166	50.51	11,979	47.41	
CCI							
0	24,501	41.35	14,208	41.81	10,293	40.74	
1	15,333	25.88	8699	25.60	6634	26.26	0.003
2	9613	16.22	5394	15.87	4219	16.70	
≥3	9804	16.55	5684	16.73	4120	16.31	
Comorbidities							
Diabetes	13,422	22.65	7725	22.73	5697	22.55	0.600
Dyslipidemia	15,062	25.42	9087	26.74	5975	23.65	<0.001
Atrial fibrillation	3726	6.29	1636	4.81	2090	8.27	<0.001
Anti-hypertension medications							
Antihypertenives	12,255	20.68	5343	15.72	6912	27.36	<0.001
Diuretics	33,998	57.38	17,076	50.25	16,922	66.98	<0.001
Beta blocking agents	31,978	53.97	16,696	49.13	15,282	60.48	<0.001
Calcium channel blockers	44,966	75.89	24,277	71.43	20,689	81.88	<0.001
RAA	40,146	67.76	21,659	63.73	18,487	73.17	<0.001
Co-medications							
Statin drugs							
<28 days	38,564	65.09	22,849	67.23	15,715	62.20	
28–365 days	10,204	17.22	5829	17.15	4375	17.32	<0.001
>365 days	10,483	17.69	5307	15.62	5176	20.49	
Metformin drug							
<28 days	45,017	75.98	26,178	77.03	18,839	74.56	
28–365 days	4335	7.32	2677	7.88	1658	6.56	<0.001
>365 days	9899	16.71	5130	15.09	4769	18.88	
Aspirin drug							
<28 days	34,022	57.42	21,900	64.44	12,122	47.98	
28–365 days	12,351	20.85	6419	18.89	5932	23.48	<0.001
>365 days	12,878	21.73	5666	16.67	7212	28.54	
Level of Urbanization							
Urban	41,015	69.22	25,268	74.35	15,747	62.32	
Suburban	12,129	20.47	6158	18.12	5971	23.63	<0.001
Rural	6107	10.31	2559	7.53	3548	14.04	
Monthly income (NT$)							
0	5709	9.64	2818	8.29	2891	11.44	
1–20,100	19,825	33.46	10,282	30.25	9543	37.77	<0.001
20,100–30,300	19,665	33.19	10,363	30.49	9302	36.82	
≥30,301	14,052	23.72	10,522	30.96	3530	13.97	

2.2. Potential Confounders

Each subject's history was followed to evaluate the risk of stroke or to determine protective factors. Demographic characteristics (age and sex), comorbidities (e.g., diabetes, dyslipidemia, atrial fibrillation (AF) and Charlson comorbidity index [CCI]), level

of urbanization, monthly income and the use of various drugs (e.g., statin, metformin, aspirin), anti-hypertension medication (e.g., antihypertensives, diuretics, beta blocking agents, calcium channel blockers, renin-angiotentin antagonists) were obtained for all patients. Patients with prescribed <28 cumulative daily doses (cDDDs) of drugs were defined as nonusers [23].

2.3. Statistical Analysis

Propensity scores (PSs) were calculated using a logistic regression model to determine the effects of vaccination by accounting for covariates that predict receiving the intervention (vaccine) in observational studies to reduce selection bias [25,26]. The endpoint was the incidence of stroke (ICD-9-CM 430-437) in the vaccinated or unvaccinated patients with a subsequent outpatient visit, emergency department visit or inpatient hospitalization for stroke within 12 months; the unvaccinated patients served as the reference arm. The protective effects of the vaccination are specific to the influenza season; therefore, evaluating patients in the non-influenza season can indicate the possible contribution of bias to estimates obtained during the influenza season. Thus, we analyzed the relationship between the seasonal effects of the vaccination and risk of stroke.

The cumulative incidence of stroke in the vaccinated and unvaccinated patients with hypertension was calculated using the Kaplan–Meier method. To examine the effects of the total number of vaccinations on the cumulative incidence of stroke, we categorized the patients into 4 groups according to their vaccination status: unvaccinated and 1, 2 or 3 and ≥4 total vaccinations. A time-dependent Cox proportional hazard model was used to calculate the hazard ratios (HRs) for hypertension in both vaccinated and unvaccinated patients [27]. A stratified analysis was conducted to evaluate the effects of vaccination according to age and sex (Table 2). All analyses were performed using SAS (Version 9.4, SAS, Cary, NC, USA); 2-tailed P b 0.05 was considered significant. In the sensitivity analyses, external adjustments clarify the effects of drugs and other covariates in epidemiological database studies [28]. Most of the statistically different variables between groups were adjusted in our analyses.

Table 2. Risk of All Strokes among the Unvaccinated and Vaccinated in the Study Cohort.

All Group (n = 59,521)	Unvaccinated (Total Follow-Up 177,838.0 Person Years)				Vaccinated (Total Follow-Up 201,118.5 Person Years)				Adjusted HR † (95% CI)
	No. of Patients with Stroke	Incidence Rate (per 10^5 Person Years) (95% CI)			No. of Patients with Stroke	Incidence Rate (per 10^5 Person Years) (95% CI)			
Whole cohort									
Influenza season	2579	1450.2	(1394.2,	1506.2)	2809	1396.7	(1345.0,	1448.3)	0.60 (0.56, 0.63) ***
Non-influenza season	1779	1000.3	(953.9,	1046.8)	1649	819.9	(780.3,	859.5)	0.56 (0.52, 0.60) ***
All seasons	4358	2450.5	(2377.8,	2523.3)	4458	2216.6	(2151.5,	2281.7)	0.58 (0.56, 0.61) ***
Age, 55–64 [a]									
Influenza season	1374	1127.7	(1068.1,	1187.4)	668	895.6	(827.7,	963.6)	0.53 (0.48, 0.58) ***
Non-influenza season	886	727.2	(679.3,	775.1)	298	399.5	(354.2,	444.9)	0.44 (0.38, 0.50) ***
All seasons	2260	1854.9	(1778.5,	1931.4)	966	1295.2	(1213.5,	1376.9)	0.49 (0.46, 0.53) ***
Age, ≥65 [b]									
Influenza season	1205	2151.8	(2030.3,	2273.3)	2141	1692.0	(1620.4,	1763.7)	0.61 (0.57, 0.66) ***
Non-influenza season	893	1594.6	(1490.0,	1699.2)	1351	1067.7	(1010.8,	1124.6)	0.58 (0.53, 0.63) ***
All seasons	2098	3746.4	(3586.1,	3906.7)	3492	2759.7	(2668.2,	2851.3)	0.60 (0.57, 0.63) ***
Female [c]									
Influenza season	1104	1195.8	(1125.3,	1266.4)	1321	1218.6	(1152.9,	1284.4)	0.63 (0.58, 0.68) ***
Non-influenza season	807	874.1	(813.8,	934.4)	797	735.2	(684.2,	786.3)	0.58 (0.52, 0.64) ***
All seasons	1911	2069.9	(1977.1,	2162.7)	2118	1953.9	(1870.7,	2037.1)	0.61 (0.57, 0.65) ***
Male [d]									
Influenza season	1475	1724.8	(1636.8,	1812.8)	1488	1604.9	(1523.3,	1686.4)	0.57 (0.53, 0.62) ***
Non-influenza season	972	1136.6	(1065.2,	1208.1)	852	918.9	(857.2,	980.6)	0.53 (0.48, 0.59) ***
All seasons	2447	2861.5	(2748.1,	2974.8)	2340	2523.8	(2421.5,	2626.0)	0.56 (0.52, 0.59) ***

***: $p < 0.001$. [a] Total follow-up 121,837.4 person years for unvaccinated and 74,584.2 for vaccinated. [b] Total follow-up 56,000.6 person years for unvaccinated and 126,534.3 for vaccinated. [c] Total follow-up 92,322.1 person years for unvaccinated and 108,399.9 for vaccinated. [d] Total follow-up 85,516.0 person years for unvaccinated and 92,718.6 for vaccinated. CI: confidence interval. HR: hazard ratio. † Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, dyslipidemia, AF, antihypertensives, diuretics, beta blocker agents, calcium channel blockers, RAA, statin, metformin, aspirin, level of urbanization, and monthly income in propensity score.

3. Results

3.1. Baseline Characteristics

The demographics for the study population (59,251 subjects), the cases (25,266 vaccinated subjects) and controls (33,985 unvaccinated subjects) are shown in Table 1. The mean age for entire cohort was 66.2 (standard deviation, SD 8.2) years for entire cohort, 69.1 (SD 7.4) years for the case group and 64.1 (SD 8.2) years for the control group. The prevalence of preexisting medical comorbidities, which include diabetes ($p = 0.600$) and dyslipidemia ($p < 0.001$) was higher in the unvaccinated patients than in the vaccinated subjects. Additionally, a higher number of vaccinated subjects in the study cohort were taking medication such as diuretics, beta blockers, calcium channel blockers and renin-angiotensin antagonists, as well as co-medications (statins, metformin and aspirin) as compared to the unvaccinated subjects. A lower number of vaccinated subjects had a monthly income of ≥NT$30,301 and resided in urban areas as compared to unvaccinated subjects (Table 1).

3.2. The Association between the Risk of Stroke and the Influenza Vaccination for Different Age and Sex

The total follow-up period was 177,838.0 and 201,118.5 person years for the unvaccinated and vaccinated patients, respectively, and the risk of stroke in both groups of subjects in this study is shown in Table 2. Propensity scores were calculated after adjusting for age, sex, Charlson comorbidity index, diabetes, dyslipidemia, atrial fibrillation, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, renin-angiotensin antagonists, statins, metformin, aspirin, residential area and monthly income. The adjusted HRs (aHRs) and 95% confidence intervals (CIs) of stroke in vaccinated subjects were significantly lower during all seasons when compared to those in the unvaccinated subjects (aHRs [95% CI] of all seasons: 0.58 [0.56, 0.61]). During non-influenza season, the risk reduction was potentially more profound than during the influenza season (aHRs [95% CI] = 0.60 [0.56, 0.63] and 0.56 [0.52, 0.60] during influenza and non-influenza season, respectively).

The same results could be found in all strata of age. The stratified analysis revealed that aHRs decreased significantly in the vaccinated subjects during the influenza season, non-influenza season and all seasons, in the subjects aged between 55 to 64 and 65 years and older. Among patients with a relative younger age, the risk reduction was potentially lower compared with those aged more than 65 years (aHRs [95% CI] = 0.53 [0.48, 0.58], 0.44 [0.38, 0.50], 0.49 [0.46, 0.53] in patients age between 55 to 64 during the influenza and non-influenza season, and all seasons, respectively; aHRs [95% CI] = 0.61 [0.57, 0.66], 0.58 [0.53, 0.63], 0.60 [0.57, 0.63] in patients age ≥ 64 years during influenza and non-influenza season, and all seasons, respectively) (Table 2).

Both female and male patients had a significant lower risk of stroke occurrence after receiving vaccination. The risk reduction was potentially more significant among male patients (aHRs [95% CI] = 0.63 [0.58, 0.68], 0.58 [0.52, 0.64], 0.61 [0.57, 0.65] during influenza season, non-influenza season and all seasons among female patients; aHRs [95% CI] = 0.57 [0.53, 0.62], 0.53 [0.48, 0.59], 0.56 [0.52, 0.59] during influenza season, non-influenza season and all seasons among male patients) (Table 2).

3.3. Sensitivity Analysis of Stroke Risk Reduction after Different Times of Vaccination during Influenza Season, Non-Influenza Season and All Seasons

Influenza vaccination is not only significantly associated with stroke risk reduction in every stratum of the cohort, the effect is also dose dependent. Tables 3–5 contain the aHRs of vaccination in the risk reduction of stroke during the influenza, non-influenza and all seasons. There is a marked trend of lowering aHRs in subjects obtaining one to four vaccinations as compared to those unvaccinated, either in the whole cohort or in every stratum (Tables 3–5). Regardless of the underlying co-morbidities and medication history, the risk of stroke decreased after receiving the influenza vaccination more than two times and the trend was significant during the influenza season (Table 3). The neuroprotective

effect after multiple times of influenza vaccination was also observed during the non-influenza season and all seasons (Tables 4 and 5).

Table 3. Sensitivity Analysis of Adjusted HRs of Vaccination in the Risk Reduction of All Strokes in the Influenza Season.

	Unvaccinated	Vaccinated			*p* for Trend
		1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	
Main model †	1.00	0.85 (0.78, 0.92) ***	0.69 (0.64, 0.75) ***	0.41 (0.38, 0.45) ***	<0.001
Subgroup effects					
Age, years					
55–64	1.00	0.67 (0.59, 0.77) ***	0.53 (0.46, 0.60) ***	0.41 (0.35, 0.48) ***	<0.001
≥65	1.00	0.95 (0.86, 1.05)	0.77 (0.70, 0.84) ***	0.41 (0.37, 0.45) ***	<0.001
Sex					
Female	1.00	0.86 (0.76, 0.97) *	0.73 (0.66, 0.82) ***	0.45 (0.41, 0.51) ***	<0.001
Male	1.00	0.84 (0.76, 0.94) **	0.66 (0.60, 0.73) ***	0.38 (0.34, 0.42) ***	<0.001
Diabetes					
No	1.00	0.86 (0.79, 0.94) **	0.72 (0.66, 0.78) ***	0.43 (0.39, 0.47) ***	<0.001
Yes	1.00	0.81 (0.69, 0.95) **	0.63 (0.54, 0.74) ***	0.37 (0.32, 0.44) ***	<0.001
Dyslipidemia					
No	1.00	0.87 (0.80, 0.95) **	0.70 (0.65, 0.76) ***	0.42 (0.38, 0.45) ***	<0.001
Yes	1.00	0.74 (0.62, 0.89) **	0.66 (0.56, 0.77) ***	0.40 (0.34, 0.48) ***	<0.001
AF					
No	1.00	0.85 (0.78, 0.93) ***	0.69 (0.64, 0.75) ***	0.41 (0.38, 0.44) ***	<0.001
Yes	1.00	0.79 (0.63, 1.00)	0.68 (0.54, 0.84) ***	0.44 (0.36, 0.54) ***	<0.001
Antihypertensive					
No (<28 days)	1.00	0.82 (0.74, 0.90) ***	0.66 (0.60, 0.72) ***	0.38 (0.34, 0.42) ***	<0.001
Yes (≥28 days)	1.00	0.98 (0.84, 1.14)	0.82 (0.71, 0.95) **	0.51 (0.45, 0.59) ***	<0.001
Diuretics					
No (<28 days)	1.00	0.89 (0.78, 1.02)	0.65 (0.56, 0.74) ***	0.35 (0.30, 0.41) ***	<0.001
Yes (≥28 days)	1.00	0.84 (0.76, 0.92) ***	0.72 (0.66, 0.79) ***	0.44 (0.40, 0.48) ***	<0.001
Beta blocking agents					
No (<28 days)	1.00	0.84 (0.74, 0.94) **	0.64 (0.56, 0.72) ***	0.37 (0.33, 0.43) ***	<0.001
Yes (≥28 days)	1.00	0.85 (0.77, 0.95) **	0.73 (0.67, 0.81) ***	0.44 (0.40, 0.48) ***	<0.001
Calcium channel blockers					
No (<28 days)	1.00	0.81 (0.67, 0.97) *	0.66 (0.55, 0.80) ***	0.36 (0.29, 0.44) ***	<0.001
Yes (≥28 days)	1.00	0.86 (0.79, 0.94) **	0.70 (0.65, 0.76) ***	0.43 (0.39, 0.46) ***	<0.001
RAA					
No (<28 days)	1.00	0.98 (0.84, 1.14)	0.72 (0.62, 0.84) ***	0.39 (0.33, 0.47) ***	<0.001
Yes (≥28 days)	1.00	0.81 (0.74, 0.89) ***	0.69 (0.63, 0.75) ***	0.42 (0.39, 0.46) ***	<0.001
Statin drugs					
<28 days	1.00	0.89 (0.80, 0.98) *	0.72 (0.66, 0.80) ***	0.42 (0.38, 0.46) ***	<0.001
28–365 days	1.00	0.76 (0.64, 0.90) **	0.63 (0.53, 0.75) ***	0.39 (0.32, 0.46) ***	<0.001
>365 days	1.00	0.82 (0.69, 0.99) *	0.67 (0.57, 0.79) ***	0.45 (0.38, 0.53) ***	<0.001
Metformin drug					
<28 days	1.00	0.85 (0.77, 0.93) ***	0.71 (0.65, 0.77) ***	0.41 (0.37, 0.45) ***	<0.001
28–365 days	1.00	0.88 (0.68, 1.16)	0.68 (0.52, 0.88) **	0.42 (0.32, 0.57) ***	<0.001
>365 days	1.00	0.85 (0.71, 1.01)	0.68 (0.57, 0.81) ***	0.45 (0.38, 0.53) ***	<0.001
Aspirin drug					
<28 days	1.00	0.85 (0.73, 0.98) *	0.76 (0.66, 0.88) ***	0.40 (0.34, 0.47) ***	<0.001
28–365 days	1.00	0.88 (0.77, 1.01)	0.64 (0.56, 0.73) ***	0.37 (0.32, 0.43) ***	<0.001
>365 days	1.00	0.84 (0.74, 0.96) **	0.70 (0.62, 0.79) ***	0.45 (0.41, 0.51) ***	<0.001

*: $p < 0.05$ **: $p < 0.01$ ***: $p < 0.001$ HR: hazard ratio. † Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, dyslipidemia, AF, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, RAA, statin, metformin, aspirin, level of urbanization and monthly income in propensity score.

Table 4. Sensitivity Analysis of Adjusted HRs of Vaccination in the Risk Reduction of All Strokes in the Non-Influenza Season.

	Unvaccinated	Vaccinated			*p* for Trend
		1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	
Main model †	1.00	0.83 (0.75, 0.91) ***	0.63 (0.57, 0.69) ***	0.35 (0.32, 0.39) ***	<0.001
Subgroup effects					
Age, years					
55–64	1.00	0.58 (0.48, 0.70) ***	0.48 (0.39, 0.58) ***	0.27 (0.20, 0.34) ***	<0.001
≥65	1.00	0.94 (0.83, 1.05)	0.67 (0.60, 0.75) ***	0.35 (0.31, 0.39) ***	<0.001
Sex					
Female	1.00	0.87 (0.76, 1.00)	0.65 (0.57, 0.75) ***	0.36 (0.31, 0.42) ***	<0.001
Male	1.00	0.79 (0.69, 0.90) ***	0.60 (0.53, 0.69) ***	0.34 (0.29, 0.39) ***	<0.001
Diabetes					
No	1.00	0.80 (0.72, 0.90) ***	0.59 (0.53, 0.66) ***	0.34 (0.30, 0.38) ***	<0.001
Yes	1.00	0.89 (0.74, 1.08)	0.72 (0.60, 0.86) ***	0.39 (0.32, 0.47) ***	<0.001
Dyslipidemia					
No	1.00	0.82 (0.74, 0.92) ***	0.62 (0.56, 0.69) ***	0.36 (0.32, 0.40) ***	<0.001
Yes	1.00	0.83 (0.67, 1.03)	0.63 (0.51, 0.78) ***	0.33 (0.26, 0.41) ***	<0.001
AF					
No	1.00	0.82 (0.74, 0.91) ***	0.62 (0.56, 0.69) ***	0.35 (0.31, 0.39) ***	<0.001
Yes	1.00	0.85 (0.64, 1.13)	0.63 (0.48, 0.83) **	0.38 (0.29, 0.50) ***	<0.001
Antihypertensive					
No (<28 days)	1.00	0.88 (0.79, 0.99) *	0.65 (0.58, 0.72) ***	0.33 (0.29, 0.38) ***	<0.001
Yes (≥28 days)	1.00	0.69 (0.57, 0.85) ***	0.59 (0.49, 0.70) ***	0.38 (0.32, 0.45) ***	<0.001
Diuretics					
No (<28 days)	1.00	0.87 (0.74, 1.02)	0.63 (0.53, 0.74) ***	0.33 (0.27, 0.40) ***	<0.001
Yes (≥28 days)	1.00	0.81 (0.72, 0.91) ***	0.62 (0.55, 0.70) ***	0.35 (0.31, 0.40) ***	<0.001
Beta blocking agents					
No (<28 days)	1.00	0.78 (0.67, 0.91) **	0.65 (0.56, 0.75) ***	0.31 (0.26, 0.37) ***	<0.001
Yes (≥28 days)	1.00	0.85 (0.75, 0.96) *	0.61 (0.54, 0.69) ***	0.37 (0.33, 0.42) ***	<0.001
Calcium channel blockers					
No (<28 days)	1.00	0.87 (0.70, 1.08)	0.56 (0.44, 0.71) ***	0.33 (0.25, 0.43) ***	<0.001
Yes (≥28 days)	1.00	0.81 (0.73, 0.91) ***	0.64 (0.57, 0.71) ***	0.35 (0.32, 0.39) ***	<0.001
RAA					
No (<28 days)	1.00	0.70 (0.58, 0.85) ***	0.52 (0.43, 0.63) ***	0.25 (0.20, 0.32) ***	<0.001
Yes (≥28 days)	1.00	0.88 (0.79, 0.99) *	0.67 (0.60, 0.75) ***	0.39 (0.34, 0.43) ***	<0.001
Statin drugs					
<28 days	1.00	0.83 (0.73, 0.93) **	0.64(0.57, 0.72) ***	0.33 (0.29, 0.37) ***	<0.001
28–365 days	1.00	0.72 (0.58, 0.89) **	0.55(0.44, 0.68) ***	0.37 (0.30, 0.46) ***	<0.001
>365 days	1.00	0.95 (0.73, 1.24)	0.66(0.51, 0.86) **	0.44 (0.35, 0.57) ***	<0.001
Metformin drug					
<28 days	1.00	0.83 (0.74, 0.93) **	0.62 (0.55, 0.69) ***	0.34 (0.30, 0.38) ***	<0.001
28–365 days	1.00	0.72 (0.53, 0.99) *	0.51 (0.37, 0.70) ***	0.31 (0.22, 0.44) ***	<0.001
>365 days	1.00	0.88 (0.70, 1.10)	0.72 (0.58, 0.90) **	0.42 (0.34, 0.53) ***	<0.001
Aspirin drug					
<28 days	1.00	0.87 (0.74, 1.02)	0.59 (0.49, 0.70) ***	0.27 (0.22, 0.34) ***	<0.001
28–365 days	1.00	0.76 (0.64, 0.89) ***	0.54 (0.46, 0.64) ***	0.36 (0.30, 0.42) ***	<0.001
>365 days	1.00	0.90 (0.76, 1.08)	0.78 (0.66, 0.92) **	0.41 (0.35, 0.49) ***	<0.001

*: $p < 0.05$ **: $p < 0.01$ ***: $p < 0.001$ HR: hazard ratio. † Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, dyslipidemia, AF, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, RAA, statin, metformin, aspirin, level of urbanization and monthly income in propensity score.

Table 5. Sensitivity Analysis of Adjusted HRs of Vaccination in the Risk Reduction of All Strokes in All Seasons.

	Unvaccinated	Vaccinated			*p* for Trend
		1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	
Main model †	1.00	0.84 (0.79, 0.89) ***	0.67 (0.63, 0.71) ***	0.39 (0.37, 0.41) ***	<0.001
Subgroup effects					
Age, years					
55–64	1.00	0.64 (0.57, 0.71) ***	0.51 (0.45, 0.57) ***	0.36 (0.31, 0.41) ***	<0.001
≥65	1.00	0.94 (0.87, 1.02)	0.72 (0.67, 0.78) ***	0.39 (0.36, 0.41) ***	<0.001
Sex					
Female	1.00	0.87 (0.79, 0.95) **	0.70 (0.64, 0.76) ***	0.42 (0.38, 0.45) ***	<0.001
Male	1.00	0.82 (0.76, 0.89) ***	0.64 (0.59, 0.69) ***	0.36 (0.33, 0.40) ***	<0.001
Diabetes					
No	1.00	0.84 (0.78, 0.90) ***	0.67 (0.62, 0.71) ***	0.39 (0.37, 0.42) ***	<0.001
Yes	1.00	0.84 (0.75, 0.95) **	0.67 (0.59, 0.75) ***	0.38 (0.33, 0.43) ***	<0.001
Dyslipidemia					
No	1.00	0.85 (0.80, 0.91) ***	0.67 (0.63, 0.72) ***	0.39 (0.37, 0.42) ***	<0.001
Yes	1.00	0.78 (0.68, 0.89) ***	0.65 (0.57, 0.74) ***	0.37 (0.33, 0.43) ***	<0.001
AF					
No	1.00	0.84 (0.79, 0.90) ***	0.67 (0.63, 0.71) ***	0.38 (0.36, 0.41) ***	<0.001
Yes	1.00	0.82 (0.68, 0.98) *	0.66 (0.55, 0.78) ***	0.42 (0.35, 0.49) ***	<0.001
Antihypertensive					
No (<28 days)	1.00	0.84 (0.78, 0.90) ***	0.65 (0.61, 0.70) ***	0.36 (0.34, 0.39) ***	<0.001
Yes (≥28 days)	1.00	0.86 (0.76, 0.97) *	0.72 (0.65, 0.81) ***	0.46 (0.41, 0.51) ***	<0.001
Diuretics					
No (<28 days)	1.00	0.88 (0.80, 0.98) *	0.64 (0.57, 0.71) ***	0.34 (0.31, 0.39) ***	<0.001
Yes (≥28 days)	1.00	0.83 (0.76, 0.89) ***	0.68 (0.64, 0.73) ***	0.40 (0.38, 0.43) ***	<0.001
Beta blocking agents					
No (<28 days)	1.00	0.81 (0.74, 0.90) ***	0.64 (0.58, 0.71) ***	0.35 (0.32, 0.39) ***	<0.001
Yes (≥28 days)	1.00	0.85 (0.79, 0.92) ***	0.68 (0.63, 0.74) ***	0.41 (0.38, 0.44) ***	<0.001
Calcium channel blockers					
No (<28 days)	1.00	0.83 (0.73, 0.96) *	0.62 (0.54, 0.72) ***	0.34 (0.29, 0.41) ***	<0.001
Yes (≥28 days)	1.00	0.84 (0.79, 0.90) ***	0.68 (0.63, 0.72) ***	0.40 (0.37, 0.42) ***	<0.001
RAA					
No (<28 days)	1.00	0.85 (0.76, 0.96) **	0.63 (0.56, 0.71) ***	0.33 (0.29, 0.38) ***	<0.001
Yes (≥28 days)	1.00	0.84 (0.78, 0.90) ***	0.68 (0.64, 0.73) ***	0.41 (0.38, 0.44) ***	<0.001
Statin drugs					
<28 days	1.00	0.86 (0.80, 0.93) ***	0.69 (0.64, 0.74) ***	0.38 (0.35, 0.41) ***	<0.001
28–365 days	1.00	0.74 (0.65, 0.85) ***	0.60 (0.52, 0.68) ***	0.38 (0.33, 0.44) ***	<0.001
>365 days	1.00	0.86 (0.74, 1.00) *	0.67 (0.58, 0.77) ***	0.45 (0.39, 0.51) ***	<0.001
Metformin drug					
<28 days	1.00	0.84 (0.78, 0.90) ***	0.67 (0.63, 0.72) ***	0.38 (0.35, 0.41) ***	<0.001
28–365 days	1.00	0.81 (0.66, 0.99) *	0.60 (0.49, 0.73) ***	0.37 (0.30, 0.46) ***	<0.001
>365 days	1.00	0.86 (0.75, 0.99) *	0.70 (0.61, 0.80) ***	0.44 (0.39, 0.51) ***	<0.001
Aspirin drug					
<28 days	1.00	0.86 (0.77, 0.96) **	0.69 (0.61, 0.77) ***	0.35 (0.31, 0.40) ***	<0.001
28–365 days	1.00	0.83 (0.74, 0.92) ***	0.60 (0.54, 0.66) ***	0.36 (0.33, 0.41) ***	<0.001
>365 days	1.00	0.86 (0.78, 0.96) **	0.73 (0.66, 0.80) ***	0.44 (0.40, 0.48) ***	<0.001

*: $p < 0.05$ **: $p < 0.01$ ***: $p < 0.001$ HR: hazard ratio. † Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, dyslipidemia, AF, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, RAA, statin, metformin, aspirin, level of urbanization and monthly income in propensity score.

4. Discussion

Previous studies revealed that influenza infections are associated with incidents of stroke [17,29]. The infections and associated inflammation were determined to lead to the progression of atherosclerosis, plaque rupture and formation of thrombosis through various mechanisms, thereby increasing the incidence of stroke [30,31]. Additionally, high

metabolic demands due to changes in sympathetic activity and hyperdynamic cardiovascular response increase the risk of strokes. The findings of this study support the protective effect of the influenza vaccination on the incidence of stroke in older individuals with hypertension. A 42% risk reduction was observed for the entire cohort throughout all seasons with stronger effects seen in the 55–64-year-old group and in male subjects (Tables 2–5). The protective effect of the influenza vaccination could stem mainly from the prevention of infection and inflammation-induced sequelae.

Various neurological complications besides stroke may occur in patients with pandemic H1N1 influenza A infection [6,7,32]. There have been reports of increased risk for hospital admissions and a high rate of mortality in elderly men during the influenza season [33–35]. As high mortality during the influenza season could mask the incidence of strokes, individuals with various diseases and health conditions (e.g., AF, hypertension) may die before encountering a stroke [17]. However, during the non-influenza season, the mortality rate usually decreases and the actual effect of the influenza vaccination can be observed. This likely explains why the influenza vaccination exerted marked protective effects against stroke during the non-influenza season (Tables 2–5). A similar phenomenon was reported in a previous study [23].

Men and women may have competing risk factors during the influenza and non-influenza seasons [17,23]. Epidemiological evidence from influenza outbreaks and pandemics reveals that morbidity and mortality are often higher for women than men. Females generate higher proinflammatory cytokine and chemokine responses and experience greater morbidity and mortality than males. Males and females also respond differently to influenza vaccines, with women initiating higher humoral immune responses but experiencing more adverse reactions to seasonal influenza vaccines than men. Sex-hormones, including estradiol and testosterone, as well as genetic differences between the sexes may play roles in modulating sex differences in immune responses to influenza virus infection and vaccination [36]. The present study demonstrated the consistent neuroprotective effect of influenza among male and female patients.

This study found that more unvaccinated subjects live in the urban areas and have a higher income. Urban habitats with a higher income are supposed to have better living standards, educational background, healthcare support and consequently a reduced risk of major complications (e.g., stroke) from chronic diseases such as hypertension. However, that was in contrast to the finding of the current study. Our results showed that individuals who receive the influenza vaccination, despite living in a rural area with lower income, have a reduced risk of stroke.

Nevertheless, stroke prevention in elderly individuals remains challenging and a growing health concern as the elderly population is rapidly increasing worldwide [3]. Our study indicates the importance of the influenza vaccination in elderly individuals, particularly males with hypertension in the 55–64-year-old group, and the overall relatively high risk of stroke. Hypertension is known to increase the risk of hemorrhagic stroke [37], whereas diabetes increases the risk of ischemic stroke but not hemorrhagic stroke [38]. Additionally, the protective effects of the influenza vaccination are likely to be related to the prevention of acute infection, which can elicit both systemic and local vascular inflammatory responses [23].

The influenza vaccination exerted protective effects in patients with AF who were receiving statins (Tables 4 and 5). Furthermore, studies show that prevention of vascular remodeling by metformin can reduce hemorrhage and improve functional outcomes, emphasizing the importance of vascular protection in cases of hemorrhage stroke [39]. Our findings suggest that the influenza vaccination exerts dose–response and synergistic protective effects against strokes in patients with AF (i.e., male sex, age 55–64 years, CCI $\geq$ 3, hypertension, use of statin or warfarin) and reduces the incidence of strokes. The current rate of the influenza vaccination in Taiwan is approximately 35% [40,41]. The results of our study are comparable with those obtained in the general population in Taiwan.

5. Limitations

Studies suggest that lifestyle factors, race, ethnicity, family history, genetic disorders and physical activity are all associated with the risk of strokes. However, study methodology may interfere with the exact relationship between these factors and stroke risk. In this study, we used PSs to match age, sex, CCI for diabetes, dyslipidemia, atrial fibrillation, antihypertensives, diuretics, beta blockers, calcium channel blockers renin-angiotensin antagonists, residential areas and monthly income. Residential areas and monthly income are invalidated alternatives to lifestyle factors. Stroke and the various comorbidities were diagnosed entirely based on the ICD-9-CM codes. The NHI Administration randomly reviews charts and patient interviews to validate diagnoses. A positive predictive value (PPV) of 88.4% (95% CI: 86.8%, 89.8%) and sensitivity of 97.3% (95% CI: 96.4%, 98.1%) for diagnoses were reported by a study in Taiwan and the PPVs of stroke diagnoses, hypertension or diseases included in the NHI claims data are high [42,43]. Hospitals with conspicuous diagnoses and practices are audited and heavily penalized for documented malpractice or discrepancies. Another limitation is that data on several unmeasured confounders, including body mass index, smoking, alcohol intake and other over-the-counter drug use (associated with dementia), are unavailable in the NHIRD. Moreover, all subjects in this cohort are Asian, therefore ethnic susceptibility is unclear. As this study was not a prospective randomized blinded study, a cause–effect relationship was not established. These findings imply significant protective effects of the vaccination; however, additional randomized studies are necessary to further validate these findings.

6. Conclusions

The results of this cohort revealed that the influenza vaccination exerts dose–response and synergistic protective effects against strokes in patients with hypertension at a higher risk of stroke (e.g., males, age 55–64 years, CCI ≥ 3 and atrial fibrillation).

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Institutional Review Board 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).

Informed Consent Statement: The NHIRD research committee and the Joint Institutional Review Board of Taipei Medical University approved our study protocol (TMU-JIRB No. N201804043) and waived the need for informed consents from participants. This waiver does not affect the rights and welfare of the participants.

Data Availability Statement: The data supporting the findings of the present 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.

Conflicts of Interest: The authors declare no conflict of interest.

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