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Influenza Vaccination Reduces Dementia Risk in Chronic Kidney Disease Patients: A Population-Based Cohort Study

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Background: Taiwan has the highest prevalence of chronic kidney disease (CKD) worldwide. CKD, a manifestation of vascular diseases, is associated with a high risk of dementia. Here, we estimated the association between influenza vaccination and dementia risk in patients with CKD.

Materials and methods: Data from the National Health Insurance Research Database of Taiwan were used in this study. The study cohort included all patients diagnosed with CKD (according to International Classification of Disease, Ninth Revision, Clinical Modification codes) at healthcare facilities in Taiwan (n = 32,844) from January 1, 2000, to December 31, 2007. Each patient was followed up to assess dementia risk or protective factors: demographic characteristics of age and sex; comorbidities of diabetes, hypertension, dyslipidemia, cerebrovascular diseases, parkinsonism, epilepsy, substance and alcohol use disorders, mood disorder, anxiety disorder, psychotic disorder, and sleep disorder; urbanization level; monthly income; and statin, metformin, aspirin, and angiotensin-converting enzyme inhibitor (ACEI) use. A propensity score was derived using a logistic regression model for estimating the effect 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) of dementia among vaccinated and unvaccinated CKD patients.

Results: The study population comprised 11,943 eligible patients with CKD; 5745 (48%) received influenza vaccination and the remaining 6198 (52%) did not. The adjusted HRs (aHRs) of dementia decreased in vaccinated patients compared with those in unvaccinated patients (influenza season, noninfluenza season, and all seasons: aHRs = 0.68, 0.58, and 0.64; P < 0.0001, P < 0.0001, and P < 0.0001, respectively). In the sensitivity analysis, adjustments were made to estimate the association of age and sex; diabetes, dyslipidemia, hypertension, cerebrovascular diseases, anxiety disorder; and statin, metformin, ACEI, and aspirin use with the incidence of dementia in various models. A stronger protective effect against dementia risk was demonstrated during the noninfluenza season.

Conclusions: Regardless of comorbidities or drug use, influenza vaccination was an independent protective factor and dose-dependently reduced the risk of dementia in CKD patients.Influenza vaccination exerts dose-response and synergistic protective effects against dementia in CKD patients with dementia risk factors by reducing the incidence of dementia.

TABLE 1. Characteristics of the Study Population

	Whole Cohort (n = 11,943)		Unvaccinated (n = 6198)		Vaccinated (n = 5745)		
	n	%	n	%	n	%	P*
Age, y (mean ± SD)	72.95 (7.98)	73.08 (8.69)	72.81 (7.14)	0.058			
60–69	4729	39.60	2542	41.01	2187	38.07	<0.001
70–79	4826	40.41	2226	35.91	2600	45.26	
≥80	2388	19.99	1430	23.07	958	16.68	
Sex							
Female	5162	43.22	2768	44.66	2394	41.67	0.001
Male	6781	56.78	3430	55.34	3351	58.33	
Comorbidities							
Diabetes	6057	50.72	3438	55.47	2619	45.59	<0.001
Cerebrovascular diseases	3912	32.76	2202	35.53	1710	29.77	<0.001
Hypertension	9753	81.66	5183	83.62	4570	79.55	<0.001
Dyslipidemia	6077	50.88	3390	54.70	2687	46.77	<0.001
Parkinsonism	1080	9.04	436	7.03	644	11.21	<0.001
Epilepsy	510	4.27	258	4.16	252	4.39	0.546
Substance and alcohol use disorders	492	4.12	278	4.49	214	3.72	0.037
Mood disorder	1813	15.18	797	12.86	1016	17.68	<0.001
Anxiety disorder	3715	31.11	2025	32.67	1690	29.42	<0.001
Psychotic disorder	334	2.80	152	2.45	182	3.17	0.018
Sleep disorder	4653	38.96	2616	42.21	2037	35.46	<0.001
Statin							
<28 days	7475	62.59	4090	65.99	3385	58.92	<0.001
28–365 days	2399	20.09	1252	20.20	1147	19.97	
>365 days	2069	17.32	856	13.81	1213	21.11	
Metformin							
<28 days	9447	79.10	5032	81.19	4415	76.85	<0.001
28–365 days	1233	10.32	676	10.91	557	9.70	
>365 days	1263	10.58	490	7.91	773	13.46	
ACEI							
<28 days	3646	30.53	2323	37.48	1323	23.03	<0.001
28–365 days	3475	29.10	1975	31.87	1500	26.11	
>365 days	4822	40.38	1900	30.66	2922	50.86	
Aspirin							
<28 days	6057	50.72	3698	59.66	2359	41.06	<0.001
28–365 days	2984	24.99	1461	23.57	1523	26.51	
>365 days	2902	24.30	1039	16.76	1863	32.43	
Level of urbanization							
Urban	7894	66.10	4320	69.70	3574	62.21	<0.001
Suburban	2700	22.61	1301	20.99	1399	24.35	
Rural	1349	11.30	577	9.31	772	13.44	
Monthly income (NT$)							
0	1552	13.00	795	12.83	757	13.18	<0.001
1–21,000	3190	26.71	1556	25.10	1634	28.44	
21,000–33,300	4572	38.28	2242	36.17	2330	40.56	
≥33,301	2629	22.01	1605	25.90	1024	17.82	

*Comparison of unvaccinated with vaccinated patients. ACEI = angiotensin-converting enzyme inhibitor, SD = standard deviation.

TABLE 3. Sensitivity Analysis of Adjusted HRs of Vaccination in Risk Reduction of Dementia in Influenza Season

	Unvaccinated	Vaccinated 1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	P for Trend
Main model†	1.00	1.17 (0.96, 1.41)	0.91 (0.76, 1.08)	0.39 (0.32, 0.47)***	<0.001
Additional covariates‡					
Main model + statin	1.00	1.18 (0.98, 1.43)	0.92 (0.77, 1.10)	0.39 (0.33, 0.48)***	<0.001
Main model + metformin	1.00	1.16 (0.96, 1.41)	0.91 (0.76, 1.09)	0.39 (0.33, 0.47)***	<0.001
Main model + ACEI	1.00	1.20 (0.99, 1.45)	0.93 (0.78, 1.11)	0.40 (0.33, 0.48)***	<0.001
Main model + aspirin	1.00	1.17 (0.97, 1.42)	0.91 (0.76, 1.09)	0.39 (0.32, 0.47)***	<0.001
Subgroup effects Age, years					
60–69	1.00	1.30 (0.89, 1.88)	0.94 (0.66, 1.34)	0.53 (0.37, 0.74)***	<0.001
≥70	1.00	1.00 (0.81, 1.25)	0.79 (0.65, 0.97)*	0.29 (0.23, 0.36)***	<0.001
Sex					
Female	1.00	1.06 (0.81, 1.39)	0.85 (0.66, 1.10)	0.39 (0.30, 0.52)***	<0.001
Male	1.00	1.28 (0.98, 1.66)	0.96 (0.75, 1.22)	0.38 (0.29, 0.49)***	<0.001
Diabetes					
No	1.00	1.27 (0.97, 1.65)	0.89 (0.69, 1.15)	0.46 (0.36, 0.58)***	<0.001
Yes	1.00	1.04 (0.79, 1.37)	0.87 (0.68, 1.12)	0.30 (0.22, 0.41)***	<0.001
Dyslipidemia					
No	1.00	1.28 (0.99, 1.67)	1.02 (0.80, 1.29)	0.44 (0.34, 0.56)***	<0.001
Yes	1.00	1.00 (0.76, 1.32)	0.75 (0.58, 0.99)*	0.31 (0.23, 0.42)***	<0.001
Hypertension					
No	1.00	1.44 (0.92, 2.27)	0.99 (0.63, 1.55)	0.39 (0.25, 0.61)***	<0.001
Yes	1.00	1.09 (0.89, 1.35)	0.85 (0.70, 1.04)	0.37 (0.30, 0.46)***	<0.001
Cerebrovascular diseases					
No	1.00	1.06 (0.83, 1.36)	0.85 (0.68, 1.06)	0.38 (0.31, 0.48)***	<0.001
Yes	1.00	1.24 (0.92, 1.66)	0.92 (0.69, 1.23)	0.36 (0.26, 0.51)***	<0.001
Anxiety disorder					
No	1.00	1.29 (1.03, 1.62)*	1.01 (0.81,1.24)	0.39 (0.31, 0.49)***	<0.001
Yes	1.00	0.92 (0.65, 1.30)	0.69 (0.50, 0.95)*	0.38 (0.27, 0.54)***	<0.001
Statin					
<28 days	1.00	1.19 (0.94, 1.50)	0.96 (0.77, 1.19)	0.41 (0.32, 0.52)***	<0.001
28–365 days	1.00	1.04 (0.66, 1.63)	0.77 (0.52, 1.13)	0.27 (0.17, 0.43)***	<0.001
>365 days	1.00	1.31 (0.79, 2.16)	0.94 (0.58, 1.53)	0.50 (0.32, 0.79)**	<0.001
Metformin					
<28 days	1.00	1.19 (0.96, 1.47)	0.89 (0.72, 1.09)	0.41 (0.33, 0.51)***	<0.001
28–365 days	1.00	0.81 (0.44, 1.50)	0.87 (0.50, 1.50)	0.29 (0.14, 0.59)***	0.002
>365 days	1.00	1.42 (0.81, 2.50)	1.03 (0.64, 1.67)	0.37 (0.22, 0.62)***	<0.001
ACEI					
<28 days	1.00	1.43 (1.00, 2.04)	1.16 (0.82, 1.63)	0.42 (0.28, 0.62)***	<0.001
28–365 days	1.00	1.04 (0.72, 1.50)	0.94 (0.68, 1.30)	0.41 (0.29, 0.59)***	<0.001
>365 days	1.00	1.12 (0.84, 1.49)	0.78 (0.60, 1.03)	0.37 (0.28, 0.48)***	<0.001
Aspirin					
<28 days	1.00	1.07 (0.79, 1.44)	0.98 (0.74, 1.29)	0.48 (0.35, 0.65)***	<0.001
28–365 days	1.00	1.39 (0.98, 1.95)	0.97 (0.70, 1.34)	0.30 (0.21, 0.45)***	<0.001
>365 days	1.00	1.17 (0.82, 1.67)	0.83 (0.60, 1.15)	0.41 (0.30, 0.57)***	<0.001

TABLE 2. Risk of Dementia Among Unvaccinated and Vaccinated Patients in the Study Cohort

	Unvaccinated (Total Follow-Up of 17,234.8 Person-Years)			Vaccinated (Total Follow-Up of 35,899.1 Person-Years)			
Whole Cohort (n = 11,943)	No. of Patients With Dementia	Incidence Rate (per 10^5 Person-Years) (95% CI)		No. of Patients With Dementia	Incidence Rate (per 10^5 Person-Years) (95% CI)		Adjusted HR† (95% CI)
Whole cohort							
Influenza season	300	1740.7	(1543.7, 1937.6)	573	1596.1	(1465.4, 1726.8)	0.68 (0.59, 0.79)***
Noninfluenza season	241	1398.3	(1221.8, 1574.9)	357	994.5	(891.3, 1097.6)	0.58 (0.48, 0.68)***
All seasons	541	3139.0	(2874.5, 3403.5)	930	2590.6	(2424.1, 2757.1)	0.64 (0.57, 0.71)***
Age, 60–69*							
Influenza season	78	917.6	(713.9, 1121.2)	163	1002.5	(848.6, 1156.3)	0.76 (0.57, 1.00)*
Noninfluenza season	51	599.9	(435.3,764.6)	90	553.5	(439.1, 667.9)	0.72 (0.50, 1.02)
All seasons	129	1517.5	(1255.6,1779.4)	253	1556.0	(1364.2, 1747.7)	0.74 (0.60, 0.92)**
Age, ≥70‖							
Influenza season	222	2541.8	(2207.4, 2876.2)	410	2087.7	(1885.6, 2289.8)	0.58 (0.49, 0.68)***
Noninfluenza season	190	2175.4	(1866.1, 2484.7)	267	1359.5	(1196.5, 1522.6)	0.47 (0.39, 0.57)***
All seasons	412	4717.2	(4261.7, 5172.7)	677	3447.2	(3187.5, 3706.9)	0.53 (0.46, 0.60)***
Female‡							
Influenza season	156	2050.5	(1728.7, 2372.2)	260	1723.7	(1514.2, 1933.2)	0.68 (0.55, 0.84)***
Noninfluenza season	111	1459.0	(1187.6, 1730.4)	141	934.8	(780.5, 1089.1)	0.56 (0.43, 0.73)***
All season	267	3509.5	(3088.5, 3930.4)	401	2658.4	(2398.2, 2918.6)	0.63 (0.54, 0.74)***
Male§							
Influenza season	144	1495.8	(1251.5, 1740.1)	313	1503.7	(1337.1, 1670.3)	0.68 (0.56, 0.84)***
Noninfluenza season	130	1350.4	(1118.2, 1582.5)	216	1037.7	(899.3, 1176.1)	0.59 (0.47, 0.74)***
All seasons	274	2846.2	(2509.2, 3183.2)	529	2541.4	(2324.9, 2758.0)	0.64 (0.55, 0.74)***

CI = confidence interval, HR = hazard ratio.
*Total follow-up of 8500.8 person-years for unvaccinated patients and 16,260.1 person-years for vaccinated patients.
†Total follow-up of 8734.0 person-years for unvaccinated patients and 19,639.0 person-years for vaccinated patients.
‡Total follow-up of 7608.0 person-years for unvaccinated patients and 15,084.0 person-years for vaccinated patients.
§Total follow-up of 9626.9 person-years for unvaccinated patients and 20,815.1 person-years for vaccinated patients.
‖The main model was adjusted for age, sex, diabetes, hypertension, dyslipidemia, cerebrovascular diseases, parkinsonism, epilepsy, substance- and alcohol-use disorders, mood disorder, anxiety disorder, psychotic disorder, sleep disorder, level of urbanization, and monthly income in propensity score.

TABLE 4. Sensitivity Analysis of Adjusted HRs of Vaccination in Risk Reduction of Dementia in Noninfluenza Season

	Unvaccinated	Vaccinated 1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	P for Trend
Main model†	1.00	1.00 (0.80, 1.25)	0.66 (0.53, 0.82)***	0.36 (0.29, 0.45)***	<0.001
Additional covariates‡					
Main model + statin	1.00	1.01 (0.81, 1.27)	0.68 (0.54, 0.85)***	0.37 (0.30, 0.47)***	<0.001
Main model + metformin	1.00	0.99 (0.79, 1.24)	0.67 (0.54, 0.84)***	0.37 (0.30, 0.46)***	<0.001
Main model + ACEI	1.00	1.03 (0.83, 1.29)	0.68 (0.55, 0.86)***	0.38 (0.30, 0.48)***	<0.001
Main model + aspirin	1.00	1.00 (0.80, 1.25)	0.67 (0.53, 0.83)***	0.37 (0.29, 0.46)***	<0.001
Subgroup effects					
Age, y					
60–69	1.00	1.20 (0.75, 1.92)	0.75 (0.47, 1.21)	0.51 (0.33, 0.79)**	<0.001
≥70	1.00	0.84 (0.65, 1.08)	0.56 (0.43, 0.72)***	0.27 (0.21, 0.35)***	<0.001
Sex					
Female	1.00	0.81 (0.57, 1.15)	0.68 (0.49, 0.95)*	0.37 (0.26, 0.52)***	<0.001
Male	1.00	1.17 (0.88, 1.57)	0.66 (0.49, 0.88)**	0.36 (0.27, 0.48)***	<0.001
Diabetes					
No	1.00	1.12 (0.82, 1.53)	0.74 (0.54, 1.00)*	0.46 (0.35, 0.61)***	<0.001
Yes	1.00	0.87 (0.63, 1.21)	0.58 (0.42, 0.80)***	0.25 (0.17, 0.38)***	<0.001
Dyslipidemia					
No	1.00	1.16 (0.87, 1.54)	0.75 (0.57, 1.00)	0.39 (0.30, 0.52)***	<0.001
Yes	1.00	0.78 (0.54, 1.11)	0.53 (0.37, 0.76)***	0.31 (0.21, 0.45)***	<0.001
Hypertension					
No	1.00	1.60 (0.96, 2.68)	1.03 (0.62, 1.72)	0.65 (0.41, 1.04)	0.028
Yes	1.00	0.89 (0.69, 1.14)	0.58 (0.46, 0.75)***	0.30 (0.23, 0.39)***	<0.001
Cerebrovascular diseases					
No	1.00	1.02 (0.76, 1.37)	0.67 (0.50, 0.90)**	0.39 (0.30, 0.52)***	<0.001
Yes	1.00	0.89 (0.63, 1.26)	0.59 (0.42, 0.84)**	0.29 (0.19, 0.44)***	<0.001
Anxiety disorder					
No	1.00	1.01 (0.78, 1.32)	0.66 (0.51, 0.86)**	0.34 (0.26, 0.45)***	<0.001
Yes	1.00	0.95 (0.62, 1.45)	0.65 (0.43, 0.98)*	0.40 (0.26, 0.62)***	<0.001
Statin					
<28 days	1.00	0.99 (0.76, 1.28)	0.64 (0.49, 0.83)***	0.36 (0.27, 0.47)***	<0.001
28–365 days	1.00	0.95 (0.53, 1.70)	0.63 (0.37, 1.07)	0.44 (0.26, 0.74)**	0.001
>365 days	1.00	1.31 (0.64, 2.65)	1.05 (0.54, 2.03)	0.37 (0.18, 0.75)**	0.004
Metformin					
<28 days	1.00	1.00 (0.78, 1.28)	0.65 (0.51, 0.84)***	0.38 (0.30, 0.49)***	<0.001
28–365 days	1.00	0.93 (0.47, 1.82)	0.65 (0.33, 1.29)	0.45 (0.22, 0.92)*	0.020
>365 days	1.00	1.07 (0.48, 2.38)	0.84 (0.42, 1.66)	0.27 (0.12, 0.62)**	0.002
ACEI					
<28 days	1.00	0.88 (0.58, 1.35)	0.41 (0.24, 0.68)***	0.35 (0.22, 0.56)***	<0.001
28–365 days	1.00	1.00 (0.67, 1.47)	0.69 (0.47, 1.00)	0.38 (0.25, 0.57)***	<0.001
>365 days	1.00	1.21 (0.83, 1.75)	0.89 (0.63, 1.27)	0.41 (0.28, 0.58)***	<0.001
Aspirin					
<28 days	1.00	0.95 (0.67, 1.35)	0.62 (0.43, 0.89)**	0.34 (0.23, 0.51)***	<0.001
28–365 days	1.00	0.96 (0.65, 1.41)	0.53 (0.35, 0.79)**	0.32 (0.21, 0.48)***	<0.001
>365 days	1.00	1.22 (0.76, 1.93)	0.99 (0.66, 1.51)	0.50 (0.32, 0.75)***	<0.001

TABLE 5. Sensitivity Analysis of Adjusted HRs of Vaccination in Risk Reduction of Dementia in All Seasons

	Unvaccinated Adjusted HR (95% CI)	Vaccinated 1 Adjusted HR (95% CI)	2–3 Adjusted HR (95% CI)	≥4 Adjusted HR (95% CI)	P for Trend
Main model†	1.00	1.09 (0.94, 1.26)	0.80 (0.70, 0.92)**	0.38 (0.32, 0.43)***	<0.001
Additional covariates‡					
Main model + statin	1.00	1.11 (0.96, 1.28)	0.81 (0.71, 0.93)**	0.38 (0.33, 0.44)***	<0.001
Main model + metformin	1.00	1.09 (0.94, 1.26)	0.81 (0.70, 0.93)**	0.38 (0.33, 0.44)***	<0.001
Main model + ACEI	1.00	1.12 (0.97, 1.30)	0.82 (0.72, 0.94)**	0.39 (0.34, 0.45)***	<0.001
Main model + aspirin	1.00	1.10 (0.95, 1.27)	0.81 (0.70, 0.92)**	0.38 (0.33, 0.44)***	<0.001
Subgroup effects					
Age, y					
60–69	1.00	1.26 (0.94, 1.69)	0.87 (0.66, 1.15)	0.52 (0.40, 0.68)***	<0.001
≥70	1.00	0.93 (0.78, 1.09)	0.69 (0.59, 0.80)***	0.28 (0.23, 0.33)***	<0.001
Sex					
Female	1.00	0.96 (0.77, 1.19)	0.78 (0.64, 0.96)*	0.38 (0.31, 0.47)***	<0.001
Male	1.00	1.23 (1.01, 1.49)*	0.82 (0.68, 0.99)*	0.37 (0.30, 0.45)***	<0.001
Diabetes					
No	1.00	1.20 (0.98, 1.47)	0.83 (0.68, 1.00)	0.46 (0.38, 0.55)***	<0.001
Yes	1.00	0.97 (0.78, 1.19)	0.74 (0.61, 0.90)**	0.28 (0.22, 0.36)***	<0.001
Dyslipidemia					
No	1.00	1.23 (1.01, 1.49)*	0.90 (0.75, 1.07)	0.42 (0.35, 0.50)***	<0.001
Yes	1.00	0.91 (0.73, 1.13)	0.66 (0.54, 0.82)***	0.31 (0.25, 0.39)***	<0.001
Hypertension					
No	1.00	1.51 (1.08, 2.13)*	1.01 (0.72, 1.41)	0.50 (0.36, 0.68)***	<0.001
Yes	1.00	1.00 (0.85, 1.18)	0.74 (0.63, 0.86)***	0.34 (0.29, 0.40)***	<0.001
Cerebrovascular diseases					
No	1.00	1.04 (0.86, 1.26)	0.77 (0.65, 0.92)**	0.39 (0.32, 0.46)***	<0.001
Yes	1.00	1.07 (0.86, 1.34)	0.77 (0.62, 0.96)*	0.33 (0.25, 0.43)***	<0.001
Anxiety disorder					
No	1.00	1.16 (0.98, 1.38)	0.85 (0.72, 1.00)*	0.37 (0.31, 0.44)***	<0.001
Yes	1.00	0.93 (0.71, 1.22)	0.67 (0.52, 0.87)**	0.39 (0.30, 0.51)***	<0.001
Statin					
<28 days	1.00	1.09 (0.92, 1.30)	0.81 (0.68, 0.96)*	0.38 (0.32, 0.46)***	<0.001
28–365 days	1.00	1.00 (0.70, 1.43)	0.71 (0.52, 0.98)*	0.33 (0.23, 0.46)***	<0.001
>365 days	1.00	1.31 (0.87, 1.97)	0.98 (0.66, 1.44)	0.46 (0.31, 0.67)***	<0.001
Metformin					
<28 days	1.00	1.10 (0.94, 1.29)	0.78 (0.67, 0.92)**	0.40 (0.34, 0.47)***	<0.001
28–365 days	1.00	0.86 (0.55, 1.35)	0.77 (0.50, 1.18)	0.36 (0.22, 0.60)***	<0.001
>365 days	1.00	1.29 (0.82, 2.05)	0.96 (0.65, 1.42)	0.34 (0.22, 0.52)***	<0.001
ACEI					
<28 days	1.00	1.16 (0.88, 1.52)	0.79 (0.60, 1.05)	0.38 (0.28, 0.52)***	<0.001
28–365 days	1.00	1.02 (0.78, 1.33)	0.82 (0.64, 1.05)	0.39 (0.30, 0.52)***	<0.001
>365 days	1.00	1.15 (0.92, 1.44)	0.82 (0.66, 1.02)	0.38 (0.31, 0.47)***	<0.001
Aspirin					
<28 days	1.00	1.02 (0.81, 1.28)	0.82 (0.65, 1.02)	0.42 (0.33, 0.53)***	<0.001
28–365 days	1.00	1.17 (0.91, 1.51)	0.76 (0.59, 0.97)*	0.30 (0.23, 0.40)***	<0.001
>365 days	1.00	1.19 (0.89, 1.58)	0.89 (0.69, 1.15)	0.44 (0.34, 0.57)***	<0.001

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