

Supplementary Material

Risk of Alzheimer’s Disease Following Influenza Vaccination: A Claims-Based Cohort Study Using Propensity Score Matching

Supplementary Table 1. Definitions of Variables, Study Dates, and Study Periods

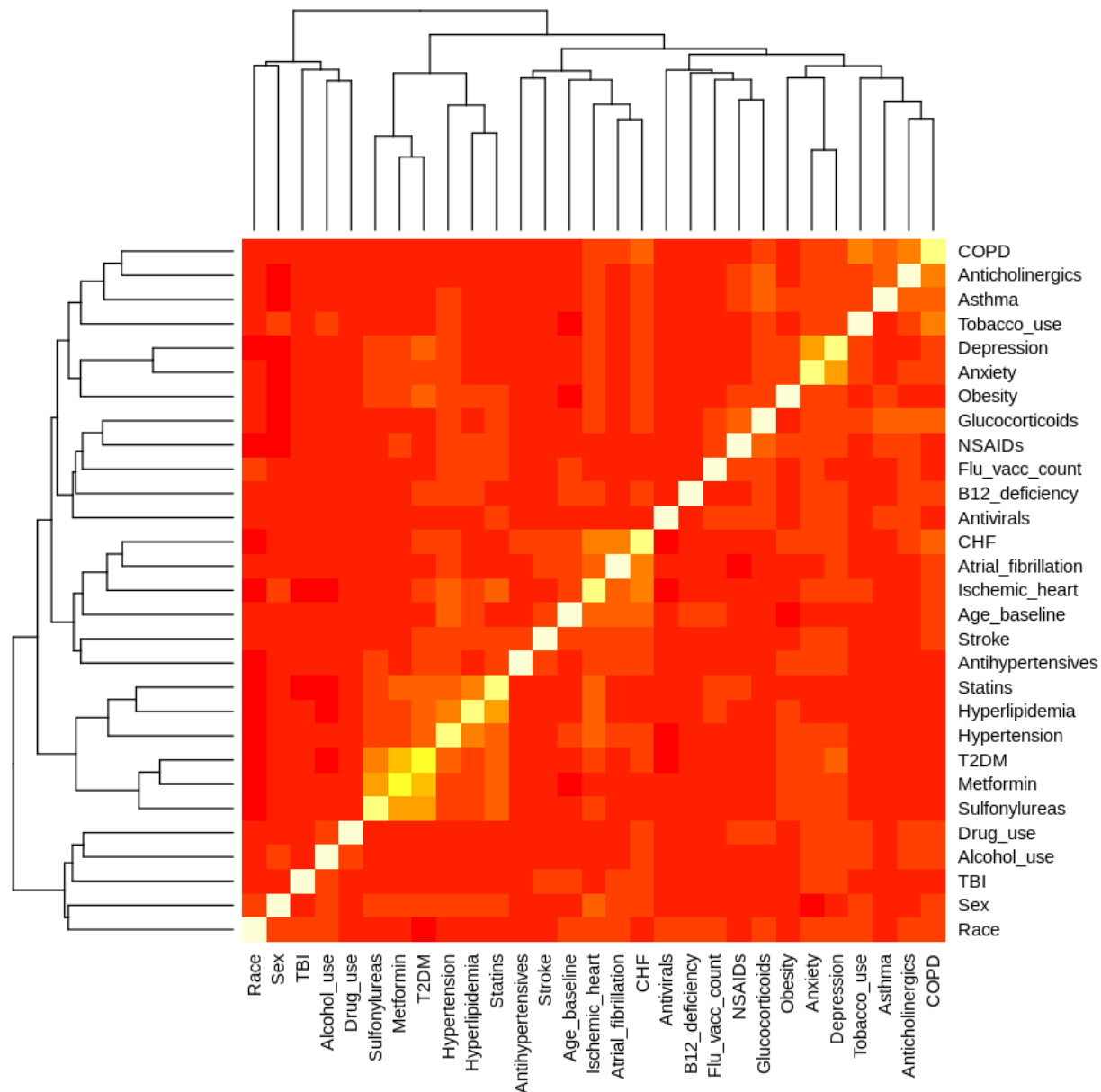
Variable, Date, or Period	Definition
General	
Look-back period	September 1, 2009, through August 31, 2015
Follow-up period	September 1, 2015, through August 31, 2019
Follow-up duration for each patient	Number of months from the start of follow-up (i.e., September 1, 2015) to the date of the first AD-related record (see “Incident AD Codes” below), death, or censoring (i.e., patient’s last record in the Optum Clinformatics Data Mart)
Outcome and Exclusions	
Alzheimer Disease (AD) Medications Used during the look-back period for exclusion of patients with preexisting cognitive impairment (see “Diagnosis Exclusion Codes” below). Used during the follow-up period for identification of patients with incident AD (see “Incident AD Diagnosis Codes” below).	Donepezil, galantamine, rivastigmine, memantine
Diagnosis Codes for Exclusion Criteria Used with AD-related medications to exclude patients with dementia (of any cause), mild cognitive impairment, or encephalopathy during the look-back period.	<i>ICD-9</i> codes: 046.1x, 046.3, 290.x, 291.1, 291.2, 294.x, 294.1x, 294.2x, 331.x, 332.x, 333.0, 333.4, 438.0, 780.93, 797 <i>ICD-10</i> codes: A81.0x, A81.2, F01.x, F02.x, F03.x, F04, F05, F10.26, F10.27, F10.96, F10.97, G10, G20, G21.1x, G21.2, G21.3, G21.4, G21.8, G21.9, G23.x, G30.x, G31.0x, G31.1, G31.2, G31.83, G31.84, G31.85, G31.89, G31.9, G91.x, G93.7, G94, I69.91, R41.2, R41.3, R41.81 - Required ≥ 1 occurrence (<i>ICD</i> code or AD-related medication) during the look-back period
Diagnosis Codes for Incident AD Case-Detection Algorithm Used with AD medication records to identify patients with incident AD during the follow-up period. Includes diagnostic codes for AD, dementia of unspecified cause, and “senile” dementia.	<i>ICD-9</i> codes: 290.0, 290.1x, 290.2x, 290.3, 294.2x, 331.0, 331.2, 331.9 <i>ICD-10</i> codes: F03.9x, G30.x, G31.1, G31.9 - Required ≥ 2 occurrences (<i>ICD</i> code[s] and/or AD medication record[s]) on different days within the same 12-month period during the follow-up period - The date of AD onset was defined as the date of the first AD-related record in the first 12-month period that criteria were met

Outcome Diagnosis Codes for Sensitivity Analyses	
Incident AD <i>without</i> Unspecified or “Senile” Dementias	<p><u>ICD-9 codes</u>^a: 331.0 <u>ICD-10 codes</u>^a: G30.x</p> <p>- Required ≥ 2 occurrences (<i>ICD</i> code[s] and/or AD medication record[s]) on different days within the same 12-month period during the follow-up period - The date of AD onset was defined as the date of the first AD-related record in the first 12-month period that criteria were met</p> <p>^a Schliep KC, Ju S, Foster NL, Smith KR, Varner MW, Ostbye T, Tschanz JT (2021) How good are medical and death records for identifying dementia? <i>Alzheimers Dement</i>, doi: 10.1002/alz.12526.</p>
Incident Alzheimer Disease and Related Dementias (ADRD)	<p><u>ICD-9 codes</u>^a: 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, 331.0, 331.11, 331.19, 331.2, 331.7, 797 <u>ICD-10 codes</u>^b: F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1, R41.81</p> <p>- Required ≥ 2 occurrences (<i>ICD</i> code[s] and/or AD medication record[s]) on different days within the same 12-month period during the follow-up period - The date of AD onset was defined as the date of the first AD-related record in the first 12-month period that criteria were met</p> <p>^a Lee E, Gatz M, Tseng C, Schneider LS, Pawluczyk S, Wu AH, Deapen D (2019) Evaluation of Medicare Claims Data as a Tool to Identify Dementia. <i>J Alzheimers Dis</i> 67, 769-778. ^b Moura L, Festa N, Price M, Volya M, Benson NM, Zafar S, Weiss M, Blacker D, Normand SL, Newhouse JP, Hsu J (2021) Identifying Medicare Beneficiaries with Dementia. <i>J Am Geriatr Soc</i> 69, 2240-2251.</p>
Influenza Vaccination	
Influenza vaccination (<i>intramuscular</i>)	<p><u>Drug names</u>: Afluria, Agriflu, Fluad, Fluarix, Flublok, Flucelvax, Flulaval, Fluzone, Flushield, Fluvirin, Fluogen, Flu-Imune <u>CPT codes</u>: 90630, 90653-90659, 90661, 90662, 90663, 90664, 90673, 90674, 90682, 90685-90689, 90694, 90724, 90756 <u>Healthcare Common Procedure Coding System (HCPCS) codes</u>: Q2034, Q2035, Q2036, Q2037, Q2038, Q2039, G0008</p>
Covariates – measured during the look-back period (except for age, which was measured at the index date)	
Age	Age in years at the index date (i.e., first day of the follow-up period)
Sex	Female, male, unknown

Race	<p>Asian, Black, Hispanic, White, unknown</p> <ul style="list-style-type: none"> - The Optum CDM includes persons identifying as Pacific Islander within the “Asian” race/ethnicity category. - The Optum CDM does not identify Native Americans as a separate racial/ethnic category.
Geographic region	<p>Based on the region of the primary beneficiary’s residence in the Optum CDM enrollment data. States were grouped into the following regions:</p> <ul style="list-style-type: none"> • Northeast (CT, ME, MA, NH, RI, VT, NJ, NY, PA) • North Central (IL, IN, MI, OH, WI, IA, KS, MN, MO, NE, ND, SD) • South (DC, DE, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX) • West (AZ, CO, ID, MT, NV, NM, UT, WY, AK, CA, HI, OR, WA) • Unknown
Number of healthcare encounters	<p>The number of outpatient and inpatient healthcare encounters during the look-back period.</p> <ul style="list-style-type: none"> - Each inpatient admission (i.e., hospitalization) was counted as 1 health care encounter, regardless of the length of stay. - To exclude pharmacy records, only outpatient records with ≥ 1 ICD codes were counted as a healthcare encounter.
Number of routine “well visit” examinations	<p><u>CPT codes</u>: 99386, 99387, 99396, 99397 <u>HCPCS codes</u>: G0402, G0438, G0439, G0444, S0610, S0612, S0613, G0101, G0091 <u>ICD-9 codes</u>: V70.0, V72.31 <u>ICD-10 codes</u>: Z00.00, Z00.01, Z01.411, Z01.419</p>
Asthma	<p><u>ICD-9 codes</u>: 493.x; <u>ICD-10 codes</u>: J45.x</p> <p>- Single occurrence during the look-back period</p>
Atrial fibrillation of flutter	<p><u>ICD-9 codes</u>: 427.3x; <u>ICD-10 codes</u>: I48.x</p> <p>- Single occurrence during the look-back period</p>
Vitamin B12 deficiency	<p><u>ICD-9 codes</u>: 266.2, 281.1 <u>ICD-10 codes</u>: E53.8, D51.x</p> <p>- Single occurrence during the look-back period</p>
Congestive heart failure (CHF)	<p><u>ICD-9 codes</u>: 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x; <u>ICD-10 codes</u>: I09.81, I11.0, I13.0, I13.2, I50.x</p> <p>- Single occurrence during the look-back period</p>
Chronic obstructive pulmonary disease (COPD)	<p><u>ICD-9 codes</u>: 491.x, 492.x, 496; <u>ICD-10 codes</u>: J41.x, J42, J43.2, J43.8, J43.9, J44.x</p> <p>- Single occurrence during the look-back period</p>

Hyperlipidemia	<p><u>ICD-9 codes:</u> 272.0, 272.1, 272.2, 272.4; <u>ICD-10 codes:</u> E78.0-E78.2, E78.4-E78.5</p> <p>- Single occurrence during the look-back period</p>
Hypertension	<p><u>ICD-9 codes:</u> 401.x <u>ICD-10 codes:</u> I10</p> <p>- Single occurrence during the look-back period</p>
Ischemic heart disease (IHD)	<p><u>ICD-9 codes:</u> 410.x, 411.x, 412.x, 413.x, 414.x, V45.81, V45.82; <u>ICD-10 codes:</u> I20.x, 121.x, 122.x, 123.x, 124.x, I25.x</p> <p>- Single occurrence during the look-back period</p>
Obesity	<p><u>ICD-9 codes:</u> 278.00, 278.01, 278.03, V85.3x, V85.4x; <u>ICD-10 codes:</u> E66.01, E66.09, E66.1, E66.2, E66.8, E66.9, Z68.3x, Z68.4x <u>BMI:</u> Last BMI during the look-back period is ≥ 30 kg/m²</p> <p>- Single ICD occurrence or last recorded BMI ≥ 30 kg/m² during the look-back period</p>
Traumatic brain injury (TBI)	<p><u>ICD-9 codes:</u> 800.x-804.x, 850.x-854.x, 905.0, 907.0, 959.01, V15.52; <u>ICD-10 codes:</u> S01.90x, S02.x, S04.x, S06.x, S07.x, S09.8x, S09.9x, Z87.820</p> <p>- Single occurrence during the look-back period</p>
Type II diabetes	<p><u>ICD-9 codes:</u> 250.x0, 250.x2, 357.2, 362.0x, 366.41; <u>ICD-10 codes:</u> E11.x, E08.42, E09.42, E13.42, E08.36, E09.36, E13.36</p> <p>- 2 outpatient occurrences on different days within the same 24-month period or 1 inpatient occurrence during the look-back period</p>
Stroke	<p><u>ICD-9 codes:</u> 430, 431, 433.x1, 434.x1, 438.x; <u>ICD-10 codes:</u> I61.x, I63.3x, I63.4x, I63.5x, I63.6, I63.8, I63.9, I66.x, I69.1x, I69.2x, I69.3x, I69.8x, I69.9x</p> <p>- Single occurrence during the look-back period</p>
Alcohol-related disorder (<i>includes alcohol dependence and alcohol use disorder</i>)	<p><u>ICD-9 codes:</u> 303.9x, 305.0x; <u>ICD-10 codes:</u> F10.x</p> <p>- Single occurrence during the look-back period</p>
Anxiety disorder	<p><u>ICD-9 codes:</u> 309.81, 300.00, 300.01, 300.02, 300.23, 300.3; <u>ICD-10 codes:</u> F40.1x, F41.0, F41.1, F41.9, F42, F43.1x</p> <p>- Composite of post-traumatic stress disorder, panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, and anxiety disorder not otherwise specified.</p> <p>- 2 outpatient occurrences on different days within the same 12-month period or 1 inpatient occurrence during the look-back period</p>

Depression	<p><u>ICD-9 codes:</u> 296.2x, 296.3x, 311; <u>ICD-10 codes:</u> F32.0-F32.5, F32.9, F33.0-F33.3, F33.4x, F33.9</p> <p>- 2 outpatient occurrences on different days within the same 12-month period or 1 inpatient occurrence during the look-back period</p>
Substance use disorder (excludes alcohol- and tobacco-related disorders)	<p><u>ICD-9 codes:</u> 304.0x, 304.1x, 304.2x, 304.3x, 304.4x, 304.5x, 304.6x, 304.7x, 304.8x, 304.9x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6x, 305.7x, 305.9x <u>ICD-10 codes:</u> F11.x, F12.x, F13.x, F14.x, F15.x, F16.x, F18.x, F19.x</p> <p>- Composite of substance use disorders involving any of the following: opioids; cannabis; sedatives, hypnotics, or anxiolytics; cocaine; amphetamines or other stimulants; hallucinogens; inhalants; and/or other psychoactive substances, including polysubstance use.</p> <p>- Single occurrence during the look-back period</p>
Tobacco use (includes current or former use)	<p><u>ICD-9 codes:</u> V15.82, 305.1; <u>ICD-10 codes:</u> Z87.891, Z72.0, F17.20x, F17.21x <u>CPT codes:</u> 99406, 99407 <u>HCPCS codes:</u> G0436, G0437</p> <p>- Single occurrence during the look-back period</p>
Medications (multiple variables)	<p>A variable was created for each of the following medication classes, based on the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification system.</p> <ul style="list-style-type: none"> ● Anticholinergics - AHFS codes: 12:08, 28:36.08, 04:04 ● Antihypertensives - AHFS codes: 24:08 ● Antivirals - AHFS codes: 08:18 ● Glucocorticoids - AHFS codes: 68:04 ● Metformin - AHFS codes: 68:20.04 ● NSAIDs - AHFS codes: 28:08.04 ● Statins - AHFS codes: 24:06.08 ● Sulfonylureas - AHFS codes: 68:20.20 <p>- The variable for a given class was coded “yes” only if records indicated sustained use of a medication(s) in that class. “Sustained use” was defined as ≥ 2 pharmacy claim records within any 6-month period during the look-back period.</p>

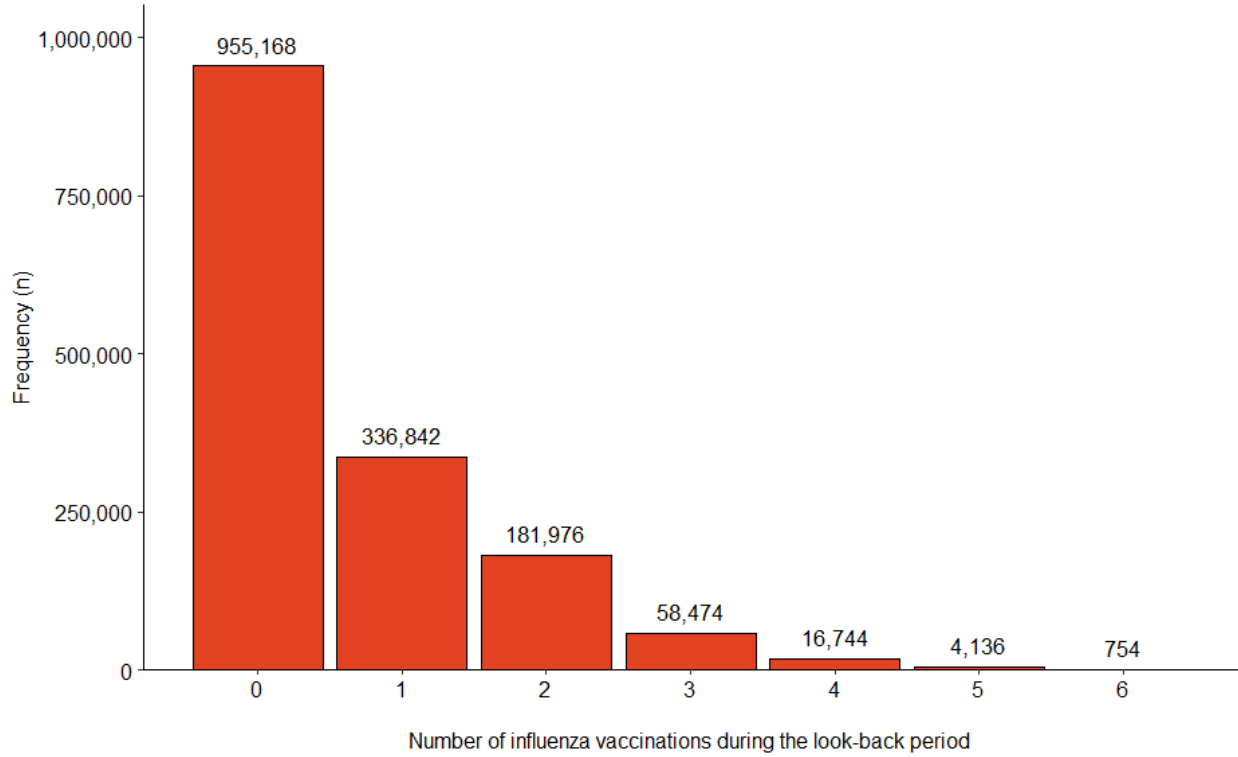


Supplementary Figure 1. Pairwise Correlation of Independent Variables in the Unmatched Sample. A heatmap of the pairwise correlations between predictors (i.e., influenza vaccination and covariates) in the unmatched sample, constructed to assess collinearity prior to creating the time-to-event model. Whiter colors indicate greater correlation; redder colors indicate weaker correlation. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; T2DM, type II diabetes mellitus; TBI, traumatic brain injury.

Supplementary Table 2. Effect Size Estimates from the Ad-hoc ATT Analyses

Duration of look-back	Minimum age (in years) at the start of follow-up	Number of vaccinated- unvaccinated PS- matched pairs	RR [95% CI]	ARR [95% CI]	NNT
6 years	≥ 65	935,887	0.60 [0.59, 0.61]	0.034 [0.033, 0.035]	29.4
6 years	≥ 75	366,235	0.62 [0.61, 0.63]	0.060 [0.059, 0.062]	16.7
2 years	≥ 65	348,714	0.74 [0.73, 0.75]	0.027 [0.025, 0.028]	37.0
2 years	≥ 75	204,134	0.75 [0.74, 0.77]	0.036 [0.034, 0.038]	27.8

The combination of a 6-year look-back period and a minimum age of 65 at the start of follow-up represents the parameters of the primary analysis (see “Primary Analysis: Estimation of ATT Using Propensity Score Matching” subsection of the Methods). The bottom three rows display the results of the ad-hoc ATT analyses in which the look-back duration was shortened to 2 years and/or the minimum age at the start of follow-up was increased to 75 years. In the designs with a 2-year look-back period, the follow-up period duration was 8 years. ATT, average treatment effect in the treated; ARR, absolute risk reduction; CI, confidence interval; NNT, number needed to treat; PS, propensity score; RR, relative risk.



Supplementary Figure 2. Frequency Distribution of Influenza Vaccinations During the 6-Year Look-back Period in the Unmatched Sample. A bar chart showing the number of patients in the unmatched sample (i.e., the sample used in the time-to-event analysis) who received each possible number of influenza vaccinations during the 6-year look-back period. See “Secondary Analysis: Time-to-Event Model” subsection of Methods for additional information.

Supplementary Table 3. Results of the Proportional Subdistribution Hazards Regression Model

		Coefficient	sHR	95% CI
No. of flu vaccinations during look-back		-0.275	0.76	(0.737, 0.784)
<i>(No. of flu vaccinations during look-back)*t</i>		0.006	1.006	(1.003, 1.009)
Age		0.149	1.16	(1.150, 1.171)
<i>Age*t</i>		-0.001	0.999	(0.998, 1.001)
Sex^a	Male	-0.106	0.899	(0.864, 0.936)
	Black	0.371	1.449	(1.398, 1.502)
Race^b	Hispanic	0.142	1.152	(1.108, 1.199)
	White	0.113	1.12	(1.079, 1.162)
Asthma		-0.073	0.93	(0.903, 0.957)
Atrial fibrillation or flutter		0.101	1.107	(1.025, 1.194)
<i>(Atrial fibrillation or flutter)*t</i>		-0.004	0.996	(0.988, 1.003)
B12 deficiency		0.125	1.133	(1.089, 1.179)
<i>(B12 deficiency)*t</i>		-0.001	0.999	(0.997, 1.001)
Congestive heart failure		0.164	1.178	(1.024, 1.356)
<i>(Congestive heart failure)*t</i>		-0.007	0.993	(0.978, 1.009)
COPD		0.134	1.143	(1.034, 1.264)
<i>COPD*t</i>		-0.003	0.997	(0.987, 1.006)
Hyperlipidemia and/or statins		-0.285	0.752	(0.706, 0.802)
<i>(Hyperlipidemia and/or statins)*t</i>		0.006	1.006	(1.000, 1.013)
Hypertension		0.075	1.429	(1.043, 1.114)
<i>Hypertension*t</i>		-0.001	0.009	(0.998, 1.001)
Ischemic heart disease		0.101	1.106	(1.062, 1.152)
<i>(Ischemic heart disease)*t</i>		-0.001	0.009	(0.996, 1.001)
Obesity		-0.254	0.776	(0.745, 0.808)
<i>Obesity*t</i>		0.004	1.004	(1.001, 1.007)

Traumatic brain injury	0.297	1.346	(1.236, 1.466)
<i>(Traumatic brain injury)*t</i>	-0.001	0.999	(0.995, 1.003)
T2DM, metformin, and/or sulfonylureas	0.204	1.226	(1.180, 1.274)
<i>(T2DM, metformin, and/or sulfonylureas)*t</i>	-0.002	0.998	(0.995, 1.002)
Stroke	0.504	1.107	(1.555, 1.761)
<i>Stroke*t</i>	-0.007	0.993	(0.987, 0.999)
Alcohol use disorder	0.357	1.655	(1.294, 1.577)
<i>(Alcohol use disorder)*t</i>	-0.003	0.996	(0.991, 1.002)
Depression and/or anxiety disorder	0.405	1.5	(1.453, 1.547)
<i>(Depression and/or anxiety disorder)*t</i>	-0.007	0.993	(0.993, 0.999)
Substance use disorder	0.244	1.276	(1.185, 1.375)
<i>(Substance use disorder)*t</i>	-0.004	0.996	(0.995, 1.001)
Tobacco use	0.036	1.037	(0.987, 1.090)
Anticholinergics	0.159	1.173	(1.079, 1.274)
<i>(Anticholinergics)*t</i>	-0.004	0.996	(0.987, 1.005)
Antihypertensives	0.097	1.102	(1.041, 1.167)
<i>(Antihypertensives)*t</i>	-0.002	0.998	(0.994, 1.003)
Antivirals	-0.038	0.963	(0.927, 1.000)
Glucocorticoids	-0.107	0.898	(0.872, 0.925)
<i>(Glucocorticoids)*t</i>	0.001	1.001	(1.000, 1.003)

Time-to-event results for a look-back period of 6 years and age ≥ 65 at the start of follow-up (see “Secondary Analysis: Time-to-Event Model” subsection of Methods for more information). Main effect terms are bolded; covariate-time interaction terms, when present, are italicized. CI, confidence interval; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; sHR, subdistribution hazard ratio; t, time; T2DM, type II diabetes mellitus.

^a Sex = female was used as the referent level.

^b Race = Asian was used as the referent level.

Supplementary Table 4. Results of the Ad-hoc Time-to-Event Analyses

Duration of look-back period	Minimum age (in years) at the start of follow-up period	Sample size	Coefficient of main effect term	sHR of main effect term [95% CI]	Coefficient of time-vaccination interaction term
6 years	≥ 65	1,554,094	-0.27	0.76 [0.74, 0.78]	0.0059
6 years	≥ 75	641,168	-0.26	0.77 [0.76, 0.78]	0.0059
2 years	≥ 65	408,151	-0.60	0.55 [0.48, 0.63]	0.0063
2 years	≥ 75	242,691	-0.62	0.54 [0.47, 0.63]	0.0065

The top set of parameters (i.e., 6-year look-back period and minimum age of 65 at the start of follow-up) represents the main study design; the bottom three rows display the results of the ad-hoc time-to-event analyses involving a 2-year look-back period and/or age ≥75 at the start of follow-up. In the designs with a 2-year look-back period, the follow-up duration was 8 years. “Main effect” refers to the time-independent flu vaccination term. Because influenza vaccination violated the proportional hazards assumption (see “Secondary Analysis: Time-to-Event Model” Methods subsection), a covariate-time interaction term (i.e., flu vaccination × time) was included in the time-to-event models. Although influenza vaccination is associated with a decreased incidence of AD (as demonstrated by sHR<1.0), the positive covariate-time interaction term indicates that the effect of influenza vaccination on AD incidence diminished with time during the follow-up period. CI, confidence interval; sHR, subdistribution hazard ratio.