

The Impact of Routine Vaccinations on Alzheimer's Disease Risk in Persons 65 Years and Older: A Claims-Based Cohort Study using Propensity Score Matching

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Abstract.

Background: Accumulating evidence suggests that adult vaccinations can reduce the risk of developing Alzheimer's disease (AD) and Alzheimer's disease related dementias.

Objective: To compare the risk for developing AD between adults with and without prior vaccination against tetanus and diphtheria, with or without pertussis (Tdap/Td); herpes zoster (HZ); or pneumococcus.

Methods: A retrospective cohort study was performed using Optum's de-identified Clinformatics® Data Mart Database. Included patients were free of dementia during a 2-year look-back period and were ≥ 65 years old by the start of the 8-year follow-up period. We compared two similar cohorts identified using propensity score matching (PSM), one vaccinated and another unvaccinated, with Tdap/Td, HZ, or pneumococcal vaccines. We calculated the relative risk (RR) and absolute risk reduction (ARR) for developing AD.

Results: For the Tdap/Td vaccine, 7.2% ($n = 8,370$) vaccinated patients and 10.2% ($n = 11,857$) unvaccinated patients developed AD during follow-up; the RR was 0.70 (95% CI, 0.68–0.72) and ARR was 0.03 (95% CI, 0.02–0.03). For the HZ vaccine, 8.1% ($n = 16,106$) vaccinated patients and 10.7% ($n = 21,273$) unvaccinated patients developed AD during follow-up; the RR was 0.75 (95% CI, 0.73–0.76) and ARR was 0.02 (95% CI, 0.02–0.02). For the pneumococcal vaccine, 7.92% ($n = 20,583$) vaccinated patients and 10.9% ($n = 28,558$) unvaccinated patients developed AD during follow-up; the RR was 0.73 (95% CI, 0.71–0.74) and ARR was 0.02 (95% CI, 0.02–0.03).

Conclusion: Several vaccinations, including Tdap/Td, HZ, and pneumococcal, are associated with a reduced risk for developing AD.

Keywords: Alzheimer's disease, cohort, dementia, diphtheria, epidemiology, herpes zoster, pertussis, pneumococcus, tetanus, vaccine

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INTRODUCTION

There are multiple theories as to the etiology of Alzheimer's disease (AD). One hypothesis is that infection may play a causative role in the development of AD and Alzheimer's disease related dementias (ADRDs) [1–4]. Viral, bacterial, and fungal infections may increase neuroinflammation, thereby causing or exacerbating neurodegeneration, and subsequently dementia [1, 3]. Vaccines may reduce the risk for developing infections, or limit their severity, reducing an individual's neuroinflammatory burden, decreasing the immune mechanisms that may contribute to the development of AD/ADRD [5]. Alternately, vaccines may activate alternative pathways of the immune system that may alter the risk for AD/ADRD [5, 6].

Three vaccines recommended by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) for older adults are against tetanus, diphtheria, with and without pertussis; herpes zoster; and pneumococcus [7].

Tetanus, diphtheria, and pertussis are bacterial infections that can lead to severe complications including hospitalization and death, especially in patients 65 and older. These infections are caused by *Clostridium tetani* through wounds [8], and *Corynebacterium diphtheria* and *Bordetella pertussis* through respiratory droplets [9, 10]. Pertussis has been of interest for researchers studying AD. One hypothesis postulates that pertussis colonization in the nasopharynx and potential accrual in the central nervous system through the olfactory nerve leads to or exacerbates amyloid-beta and tau tangle accumulation in the brain [11]. Vaccines for these three diseases are available to adults as either a combined tetanus, diphtheria, and acellular pertussis vaccine (Tdap), and tetanus and diphtheria (Td) [12]. Tetanus toxoid (TT) has been utilized in patients with a tetanus-prone wound; however, it is not recommended over Tdap and Td [13]. There are multiple brands of the Tdap (Adacel, Boostrix) and Td (TENIVAC, TDVAX) vaccines available in the United States [12]. A single dose of Tdap is given to patients who have never received Tdap previously [7]. A booster of Tdap or Td can then be given every ten years. Tdap or Td are recommended for a tetanus-prone wound if a patient has not received such a vaccine in the past five years [12, 14].

Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus [15]. Estimates of lifetime HZ incidence show that nearly one-third of the

world's population will develop HZ [16, 17]. Patients with a history of HZ have an increased risk for developing dementia [18–20]. The herpes zoster vaccine currently recommended in the US, Shingrix, has been available since 2017 to patients 50 years and older and immunocompromised patients 19 years and older [21]. Shingrix is a recombinant vaccine containing varicella-zoster glycoprotein E antigen and an adjuvant which is given as a two-dose series. It has been demonstrated to be 91% effective at preventing HZ [21]. From 2008 to 2020, the live-attenuated varicella vaccine, Zostavax, was recommended in the US for the prevention of herpes zoster among those 60 and older [22, 23]. The Zostavax vaccine reduces the risk of HZ by 51% [22, 24].

Pneumococcal infection is caused by *Streptococcus pneumoniae* (i.e., pneumococcus) [25]. Patients 65 and older are at higher risk for severe disease [26]. There are two types of pneumococcal vaccines for adults: the pneumococcal polysaccharide vaccine (PPSV-23) and the pneumococcal conjugate vaccine (PCV13, PCV15, or PCV20) [25]. The PPSV-23 vaccine contains the purified capsular polysaccharide for twenty-three different serotypes of *Streptococcus pneumoniae*; whereas the PCV-13 vaccine only contains thirteen serotypes, but also contains a modified diphtheria toxin protein as a conjugant [25]. PPSV-23 was first approved for use in 1983, and until 2021, the CDC recommended that all adults 65 and older receive a dose of PPSV-23 [25, 27]. Between 2014–2019, it was recommended that adults aged 65 years and older receive a dose of PCV-13 prior to the PPSV-23. Since June 2019, however, PCV-13 is no longer routinely recommended for immunocompetent adults 65 or older. Instead, it is given after “shared clinical decision-making” [28]. PCV-13 is 75% effective at preventing invasive serotype-specific pneumococcal disease, while PPSV-23 is 60–70% effective [29].

Previous studies on the effect of vaccinations on dementia risk have proven promising. Recent publications utilizing a retrospective design have demonstrated a decreased risk of dementia among patients who received an HZ vaccine [30–33], Tdap vaccine [30, 34], or pneumococcal vaccine [35, 36]. However, there are gaps within the literature that this study addresses, including differences in the effects of various types of vaccines (i.e., recombinant versus live attenuated, conjugated versus unconjugated) on the risk of AD. There are two purposes for this study: 1) To evaluate the relationship between exposure to either the HZ, Tdap/Td, or pneumococcal

vaccines and the risk of AD; and, 2) to investigate whether the effects of HZ or pneumococcal vaccines on the risk of AD, if present, vary by the type of vaccine (i.e., recombinant versus live attenuated for HZ vaccination, conjugated versus unconjugated for pneumococcal vaccination). Differences in immunogenicity among the vaccine types, such as the involvement of CD4+ T-cells and production of long-lasting humoral immunity induced by the conjugated pneumococcal vaccines (e.g., PCV13) but not by polysaccharide-only vaccines (e.g., PPSV23) [37], may result in differential effects on AD risk among the differing vaccine types. Alternatively, the efficacy of protection against infectious burden among vaccines targeting the same pathogen (e.g., Shingrix versus Zostavax against Herpes Zoster) may modulate the magnitude of an effect between these vaccines and AD risk. In light of the above, we hypothesize that routine adult vaccinations decrease the risk of AD in patients 65 years and older. We also hypothesize that that recombinant (when compared with live attenuated) and conjugated (when compared with unconjugated) vaccinations are associated with a greater decrease in AD risk due to the greater protection against infectious disease from Shingrix (compared to Zostavax) and the more robust adaptive immune response induced by conjugated vaccines.

METHODS

Data source and study period

The study cohort was obtained from Optum's de-identified Clinformatics® Data Mart Database (CDM). The claims database records information from different sources in the United States, such as medical, pharmaceutical, and administrative claims, as well as laboratory test results. The database includes patients who have both medical and prescription drug coverage through private insurance or Medicare Advantage with Part D. Mortality information from hospital discharge claims and the Social Security Administration Death Master file is also available in the CDM. All data are verified, adjudicated, adjusted, and de-identified before inclusion in the CDM.

The CDM for our study includes the years 2009 through 2019. With the exception of three sub-analyses (as discussed in the Analysis Overview section below), all analyses were performed using a look-back period of September 1, 2009 to August 31,

2011 and a follow-up period of September 1, 2011 to August 31, 2019.

Cohort selection

With the definition of the look-back period and the follow-up period, we implemented inclusion and exclusion criteria to build a cohort for analyzing the effects of the targeted vaccines (Fig. 1).

We included patients who were at least 65 years old at the start of the follow-up period. Patients were included if they had at least one record in the look-back period and had at least two records during the follow-up. If patients had 1) a recorded diagnosis of dementia, mild cognitive impairment, or encephalopathy, or 2) were prescribed any medication primarily indicated for AD (i.e., donepezil, galantamine, rivastigmine, or memantine) during the look-back period, they were excluded from the cohort.

Exposure measurement

Vaccinations were counted if they were received on or after the index date (i.e., the first day of the follow-up period) but before the following occurred: 1) AD onset, 2) death, or 3) the end of the follow-up period. We investigated three kinds of vaccination in this study: Tdap/Td, herpes zoster, and pneumococcal vaccines. To identify vaccinations, we queried the database for their brand names and generic names as found in Supplementary Table 1. For the Tdap/Td vaccine sample, we excluded vaccines not indicated for patients 65 years and older (i.e., DTaP). For the HZ vaccines, only the two brands of vaccines approved by the FDA for use in the U.S. were included: Zostavax and Shingrix. And for the pneumococcal vaccines, we included PCV13 and PPSV23, while excluding Pneumococcal 7-val vaccines as they are only used for pediatric patients [26].

Outcome measurement

The procedure and rationale for outcome measurement is the same as what was used in our recent study of incident AD risk following influenza vaccination [38]. We identified patients as having AD if they met any of the following three criteria in any 12-month window during the follow-up period: 1) two or more diagnoses of AD in their records, 2) one or more diagnoses of AD and one or more prescription records for AD-related medications, or 3) two

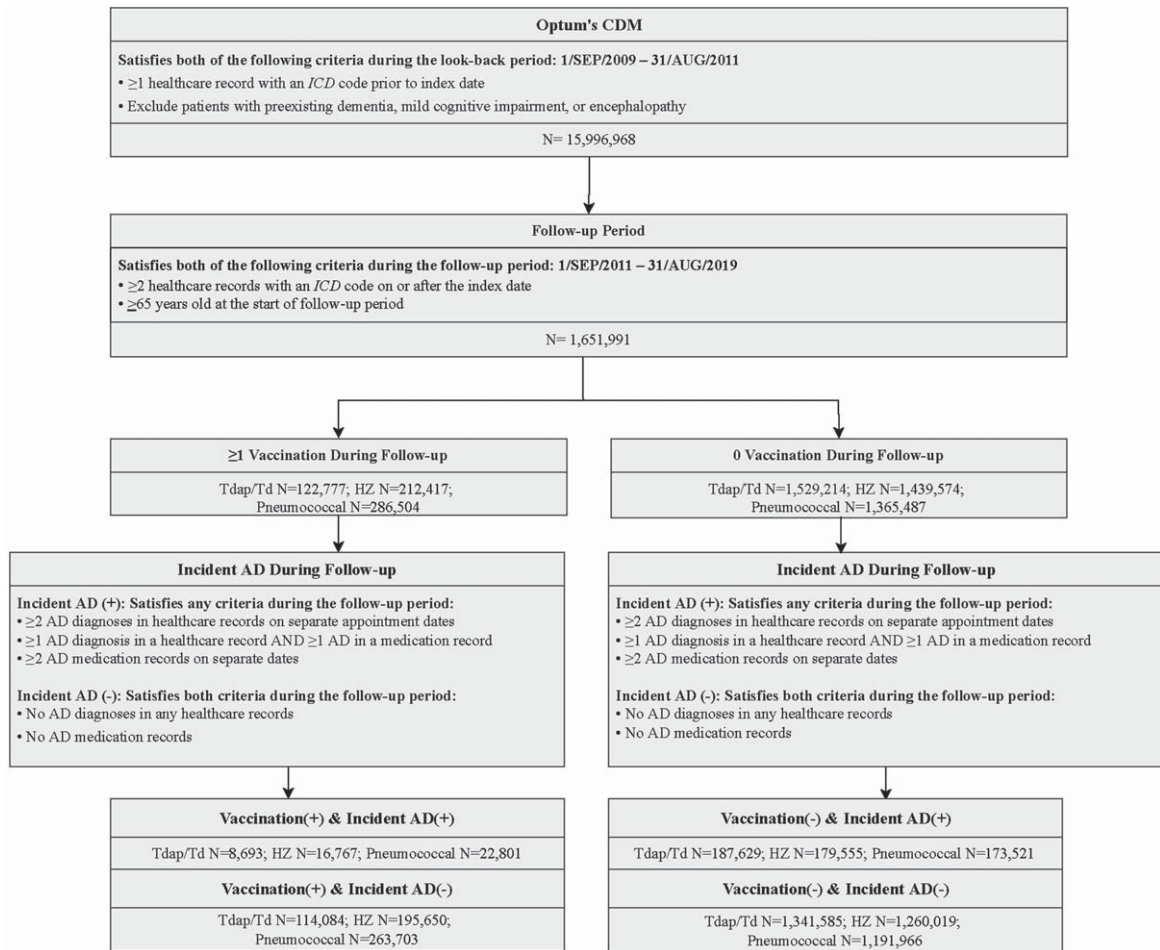


Fig. 1. Flowchart of Sampling Methodology. The three main analyses using Tdap/Td, HZ, and pneumococcal vaccinations are shown. AD, Alzheimer's disease; CDM, Optum's de-identified Clinformatics® Data Mart Database; HZ, Herpes zoster; ICD, International Classification of Diseases; Tdap/Td, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis/Tetanus toxoid, and reduced diphtheria toxoid. Figure adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through <http://dx.doi.org/10.3233/JAD-220361>.

231 or more prescription records for AD-related medica- 245
 232 tions. Patients who only have one record of an AD 246
 233 diagnosis or AD-related prescription were removed 247
 234 from the cohort. The ICD codes and medications 248
 235 used for identifying AD are located in Supplemen- 249
 236 tary Table 1. A systematic review of validation studies 250
 237 for AD and ADRD in administrative datasets provide 251
 238 support for our inclusion and exclusion criteria for 252
 239 the outcome measurement [39]. The authors found 253
 240 that the positive predictive value (PPV) of a patient 254
 241 having dementia increased from 68% to 94% if two 255
 242 or more diagnosis codes were utilized instead of just 256
 243 one. Further, they found that the PPV is 97% when 257
 244 using AD medication codes to identify patients with 258

AD. Lastly, we elected to make use of nonspecific 245
 dementia codes, as well as AD specific codes, in 246
 identifying AD patients. This is because, although 247
 60–70% of dementia cases among older adults are 248
 secondary to AD, nonspecific dementia codes (e.g., 249
 senile dementia) are significantly more common than 250
 codes for specific dementia subtypes (e.g., AD, vas- 251
 cular dementia) in administrative claims data [40, 252
 41]. For example, a study of Medicare beneficiaries 253
 found that 46.1% of patients only had a code for 254
 dementia not otherwise specified, 4.5% of patients 255
 only had a code for AD, and 29% of patients had 256
 codes for both dementia not otherwise specified and 257
 for AD [40]. 258

Covariate measurement

Similar to our previous research on influenza vaccination and AD risk [38], and to another study on influenza vaccination and dementia in a Veterans Affairs cohort [42], we included covariates for patient demographics, comorbidities, medication use, and the number of healthcare encounters and routine “well visit” examinations (as proxies for healthcare utilization rate). For this analysis, we also included information pertaining to receipt of routine vaccinations, including those against tetanus, diphtheria, with or without pertussis; herpes zoster; pneumococcus; and influenza. Importantly, the vaccine(s) used in the exposure definition (see “Analysis Overview” below) for a given analysis was not included as a covariate in that analysis; for example, in the analysis comparing persons who received either Tdap or Td with those who received neither during follow-up, Tdap and Td vaccinations during the look-back period were not included as a covariate in the propensity score model. A detailed list of the covariates and their definitions is provided in Supplementary Table 1. For all covariates except age, the last measurement recorded in the look-back period was used as the baseline covariate value.

Estimating ATT using propensity score matching

We estimate the average treatment effect on the treated (ATT) of the three vaccination groups on AD risk using propensity score matched (PSM) (Fig. 2). We utilized PSM to minimize selection bias from unbalanced confounders between the vaccinated and unvaccinated groups. The propensity scores were estimated by fitting a logistic regression model with all the baseline characteristics measured during the look-back period to predict the probability of vaccination. For non-static variables (e.g., BMI), the last measurement in the look-back period (i.e., the one closest to the start of follow-up) was used. We assumed that receiving one kind of vaccine would lead to a higher probability of receiving other kinds of adult vaccines, and therefore, we included other routine vaccines as covariates (see “Covariate Measurement” above). Patients with unknown sex, geographic region, or race were excluded from this analysis. Once we estimated the propensity scores using logistic regression, a one-to-one nearest neighbor matching with a caliper width of 0.2 standard deviations of the logit of the propensity score and without replacement was used to match each patient

that met target vaccine group criterion with a patient in the unvaccinated group [43]. To evaluate the balance between vaccinated and unvaccinated groups after matching, we calculated the standardized mean difference (SMD) for each covariate before and after matching. An adequate balance between the groups was defined as an $SMD \leq 0.10$ [44].

Analysis overview

We performed three main analyses and then separate sub-analyses for each of the vaccines recommended by the CDC. In these analyses, we created vaccinated and unvaccinated balanced cohorts by PSM and estimated ATT in order to evaluate for heterogeneity in the effect size among the vaccines targeting the same pathogenic species. Each analysis performed had a different unvaccinated cohort. There were thirteen analyses performed in total.

In the Tdap/Td vaccine group, the main analysis was performed on patients who were vaccinated with either Tdap and Td as the exposed group and unvaccinated patients in an unexposed cohort. We included four other analyses: patients who received 1) at least one Tdap, Td, or TT vaccine; 2) at least one Tdap vaccine; 3) at least one Td vaccine; and, 4) at least one TT vaccine.

With regard to HZ vaccines, the main analysis included patients who received at least one Zostavax or at least one Shingrix vaccine. The sub-analyses included patients who 1) were fully vaccinated using the Shingrix vaccine (completed two doses of the vaccine); 2) received at least one Zostavax vaccine and were fully vaccinated using the Shingrix vaccine; 3) received at least one Shingrix vaccine but no Zostavax vaccine; and, 4) received at least one Zostavax vaccine but no Shingrix vaccine.

For the pneumococcal vaccines, the main analysis included patients who received at least one PCV-13 vaccine or PPSV-23 vaccine. The two sub-analyses were for patients who received 1) at least one PCV-13 vaccine, but no PPSV-23 vaccine; and 2) at least one PPSV-23 vaccine, but no PCV-13 vaccine.

The look-back and follow-up periods were 2009–2011 and 2011–2019 for most of the analyses, with three exceptions necessary to account for the year in which two of the vaccines (Shingrix and PCV-13) were added to the CDC’s routine immunization schedule for older adults. As discussed earlier, Shingrix was first approved and recommended for use in 2017 [15, 21]. Hence, for the sub-analysis of patients who received at least one Shingrix vaccination but

Table 1
Baseline characteristics of patients with and without Tdap/Td during the follow-up period before and after PSM

	Panel 1: Before propensity score matching			Panel 2: After propensity score matching		
	No Tdap vaccinations during follow-up (n = 1,529,214)	≥ 1 Tdap vaccinations during follow-up (n = 122,777)	SMD	No Tdap vaccinations during follow-up (n = 116,400)	≥ 1 Tdap vaccinations during follow-up (n = 116,400)	SMD
Age, y, mean (SD)	73.1 (5.7)	71.9 (5.0)	0.2101	72.0 (5.2)	72.0 (5.0)	-0.0072
Sex						
Unknown	214 (0.01%)	11 (0.01%)	0.0047	NA	NA	
Female	854,745 (55.89%)	70,836 (57.69%)	-0.0364	67,025 (57.58%)	67,114 (57.66%)	-0.0015
Male	674,256 (44.09%)	51,930 (42.3%)	0.0121	49,375 (42.42%)	49,286 (42.34%)	0.0015
Race						
Unknown	114,104 (7.46%)	6,315 (5.14%)	0.0955	NA	NA	
Asian	43,079 (2.82%)	3,554 (2.89%)	-0.0047	3,035 (2.61%)	3,553 (3.05%)	-0.0268
Black	135,762 (8.88%)	11,087 (9.03%)	-0.0053	10,152 (8.72%)	11,085 (9.52%)	-0.0278
Hispanic	134,543 (8.8%)	8,636 (7.03%)	0.0669	9,367 (8.04%)	8,627 (7.41%)	0.0238
White	1,101,727 (72.05%)	93,185 (75.9%)	-0.0879	93,846 (80.62%)	93135 (80.01%)	0.0154
Geographic region						
Unknown	1,048 (0.07%)	56 (0.05%)	0.0096	NA	NA	
Northeast	138,212 (9.04%)	11,409 (9.29%)	-0.0088	10,788 (9.27%)	10,821 (9.3%)	-0.001
North central	344,302 (22.51%)	29,280 (23.85%)	-0.0316	27,113 (23.29%)	28,037 (24.09%)	-0.0187
South	566,337 (37.03%)	42,670 (34.75%)	0.0476	43,156 (37.08%)	41,018 (35.24%)	0.0382
West	479,316 (31.34%)	39,362 (32.06%)	-0.0154	35,343 (30.36%)	36,524 (31.38%)	-0.022
No. of health care encounters ^a , mean (SD)	24.9 (26.1)	22.9 (21.7)	0.0828	22.1 (22.2)	23.1 (21.8)	-0.0454
No. of routine annual check-ups ("well visits")	0.6 (1.0)	0.7 (1.0)	-0.1418	0.7 (1.1)	0.7 (1.0)	-0.0149
Comorbidities						
Asthma	119,583 (7.82%)	9,276 (7.56%)	0.0099	7,898 (6.79%)	8,863 (7.61%)	-0.0321
Atrial fibrillation or flutter	152,609 (9.98%)	8,831 (7.19%)	0.0996	7,819 (6.72%)	8,452 (7.26%)	-0.0213
B12 deficiency	53,072 (3.47%)	3,559 (2.9%)	0.0326	3,151 (2.71%)	3,406 (2.93%)	-0.0132
Congestive heart failure	139,821 (9.14%)	6,144 (5%)	0.1594	5,353 (4.6%)	5,901 (5.07%)	-0.022

COPD	221,648 (14.49%)	12,163 (9.91%)	0.1405	10,907 (9.37%)	11,663 (10.02%)	-0.022
Hyperlipidemia	1,069,831 (69.96%)	88,677 (72.23%)	-0.05	83,731 (71.93%)	84,339 (72.46%)	-0.0117
Hypertension	1,096,354 (71.69%)	84,550 (68.86%)	0.0619	79,900 (68.64%)	80,535 (69.19%)	-0.0118
Ischemic heart disease	353,523 (23.12%)	22,514 (18.34%)	0.1181	20,766 (17.84%)	21,516 (18.48%)	-0.0167
Obesity	116,184 (7.6%)	9,060 (7.4%)	0.0083	7966 (6.84%)	8,676 (7.45%)	-0.0236
Traumatic brain injury	6,961 (0.46%)	417 (0.34%)	0.0183	399 (0.34%)	401 (0.34%)	-0.0003
Type II diabetes	388,303 (25.39%)	27,155 (22.12%)	0.077	24,722 (21.24%)	25,955 (22.3%)	-0.0257
Stroke	52,951 (3.46%)	2,780 (2.26%)	0.0719	2,366 (2.03%)	2,656 (2.28%)	-0.0171
Alcohol use disorder	14,171 (0.93%)	767 (0.62%)	0.0344	690 (0.59%)	733 (0.63%)	-0.008
Anxiety disorder ^b	162,626 (10.63%)	11,050 (9%)	0.055	9667 (8.3%)	10,561 (9.07%)	-0.0273
Depression	109,197 (7.14%)	6,920 (5.64%)	0.0616	5987 (5.14%)	6,627 (5.69%)	-0.0243
Substance use disorder ^c	11,311 (0.74%)	640 (0.52%)	0.0276	591 (0.51%)	611 (0.52%)	-0.0023
Tobacco use	145,973 (9.55%)	10,088 (8.22%)	0.0467	8,870 (7.62%)	9,626 (8.27%)	-0.024
Medications (sustained use) ^d						
Anticholinergics	86,220 (5.64%)	5,464 (4.45%)	0.0543	5,056 (4.34%)	5,285 (4.54%)	-0.0095
Antihypertensives	41,071 (2.69%)	2,452 (2%)	0.0456	2,146 (1.84%)	2,362 (2.03%)	-0.0135
Antivirals	21,062 (1.38%)	1,996 (1.63%)	-0.0204	1,726 (1.48%)	1,925 (1.65%)	-0.0138
Glucocorticoids	133,544 (8.73%)	10,471 (8.53%)	0.0073	9,056 (7.78%)	10,095 (8.67%)	-0.0325
Metformin	162,350 (10.62%)	13,222 (10.77%)	-0.0049	11,886 (10.21%)	12,661 (10.88%)	-0.0217
NSAIDs	196,438 (12.85%)	17,278 (14.07%)	-0.036	15,247 (13.1%)	16,569 (14.23%)	-0.0331
Statins	623,884 (40.8%)	54,745 (44.59%)	-0.0767	51,308 (44.08%)	52,218 (44.86%)	-0.0157
Sulfonylureas	121,153 (7.92%)	8,336 (6.79%)	0.0434	7,542 (6.48%)	8,008 (6.88%)	-0.016
Vaccination						
Influenza vaccination	86,511 (5.66%)	10,418 (8.49%)	-0.1105	8,980 (7.71%)	10,003 (8.59%)	-0.0321
HZ vaccination	19,716 (1.29%)	2,928 (2.38%)	-0.0816	2,412 (2.07%)	2,752 (2.36%)	-0.0198
Pneumococcal vaccination	10,189 (0.67%)	1,404 (1.14%)	-0.0504	1,155 (0.99%)	1,335 (1.15%)	-0.015

Variable definitions are provided in Supplementary Table 1. Categorical variables are reported as frequency and percentage, and continuous variables as mean and standard deviation. Because patients with unknown geographic region, race, and sex are excluded prior to performing the propensity score matching (PSM), those rows after PSM are labelled as NA. ^aNumber of outpatient or inpatient healthcare encounters during the look-back period. ^b“Anxiety disorder” is a composite variable of post-traumatic stress disorder, panic disorder, anxiety disorder not otherwise specified, obsessive compulsive disorder, social phobia, and generalized anxiety disorder. ^c“Substance use disorder” is a composite variable 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. ^d“Sustained use” is defined as ≥ 2 prescription claims in any 6-month period during the look-back period. COPD, chronic obstructive pulmonary disease; HZ, Herpes zoster; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SMD, standardized mean difference; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid. Table adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer’s Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer’s disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through <http://dx.doi.org/10.3233/JAD-220361>.

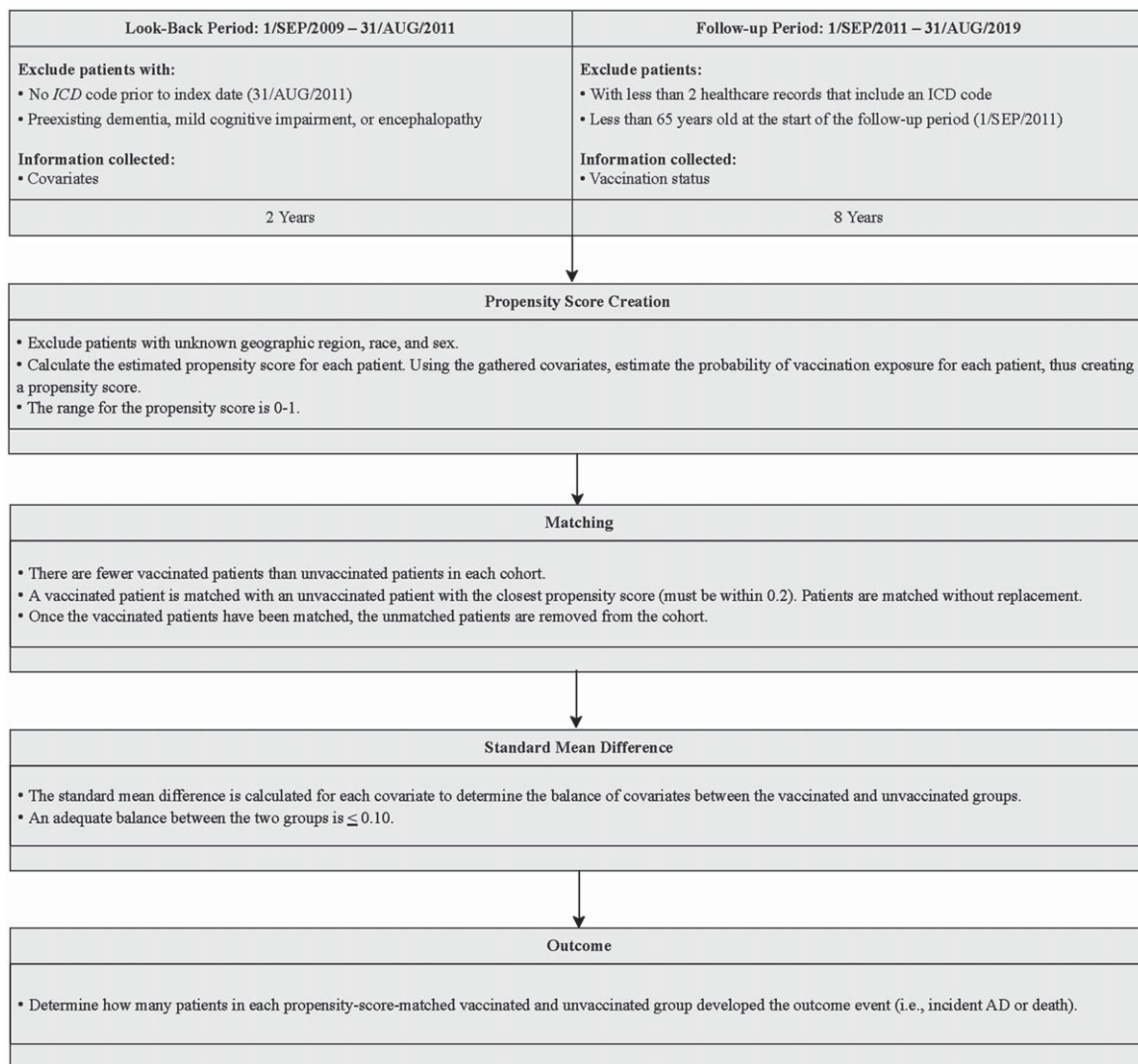


Fig. 2. Overview of Cohort Selection and Propensity Score Matching. AD, Alzheimer's disease; ICD, International Classification of Diseases. Figure adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through <http://dx.doi.org/10.3233/JAD-220361>.

358 no Zostavax vaccination, and for the patients who
 359 received the full Shingrix series (two doses) during
 360 follow-up but no Zostavax vaccines, we set the look-
 361 back period to 2009–2017 and the follow-up period
 362 to 2017–2019. Similarly, because the PCV-13 vac-
 363 cine was first recommended for older adults in 2014,
 364 the sub-analysis of patients who received at least one
 365 PCV-13 vaccination but no PPSV-23 used a look-back
 366 period spanning 2009–2014 and a follow-up period
 367 spanning 2014–2019 [25, 27, 28].

368 For all of the analyses, we computed relative risk
 369 (RR), absolute risk reduction (ARR), and the cor-

responding 95% confidence intervals (CIs). When
 constructing the 95% CI for the point estimators,
 given that the study cohort is propensity-score-
 matched cohort, we used a method that accounts for
 the pairwise dependence between matched samples
 [45, 46]. E-values for point estimates were calculated
 to assess how strongly an unmeasured confounder
 would need to be associated with both the probability
 of vaccination and the probability of AD, while con-
 trolling for the covariates in our analyses, in order to
 render the results statistically insignificant. For exam-
 ple, if the E-value for the RR of an analysis is 4,

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then an unmeasured confounder would need to have a RR of ≥ 4 (while controlling for the same covariates) with both the exposure (vaccination) and with the outcome (incident AD) for the result to become statistically insignificant. PSM was conducted with Python 3.7.7 and CausalML package v0.11.1 [47].

Sensitivity analysis

To investigate the influence of healthy adherer bias, we applied the eligibility criteria described above but then selected a subset of patients who filled at least one statin (i.e., HMG-CoA reductase inhibitor) prescription in the first half of the look-back period (2009–2010) and whose proportion of days covered (PDC) for statin therapy during the second half of the look-back period (2010–2011) was $\geq 80\%$. The remainder of the primary analysis (i.e., ATT estimation using propensity-score matching) was repeated using this subset of statin adherers.

Ethics approval

This study was reviewed by the UTHealth Institutional Review Board, the Committee for the Protection of Human Subjects (CPHS), which deemed this study “non-human subjects research” because the study uses de-identified retrospective claims data. Therefore, the study was approved with a waiver of the HIPAA authorization and waiver of informed consent.

RESULTS

Baseline characteristics

In total, 1,651,991 patients were identified after applying inclusion and exclusion criteria (Fig. 1). Prior to matching, 122,777 patients received vaccinations against tetanus and diphtheria, with and without pertussis; 212,417 received vaccinations against herpes zoster; and 286,504 received vaccines against pneumococcus. Summary of baseline characteristics before and after PSM for Tdap/Td is shown in Table 1, and for HZ and pneumococcal is shown in Supplementary Table 2A and 2B. Vaccinated patients were matched with unvaccinated patients using the nearest propensity score based on covariates such as age, sex, race, geographic region, comorbidities, medications, and vaccinations. The SMDs were all less than 0.1 after PSM, which indicates that the cohorts are balanced.

ATT estimation

The frequency of AD among patients who were vaccinated and unvaccinated after PSM for our main analyses and sub-analysis are shown in Table 2. In the main analyses, for the Tdap/Td vaccine, 7.2% ($n=8,370$) of the vaccinated patients and 10.2% ($n=11,857$) of the unvaccinated patients developed AD during the 8-year follow-up period. For the HZ vaccine, 8.1% ($n=16,106$) of the vaccinated patients and 10.7% ($n=21,273$) of the unvaccinated patients developed AD during the 8-year follow-up period. And for the pneumococcal vaccine, 7.92% ($n=20,583$) of the vaccinated patients and 10.9% ($n=28,558$) of the unvaccinated patients developed AD during the 8-year follow-up period. The estimated RR, ARR, and the number needed to treat (NNT) for the thirteen different analyses are shown in Table 3. All three main analyses showed statistically significant results: Tdap/Td vaccination (RR: 0.70; 95% CI: 0.68–0.72), HZ vaccination (RR: 0.75; 95% CI: 0.73–0.76), and pneumococcal vaccination (RR: 0.73; 95% CI: 0.71–0.74). There were also statistically significant results in several sub-analyses including: 1) at least one dose of Shingrix (excluding any Zostavax vaccinations) (RR: 0.27; 95% CI: 0.25–0.29), 2) those vaccinated with Zostavax (excluding any Shingrix vaccinations) (RR: 0.92; 95% CI: 0.90–0.94), 3) those vaccinated with PCV-13 (excluding any PPSV-23 vaccinations) (RR: 0.73; 95% CI: 0.71–0.74), and 4) those vaccinated with PPSV-23 (excluding any PCV-13 vaccinations) (RR: 0.71; 95% CI: 0.69–0.73) when compared to unvaccinated groups. The median follow-up distributions to AD onset, death, or censoring for each of the analyses are shown in Supplementary Table 3. For the vaccinated groups, the follow-up time begins when the first target vaccine was received during the follow-up period.

Sensitivity analysis

After excluding patients with missing demographics, 1,530,385 patients were identified for the sensitivity analysis cohort. For the first half of the look back period (2009–2010), 544,228 patients had statin records. Of those patients, 281,554 patients had a PDC $\geq 80\%$ during the second half of the look-back period (2010–2011). Statistically significant results were found for the sensitivity analysis: Tdap/Td vaccination (RR: 0.67; 95% CI: 0.64–0.71), HZ vaccination (RR: 0.71; 95% CI: 0.68–0.73),

Table 2
Frequency of AD in vaccinated and unvaccinated patients per analysis after PSM

Exposure Definition	Vaccinated		Unvaccinated	
	AD (+)	AD (-)	AD (+)	AD (-)
<i>Tdap, Td, and/or TT Vaccination versus Unvaccinated</i>				
≥ 1 Tdap or Td without TT*	8,370	108,030	11,857	104,543
≥ 1 Tdap or Td or TT	8,785	110,822	12,317	107,470
≥ 1 Tdap without Td and TT	6,844	90,445	9,922	87,367
≥ 1 Td without Tdap and TT	1,435	16,253	1,785	15,903
≥ 1 TT without Tdap and Td	339	2,229	323	2,245
<i>HZ Vaccination versus Unvaccinated</i>				
≥ 1 Zostavax or Shingrix*	16,106	182,741	21,417	177,430
Completed Shingrix (2 doses) without Zostavax ^a	358	30,798	1,532	29,624
≥ 1 Zostavax with 2 doses Shingrix	92	7,608	646	7,054
≥ 1 Shingrix without Zostavax ^a	789	53,091	2,863	51,017
≥ 1 Zostavax without Shingrix	15,298	128,967	16,148	128,117
<i>Pneumococcal Vaccination versus Unvaccinated</i>				
≥ 1 PCV-13 or PPSV-23*	20,583	239,454	28,558	231,479
≥ 1 PCV-13 without PPSV-23 ^b	13,425	149,606	18,342	144,689
≥ 1 PPSV-23 without PCV-13	8,072	101,854	11,325	98,601

The look back period was defined as 2009–2011 and the follow up period as 2011–2019, with the exceptions noted below. Each analysis performed includes a unique unvaccinated cohort. The unvaccinated cohort refers to patients who are not vaccinated with the specified vaccine for that analysis; patients may have still received other vaccinations that were not the exposure variable. For example, for the Zostavax or Shingrix vaccine analysis, the unvaccinated group would be those who did not receive a at least one dose of Zostavax or Shingrix; however, this group could have received a Tdap/Td/TT or pneumococcal vaccine. *Denotes a main analysis. ^aThe analysis was performed using a look back period of 2009–2017 and the follow up period of 2017–2019. ^bThe analysis was performed using a look back period of 2009–2014 and the follow up period of 2014–2019. AD (+), Alzheimer's disease during the follow-up; AD (-), did not develop incident AD during follow-up; PCV-13, pneumococcal conjugate vaccine 13; HZ, Herpes zoster; ICD, International Classification of Diseases; PPSV, Pneumococcal polysaccharide vaccine 23; PSM, Propensity score matching; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid. Table adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through <http://dx.doi.org/10.3233/JAD-220361>.

476 and pneumococcal vaccination (RR: 0.73; 95% CI:
477 0.70–0.75). A comparison between the sensitivity
478 analysis results and the main results are displayed
479 in Table 4.

480 DISCUSSION

481 Using a retrospective cohort study, we found that
482 there were significant decreases in AD for patients 65
483 and older who received a Tdap/Td vaccination (30%),
484 an HZ vaccination (25%), or a pneumococcal vac-
485 cination (27%) versus separate unvaccinated groups
486 over an 8-year period. Our main analysis results are
487 consistent with other studies of these three vaccines
488 suggesting a possible preventative effect on dementia
489 [48]. For our secondary objective (i.e., if various types
490 of HZ or pneumococcal vaccines affect the risk of AD
491 differently), we also found decreases in AD in people
492 who received at least one dose of the live-attenuated
493 HZ vaccine (Zostavax) (8% over an 8-year period),

at least one dose of the recombinant HZ vaccine
(Shingrix) (73% over a 2-year period), the conjugated
pneumococcal vaccine (i.e., PCV-13) (27% over a 5-
year period), and the polysaccharide pneumococcal
vaccine (i.e., PPSV-23) (29% over an 8-year period)
when compared to unvaccinated groups.

Mechanisms and vaccine types

The mechanisms that underlie the reduced inci-
dence of AD through vaccinations in our cohort need
to be explored further. There may be mitigation of
disease-specific mechanisms through the prevention
of the disease (e.g., herpes zoster) or the reduction
in the severity of the disease that have a diminishing
effect on the risk of AD. However, because the results
from our previous study with influenza vaccination
[38] and now the results from this study demon-
strate that multiple vaccinations are associated with
a reduced incidence of AD, it may be that there are

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Table 3
ATT Estimation for Vaccination During the Follow-up Period

Exposure Definition	Risk ratio (95% CI)	ARR (95% CI)	NNT	E-value
<i>Tdap, Td, and/or TT Vaccination versus Unvaccinated</i>				
≥ 1 Tdap or Td without TT *	0.7059 (0.6876–0.7247)	0.0300 (0.0277–0.0322)	33	2.1848
≥ 1 Tdap or Td or TT	0.7238 (0.7055–0.7427)	0.0302 (0.0280–0.0324)	33	2.1076
≥ 1 Tdap without Td and TT	0.6804 (0.6612–0.7003)	0.0330 (0.0306–0.0355)	30	2.3004
≥ 1 Td without Tdap and TT	0.8039 (0.7533–0.8579)	0.0198 (0.0139–0.0257)	51	1.7947
≥ 1 TT without Tdap and Td	1.0495 (0.9107–1.2096)	0.0062 (–0.0121–0.0245)	–	–
<i>HZ Vaccination versus Unvaccinated</i>				
≥ 1 Zostavax or Shingrix*	0.7520 (0.7378–0.7666)	0.0267 (0.0249–0.0285)	37	1.9919
Completed Shingrix (2 doses) without Zostavax ^a	0.2337 (0.2085–0.2619)	0.0377 (0.0350–0.0404)	26	5.8925
≥ 1 Zostavax with 2 doses Shingrix	0.1424 (0.1148–0.1766)	0.0719 (0.0653–0.0786)	14	13.5243
≥ 1 Shingrix without Zostavax ^a	0.2756 (0.2550–0.2979)	0.0385 (0.0363–0.0406)	26	4.3841
≥ 1 Zostavax without Shingrix	0.9274 (0.9087–0.9466)	0.0083 (0.0060–0.0105)	120	1.3687
<i>Pneumococcal Vaccination versus Unvaccinated</i>				
≥ 1 PCV-13 or PPSV-23*	0.7304 (0.7186–0.7424)	0.0297 (0.0282–0.0312)	34	2.0799
≥ 1 PCV-13 without PPSV-23 ^b	0.7319 (0.7167–0.7475)	0.0302 (0.0281–0.0322)	33	2.0736
≥ 1 PPSV-23 without PCV-13	0.7127 (0.6940–0.7320)	0.0295 (0.0273–0.0319)	34	2.1549

The look back period was defined as 2009–2011 and the follow up period as 2011–2019, with the exceptions discussed below. Each analysis performed included a unique and different unvaccinated cohort. The unvaccinated cohort refers to patients who are not vaccinated with the specified vaccine for that analysis; patients may have still received other vaccinations that were not the exposure variable. For example, for the Zostavax or Shingrix vaccine analysis, the unvaccinated group would be those who did not receive a at least one dose of Zostavax or Shingrix; however, this group could have received a Tdap/Td/TT or pneumococcal vaccine. *Denotes a main analysis. ^aDistinguishes that the analysis was performed using a look back period of 2009–2017 and the follow up period of 2017–2019. ^bCharacterizes that the analysis was performed using a look back period of 2009–2014 and the follow up period of 2014–2019. AD, Alzheimer's disease; ARR, Absolute risk reduction; CI, Confidence Interval; HZ, Herpes zoster; ICD, International Classification of Diseases; NNT, Number needed to treat; PCV-13, pneumococcal conjugate vaccine 13; PPSV, Pneumococcal polysaccharide vaccine 23; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid.

Table 4
Effect size estimates comparing the sensitivity and main analysis results

Exposure Definition	Risk ratio (95% CI) Main Analysis	Risk ratio (95% CI) Sensitivity Analysis
≥ 1 Tdap or Td without TT	0.7059 (0.6876–0.7247)	0.6783 (0.6427–0.7161)
≥ 1 Zostavax or Shingrix	0.7520 (0.7378–0.7666)	0.7122 (0.6860–0.7395)
≥ 1 PCV-13 or PPSV-23	0.7304 (0.7186–0.7424)	0.7316 (0.7069–0.7572)

For both groups of analyses, we compared two cohorts (vaccinated and unvaccinated) identified using propensity score matching (PSM). For the main analysis (the same analysis presented in Table 3), the look back period was defined as 2009–2011 and the follow up period as 2011–2019. The sensitivity analysis look back period was split into two halves: 2009–2010 for identification of patients who take statin medications, and 2010–2011 for determining which of those patients had at least 80% proportion of days covered by statin therapy. The follow up period spanned from 2011–2019. CI, Confidence Interval; PCV-13, pneumococcal conjugate vaccine 13; PPSV-23, Pneumococcal polysaccharide vaccine 23; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid.

512 other, more general mechanisms. These other mech-
513 anisms could include innate immune system training
514 and lymphocyte-mediated cross-reactivity, descrip-
515 tions of which are both expanded upon in our previous
516 influenza vaccination manuscript [38].

517 Another factor that should be considered is the age
518 of patients when they receive their vaccines against
519 tetanus and diphtheria, with and without pertussis;
520 herpes zoster; and, pneumococcus. The immuno-
521 genicity of vaccines is reduced in patients as they age,
522 therefore there is a decrease in vaccine efficacy [49].

523 Analyses in Supplementary Figure 1A-C) illustrates
524 that the incidence of AD increases with age; how-
525 ever, the risk of developing AD is still diminished
526 in association with the use of Tdap/Td (Supplemen-
527 tary Figure 1A), HZ (Supplementary Figure 1B), and
528 pneumococcal (Supplementary Figure 1C) vaccina-
529 tions. As a result, it appears to be advantageous for
530 people 65 years and older to receive these vaccina-
531 tions to prevent disease and to reduce the risk of AD.
532 Vaccines have been created and have been shown to
533 provide a more robust immune response in patients

534 65 years and older, including recombinant and con-
535 jugated vaccines.

536 *Herpes Zoster: Live-attenuated versus*
537 *recombinant*

538 Two HZ vaccines have been approved for use
539 in the United States. Zostavax was recommended
540 from 2009–2020. Like the vaccines against vari-
541 cella recommended in children for protection against
542 primary varicella infection, Zostavax contains a live-
543 attenuated form, but at a much higher titer than
544 currently approved pediatric varicella vaccines [50].
545 Shingrix, on the other hand, is a recombinant vaccine
546 against HZ that contains both the varicella-zoster gly-
547 coprotein E (gE) antigen and the AS01_B adjuvant
548 system [51]. The vaccine utilizes gE as an anti-
549 gen since it is the glycoprotein that varicella-zoster
550 exhibits most frequently; this glycoprotein is also the
551 target for varicella-zoster CD4+ T cell response [51].
552 Both Zostavax and Shingrix are capable of eliciting
553 T-cell-independent and T-cell-dependent responses;
554 however, the efficacy of protection provided by these
555 two vaccines differs significantly. The efficacy of
556 Zostavax in HZ risk reduction was only slightly over
557 50% in patients 60 years and over with previous vari-
558 cella zoster infection, and the HZ protection provided
559 by this live vaccine reduced after approximately five
560 years [52]. An advantage to Zostavax was that it was
561 given as a one-time dose. Shingrix, in contrast, has
562 an efficacy of 97.2% in reducing HZ risk and, unlike
563 Zostavax, can be safely administered to immunocom-
564 promised patients [15, 52]. Shingrix is administered
565 over two doses, with protection lasting approximately
566 seven years [21]. It is now recommended by the CDC
567 that those who previously received Zostavax also
568 receive Shingrix [7].

569 *Pneumococcal: Polysaccharide versus*
570 *conjugated*

571 For the unconjugated polysaccharide vaccine (i.e.,
572 PPSV), the antigenic component consists of polysac-
573 charides from the capsule of pneumococcus [25].
574 These vaccines can only produce a limited immune
575 response because the polysaccharides are unable to
576 be loaded into the major histocompatibility complex
577 (MHC) cavity; therefore, although they elicit produc-
578 tion of IgM antibodies by B cells, polysaccharide
579 vaccines cannot induce T-cell-dependent responses
580 and thus lack several effects of peptide-containing
581 vaccines, including the production of memory B cells,

582 antibody class switching, or affinity maturation [37].
583 In contrast, conjugated vaccines incorporate capsular
584 polysaccharides covalently bound to a carrier pro-
585 tein in order to elicit a more robust immune response
586 [25]. For PCV13, the carrier is a genetically detox-
587 ified form of the diphtheria toxin protein [53]. The
588 conjugate allows both the polysaccharide and the
589 carrier protein to be loaded into the MHC-II cavity,
590 thus allowing for activation of helper T cells [37].
591 This T-cell-dependent pathway enables the produc-
592 tion of memory B cells and non-IgM antibodies (e.g.,
593 IgG, IgE). Therefore, the PCV is thought to have a
594 more sustained immune response, overall, when com-
595 pared with PPSV. The current recommendations have
596 expanded the use of PCV vaccinations. PCV15 and
597 PCV20 were approved by the FDA in 2021. It is now
598 recommended that patients 65 years and older receive
599 either a dose of PCV20, or a dose of PCV15 followed
600 by a dose of PPSV23 one year later.

601 *Public health and an addition to a clinician's*
602 *toolkit*

603 This study suggests that it is important for patients
604 to have ready access to routine adult vaccinations.
605 Over the past 15 years there has been an incremental
606 increase in vaccine coverage every year for vaccines
607 preventing tetanus and diphtheria, with and with-
608 out pertussis; herpes zoster; and pneumococcus for
609 patients 19 years and older in the United States [54].
610 For example, from 2008 to 2018, the rate of patients
611 who received an HZ vaccine increased significantly
612 from 6.7% to 34.8% [55]. Also, it is estimated that
613 58.9% of adults 65 and older were exposed to a
614 tetanus-containing vaccine between 2008 and 2018
615 [54]. The increase continued until the COVID-19
616 pandemic and subsequent shutdowns. During this
617 period, there were reductions in the administration of
618 adult vaccines, with the HZ vaccination rates drop-
619 ping by 89% and Tdap/Td rates by 70% [56]. Despite
620 the shutdowns and physical isolation, elderly patients
621 are still at risk for developing HZ because the dis-
622 ease is caused by a reactivation of varicella-zoster,
623 as opposed to a new microbial exposure [57]. This
624 reactivation is also associated with an increase in
625 dementia risk [18]. It is estimated that 3.9 million
626 HZ vaccinations were missed in 2020 due to COVID-
627 19 shutdowns, accounting for an estimated 31,945
628 cases over two years [57]. It is not yet known whether
629 the decrease in vaccination coverage and an increase
630 in vaccine preventable diseases will affect dementia
631 rates.

632 The clinician-patient relationship, as well as the
633 understanding and knowledge of vaccinations are
634 important parts of a patient's decision to refuse or
635 accept a vaccine [58]. The value of vaccination, as we
636 have demonstrated, goes beyond preventing infection
637 or severe disease from that infection. In fact, there
638 are multiple non-specific potential benefits of vacci-
639 nation such as improving asthma severity [59], AD
640 prevention [38, 48], and use as an adjuvant cancer
641 therapy (even though it is administered through a non-
642 traditional route) [60, 61], among others. Nicholls et
643 al. [62] found that by emphasizing disease suscepti-
644 bility and vaccine efficacy/benefits, patients may be
645 more willing to receive vaccinations in the future.
646 By discussing these added non-specific advantages
647 of vaccination with patients, clinicians may be able
648 to convince hesitant patients that the benefits of vac-
649 cination with one of the routine adult vaccinations
650 outweighs the risks.

651 *Sensitivity analysis*

652 In order to assess the extent to which healthy
653 adherer bias influenced our results, we performed a
654 similar sensitivity analysis to Wiemkem et al. [30]
655 in which we only included patients who were adher-
656 ent to statin medications. Because the results from
657 the sensitivity analysis were similar to those results
658 within the original main analysis, we concluded that
659 our study findings showing the association between
660 exposure to adulthood vaccinations and a decreased
661 incidence of AD were not influenced by healthy
662 adherer bias.

663 *Limitations*

664 There are several limitations to our study. 1)
665 Optum's CDM only includes patients with both med-
666 ical and prescription coverage. Therefore, those with
667 medical insurance but no prescription coverage and
668 vice versa were not included in this study, limiting
669 the generalizability of our findings. The CDM may
670 also lack vaccine exposures for patients who pay out
671 of pocket for their vaccinations; however, if patients
672 were to use their insurance card for vaccinations, then
673 their vaccination would be recorded. 2) Because our
674 study is retrospective in nature, and the main objec-
675 tive for data collection was not adult vaccinations
676 and AD diagnosis, there is risk for misclassifica-
677 tion bias. 3) For the outcome variables, we attempted
678 to control for misclassification by including patients
679 that had no AD-related diagnoses or medications or

680 that had at least two healthcare records with some
681 combination of AD-related diagnoses or medica-
682 tions; patients with only one AD-related diagnosis or
683 medication record were excluded to minimize mis-
684 classification due to clerical errors. Furthermore, we
685 included patients with the diagnosis code of "senile"
686 or unspecified dementia as patients with AD. There-
687 fore, even though it is known that 60–70% of patients
688 diagnosed with dementia have AD [41], we are unsure
689 of how many patients actually have AD in the CDM.
690 4) Another consideration and potential limitation of
691 this study was the decision to count vaccinations as
692 valid exposures as long as they occurred at least one
693 day before the initial AD diagnosis. 5) The risk of
694 immortal time bias is another important considera-
695 tion in this study. To provide a measurement of the
696 time at-risk among vaccinated patients that does not
697 include the period of "immortality" they experience
698 between the start of the follow-up period and the date
699 of vaccination, the distribution of follow-up duration
700 (Supplementary Table 3) for vaccinated patients was
701 defined as the time from vaccine receipt (rather than
702 the start of the follow-up period) to date of incident
703 AD, death, or censoring (i.e., the patient's last record
704 before the end of the follow-up period). As shown
705 in Supplementary Table 3, the median at-risk period
706 for the vaccinated group was greater than that of the
707 unvaccinated group in most of the analyses, a dis-
708 parity that should be considered when interpreting
709 the results of this study. 6) Although the SMD for
710 each of the post-PSM covariates was <0.10 , which
711 meets the conventional definition for adequate covari-
712 ate balance between the vaccinated and unvaccinated
713 groups [44], the presence of higher disease burden
714 within the vaccinated groups is noted. If there is a bias
715 present from this difference in comorbidity distribu-
716 tions, it would predispose our analysis against finding
717 a protective effect. 7) While our study did control for
718 some sociodemographic and comorbid conditions,
719 we could not control for other behaviors and char-
720 acteristics that may influence vaccination acceptance
721 or refusal, such as marital status, educational level,
722 and income status [58, 62]. We reported E-values for
723 each of the point estimates to provide an estimate
724 of how strongly an unmeasured confounder would
725 need to be associated with both the exposure and
726 outcome (adjusting for the same covariates as this
727 analysis) in order to render the point estimate sta-
728 tistically insignificant. 8) Moreover, some vaccines
729 were approved and recommended for use in the gen-
730 eral population during our study period. Shingrix is
731 an example: it was introduced in 2017, two years

732 before the end of our study period. While we were
 733 able to move the follow-up period to start in 2017,
 734 this did result in a limited period of follow-up (2
 735 years) for patients to receive Shingrix and to study
 736 its impact on AD incidence. 9) Finally, exposure to
 737 diseases such as HZ and influenza have been asso-
 738 ciated with an increased incidence of AD; however,
 739 we did not control for this in our models because
 740 of the difficulty in obtaining an accurate diagnosis
 741 for infections, such as influenza, which may lead
 742 to misclassification. Relatedly, we cannot be certain
 743 whether our observations relate to reduced infection
 744 rates versus vaccine-related effects on the immune
 745 system.

746 CONCLUSIONS

747 Our study demonstrated a statistically signifi-
 748 cant association between the reduction of AD after
 749 exposure to several routinely administered adult vac-
 750 cinations, including Tdap/Td (30%), HZ (25%), and
 751 pneumococcal (27%), for patients 65 and older with
 752 an 8-year follow-up. We also demonstrated that there
 753 are differences in the association of AD risk between
 754 live-attenuated (8%) and recombinant (73%) vacci-
 755 nations for HZ; however, the AD risk is similar for the
 756 pneumococcal conjugate (27%) and polysaccharide
 757 (29%) vaccine types. More work is needed to con-
 758 firm these findings, including a prospective study to
 759 specifically measure the impact of vaccines on AD;
 760 due to ethical concerns about withholding an impor-
 761 tant method of preventing infection, a randomized
 762 controlled trial to assign people to placebo or immu-
 763 nization groups would not be feasible. Our previous
 764 study's finding that the influenza vaccination is asso-
 765 ciated with a significant reduction in AD risk, and
 766 now finding three other sets of vaccines that are also
 767 associated with a reduced incidence of AD suggests
 768 that vaccines work through another, more general
 769 mechanism. Further work, perhaps in animal mod-
 770 els, is needed to understand how the risk of AD is
 771 being decreased by the influenza vaccine and several
 772 routine adult vaccinations.

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 794 interest to report.

DATA AVAILABILITY

The authors cannot make data and study materi- 796
 797 als available to other investigators due to licensing
 798 restriction; however, interested parties can license the
 799 CDM by contacting Optum.

SUPPLEMENTARY MATERIAL

The supplementary material is available 801
 802 in the electronic version of this article:
 803 <https://dx.doi.org/10.3233/JAD-221231>.

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