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# Pneumococcal Vaccination Lowers the Risk of Alzheimer's Disease: A Study Utilizing Data from the IBM® MarketScan® Database

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**Abstract.** Previous studies demonstrated an association between influenza vaccination and the likelihood of developing Alzheimer's disease. This study was aimed at assessing whether pneumococcal vaccinations are associated with a lower risk of Alzheimer's disease based on analysis of data from the IBM® MarketScan® Database. Vaccinated and unvaccinated matched cohorts were generated using propensity-score matching with the greedy nearest-neighbor matching algorithm. The conditional logistic regression method was used to estimate the relationship between pneumococcal vaccination and the onset of Alzheimer's disease. There were 142,874 subjects who received the pneumococcal vaccine and 14,392 subjects who did not. The conditional logistic regression indicated that the people who received the pneumococcal vaccine had a significantly lower risk of developing Alzheimer's disease as compared to the people who did not receive any pneumococcal vaccine (OR=0.37; 95%CI: 0.33-0.42; P-value < .0001). Our findings demonstrated that the pneumococcal vaccine was associated with a 63% reduction in the risk of Alzheimer's disease among US adults aged 65 and older.

**Keywords.** healthcare data, Alzheimer's disease, pneumococcal vaccines, IBM® MarketScan® Database

## 1. Introduction

Alzheimer's disease (AD), the prevalent form of dementia, is the sixth leading cause of death for US adults and one of the major causes of death at the oldest ages, ranking fifth cause of death for those aged 65 and over and third for those aged 85 and over [1]. Thus, age has long been identified as the major risk factor for AD. A recent review showed that AD is more common in people with infections, such as certain viruses, bacteria, or fungal infections [2]. It was suggested that the immune system changes occurring in older people could heighten their susceptibility to infections. Even though influenza immunizations have been shown to be associated with a decreased risk of dementia [3-5], it is not yet clear whether infections might directly result in AD or cause accelerated progression of this disease. According to a recent research report [6], individuals who

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received at least six influenza vaccines had a significantly lower risk of developing AD and dementia than those who did not.

Though the association between influenza vaccinations and AD has been discussed in number of articles [4-5], limited information exists on similar association between pneumococcal vaccinations and AD. The goal of this study was to investigate whether pneumococcal vaccinations are associated with lower risk of Alzheimer's disease based on analysis of data from IBM® MarketScan® Database.

## 2. Methods

### *2.1. Study design*

We utilized data from the IBM® MarketScan® Commercial and Medicaid claims databases from 2013 to 2019. Specifically, the follow-up period was three years, starting from September 1, 2016, to August 31, 2019, and the look-back period was three years, starting on September 1, 2013, to August 31, 2016. Subjects were excluded if they met any of the following criteria: 1) age less than 65 years old at the start of the follow-up; 2) diagnosis of mild cognitive impairment (MCI), encephalopathy, or dementia of any cause during the look-back period; 3) prescription for medications indicated for AD (including donepezil, galantamine, rivastigmine, or memantine) during the look-back period; 4) had influenza vaccine during the entire follow-up period and look-back period.

The outcome was the incidence of AD, determined by two or more AD-related medical records, which were either the record of the AD diagnosis or a claim for an AD medication prescription during the follow-up period. In addition, the date of AD onset was established using the earliest date of a prescription claim or medical record relating to AD. The pneumococcal vaccination exposure cohort was defined as subjects who administered one dose of PCV13 (Prevnar13®) followed by one dose of PPSV23 (Pneumovax®) or one dose of PCV20 (Prevnar20®). The unvaccinated cohort included subjects who did not receive any pneumococcal vaccine (e.g., PCV13, PCV20, PPSV23) during the follow-up period. Moreover, subjects were excluded if they were given pneumococcal vaccination after the AD's onset date.

The covariates included age, sex, physical and psychiatric comorbidity (i.e., asthma, atrial fibrillation, or flutter, B12 deficiency, congestive heart failure, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, ischemic heart disease, obesity, traumatic brain injury, type II diabetes, stroke, alcohol use disorder, anxiety disorder, depression, substance use disorder, and tobacco use). The last measurement within the look-back period was used as the baseline. The subject age was divided into three groups, 65-74 years old, 75-84 years old, and 85 years and older.

We did not account for any potential interaction between influenza and pneumococcal vaccination, considering the fact that older adults who have already administrated pneumococcal vaccination may get an influenza vaccine each year as the flu increases the likelihood of contracting the pneumococcal disease. In this paper, we limited our investigation to individuals who had never received the flu shot during the observation period.

### 2.2. Statistical analysis

Using a logistic regression model that accounted for all baseline characteristics, propensity score matching (PSM) generated matched sets of vaccinated and unvaccinated subjects that share a similar value of the propensity score on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. A greedy, nearest-neighbor matching algorithm was employed to form pairs of vaccinated and unvaccinated cohorts at the ratio of 1:1. Then standardized mean difference (SMD), which compares the difference in means in units of the pooled standard deviation [7], was employed in balance diagnostics for comparing the distribution of baseline covariates between two cohorts in PSM sets.

The association between receiving pneumococcal vaccines and being diagnosed with AD was then assessed using conditional logistic regression, adjusting for all covariates, including age, sex, and comorbidities during the look-back period.

All probabilities were analyzed in SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p-value of $< 0.05$ was considered as statistically significant.

## 3. Results

The study used data from the 2013-2019 IBM® MarketScan® Commercial and Medicaid claims Databases to investigate the association between pneumococcal vaccination and the risk of developing Alzheimer's disease (AD). A total of 14,395 (9.15%) pneumococcal-vaccinated subjects, and 142,874 (90.85%) unvaccinated subjects were chosen based on the eligibility criteria. PSM was used to balance the baseline covariates between the two groups, resulting in 14,392 subjects in each cohort after matching.

Table 1 presented the summary statistics of continuous baseline covariates (i.e., age) and prevalence of binary baseline covariates between vaccinated and unvaccinated subjects in the study sample before and after PSM. The prevalence of binary variables was compared using a Chi-squared test, while a standard two-sample t-test was used to compare continuous baseline covariates. The standardized difference described the comparison of means and prevalence of baseline covariates between subjects in two cohorts in a propensity-score matched sample. In the PS-matched sample, 2.72% of subjects who received the pneumococcal vaccine developed AD during the follow-up period, compared to 8.04% of unvaccinated subjects.

The main analysis estimated the odds ratio (OR) of developing AD between vaccinated and unvaccinated subjects in the PSM sample using conditional logistic regression. (Table 2). The OR was 0.37 (95% CI: 0.33-0.42; P-value $< .0001$) either in unadjusted or adjusted analysis controlling for age, sex, and comorbidity. The results suggested that receiving the pneumococcal vaccine could significantly lower the risk of developing AD compared to not receiving the vaccine.

## 4. Discussion

We analyzed the association between the pneumococcal vaccine and the development of AD following the vaccine administration in older adults who didn't receive flu vaccine during the entire observation period. We found that pneumococcal vaccine could reduce

the risk of AD by 63%. Furthermore, when compared to a previous study of the association between flu vaccine and AD risk, it appears that the pneumococcal vaccine provides a more substantial protective effect against the risk of AD than seasonal flu shots. Our study also demonstrated that adults aged 65 years or older should have more pronounced awareness of positive impact of immunizations on their health.

## 5. Conclusions

This is the first study that used MarketScan®, a nationwide database containing over 30 million insured members annually, to assess the association between pneumococcal vaccine and AD. Our approach's novelty is based on applying the unique big data resource to test the hypothesis that pneumococcal vaccine may have protective properties against AD. Previous retrospective studies used much smaller samples and produced inconclusive results. The primary limitation of this study is the lack of inclusion of certain demographic variables that reflect social determinants of health [8] since the IBM® MarketScan® Database doesn't contain information such as race/ethnicity, socioeconomic status, and health behaviors [9]. Our results are congruent with the recent abstract presentations at the Alzheimer's Association International Conference which used a smaller dataset [10] to show that vaccination against pneumonia between ages 65 and 75 reduced AD risk by up to 40%. The difference in risk reduction estimates could be caused by different observation years, a smaller sample size, not accounting for comorbidities, and a shorter follow-up period.

**Table 1.** Comparison of baseline characteristics between pneumococcal-vaccinated and unvaccinated subjects during the follow-up period, before and after PSM.

| | Before PSM | | | After PSM | | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Vax (-)** | **Vax (+)** | **P-Value** | **Vax (-)** | **Vax (+)** | **P-Value** | **SMD** |
| Sex | | | 0.21 | | | 0.78 | -0.003 |
| Male | 63,399 (44.4%) | 6,465 (44.9%) | | 6,489 (45.1%) | 6,465 (44.9%) | | |
| Female | 79,475 (55.6%) | 7,927 (55.1%) | | 7,903 (54.9%) | 7,927 (55.1%) | | |
| Age | 76.2 (SD=6.44) | 74.7 (SD=5.67) | <.0001 | 74.7 (SD=5.67) | 74.7 (SD=5.67) | 0.93 | -0.001 |
| Asthma | 14,018 (9.8%) | 1,650 (11.5%) | <.0001 | 1,593 (11.1%) | 1,650 (11.5%) | 0.29 | -0.013 |
| Atrial fibrillation | 19,528 (13.7%) | 1,763 (12.3%) | <.0001 | 1,709 (11.9%) | 1,763 (12.3%) | 0.33 | -0.011 |
| B12 deficiency | 6,987 (4.9%) | 748(5.2%) | 0.11 | 704(4.9%) | 748(5.2%) | 0.24 | -0.014 |
| Congestive heart failure | 13,142 (9.2%) | 1,116 (7.8%) | <.0001 | 1,084 (7.5%) | 1,116 (7.8%) | 0.48 | -0.008 |
| COPD | 19,402 (13.6%) | 1,963 (13.6%) | 0.84 | 1,899 (13.2%) | 1,963 (13.6%) | 0.27 | -0.013 |
| Hyperlipidemia | 103,347 (72.3%) | 11,121 (77.3%) | <.0001 | 11,115 (77.2%) | 11,121 (77.3%) | 0.93 | -0.001 |
| Hypertension | 106,913 (74.8%) | 10,800 (75.0%) | 0.58 | 10,802 (75.1%) | 10,800 (75.0%) | 0.98 | 0.001 |
| Ischemic heart disease | 40,683 (28.5%) | 3,891 (27.0%) | 0.0003 | 3,855 (26.8%) | 3,891 (27.0%) | 0.63 | -0.006 |
| Obesity | 18,986 (13.3%) | 2,182 (15.2%) | <.0001 | 2,174 (15.1%) | 2,182 (15.2%) | 0.90 | -0.002 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Traumatic brain injury | 9,195 (6.4%) | 755 (5.3%) | <.0001 | 745 (5.2%) | 755 (5.3%) | 0.79 | -0.003 |
| Type II diabetes | 38,224 (26.8%) | 3,779 (26.3%) | 0.12 | 3,790 (26.3%) | 3,779 (26.3%) | 0.88 | 0.002 |
| Stroke | 22,682 (15.9%) | 2,168 (15.1%) | 0.01 | 2,131 (14.8%) | 2,168 (15.1%) | 0.54 | -0.007 |
| Alcohol use disorder | 1,465 (1.0%) | 162(1.1%) | 0.26 | 131(0.9%) | 162(1.1%) | 0.07 | -0.021 |
| Anxiety disorder | 17,037 (11.9%) | 1,792 (12.5%) | 0.06 | 1,771 (12.3%) | 1,792 (12.5%) | 0.71 | -0.004 |
| Depression | 14,072 (9.9%) | 1,389 (9.7%) | 0.45 | 1,353 (9.4%) | 1,389 (9.7%) | 0.47 | -0.008 |
| Substance use disorder | 916 (0.6%) | 72 (0.5%) | 0.04 | 62 (0.4%) | 72 (0.5%) | 0.39 | -0.009 |
| Tobacco use | 10,009 (7.0%) | 1,157 (8.0%) | <.0001 | 1,113 (7.7%) | 1,157 (8.0%) | 0.34 | -0.012 |

**Table 2.** Estimation of the odds of getting AD among vaccinated and unvaccinated subjects (After PSM).

| Variables | Effect | Odds ratio | 95% CI | | P-Value |
|---|---|---|---|---|---|
| *Crude analysis* | | | | | |
| Pneumococcal vaccination | Pneumococcal (+) vs Pneumococcal (-) | 0.37 | 0.33 | 0.42 | <.0001 |
| *Adjusted analysis* | | | | | |
| Pneumococcal vaccination | Pneumococcal (+) vs Pneumococcal (-) | 0.37 | 0.33 | 0.42 | <.0001 |
| Sex | Female vs Male | 1.19 | 0.73 | 1.94 | 0.490 |
| Age | Age:75-85 vs 65-75 | 1.69 | 0.74 | 3.82 | 0.212 |
| | Age:>=85 vs 65-75 | 1.87 | 0.52 | 6.75 | 0.337 |

## References


[1] Heron M. Deaths: Leading Causes for 2019. Natl Vital Stat Rep. 2021;70(9):1-114.

[2] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec;25(24):5789, doi: 10.3390/molecules25245789.

[3] Zieneldien T, Kim J, Sawmiller D, Cao C. The Immune System as a Therapeutic Target for Alzheimer's Disease. Life (Basel). 2022 Sep;12(9):1440, doi: 10.3390/life12091440.

[4] Imfeld P, Toovey S, Jick SS, Meier CR. Influenza infections and risk of Alzheimer's disease. Brain Behav Immun. 2016 Oct;57:187-192, doi: 10.1016/j.bbi.2016.03.014.

[5] Yang Y, He Z, Xing Z, Zuo Z, Yuan L, Wu Y, Jiang M, Qi F, Influenza vaccination in early Alzheimer's disease rescues amyloidosis and ameliorates cognitive deficits in APP/PS1 mice by inhibiting regulatory T cells. J Neuroinflammation. 2020 Feb;17(1):65, doi: 10.1186/s12974-020-01741-4.

[6] Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med. 2019 Jan;7(1):16.

[7] Ukraintseva S, Yashkin A, Duan M, Akushevich I, Arbeev K, Wu D, Stallard E, Tropsha A, Yashin A. Repurposing of existing vaccines for personalized prevention of Alzheimer's disease: Vaccination against pneumonia may reduce AD risk depending on genotype: Genetics/genetic factors of Alzheimer's disease. Alzheimers Dement. 2020 Dec;16:e046751, doi: 10.1002/alz.046751

[8] Huo X, Finkelstein J. Using Big Data to Uncover Association Between Sildenafil Use and Reduced Risk of Alzheimer's Disease. Stud Health Technol Inform. 2023 May 18;302:866-870.

[9] Finkelstein J, Huo X. The Efficacy of Long-Term Hydroxychloroquine Use in the Prevention of COVID-19: A Retrospective Cohort Study. Stud Health Technol Inform. 2023 Jun 29;305:303-306.

[10] Amran A, Lin Y, Kim Y, Bernstam E, Jiang X, Schulz PE. Influenza vaccination is associated with a reduced incidence of Alzheimer's disease: Epidemiology/Risk and protective factors in MCI and dementia. Alzheimers Dement. 2020 Dec;16:e041693, doi: 10.1002/alz.041693.