

Using Big Data to Uncover Association Between Sildenafil Use and Reduced Risk of Alzheimer's Disease

Xingyue HUO, MSPH^{a,1} and Joseph FINKELSTEIN, MD, PhD^a

^a*Icahn School of Medicine at Mount Sinai, New York, NY, USA*

ORCID ID: Xingyue Huo <https://orcid.org/0000-0002-5135-0292>

Abstract. Alzheimer's disease is a chronic neurodegenerative disease with multiple pathogenesis pathways. Sildenafil, one of the phosphodiesterase-5 inhibitors, was proven to have effective benefits in transgenic Alzheimer's disease mice. The purpose of the study was to investigate the relationship between sildenafil use and the risk of Alzheimer's disease based on the IBM® MarketScan® Database covering over 30 million employees and family members per year. Sildenafil and non-sildenafil-matched cohorts were generated using propensity-score matching with the greedy nearest-neighbor algorithm. The propensity score stratified univariate analysis and the Cox regression model showed that sildenafil use was significantly associated with a 60% risk reduction of developing Alzheimer's disease (HR=0.40; 95%CI:0.38-0.44; P<.0001) compared to the cohort of individuals who did not take sildenafil. Sex-stratified analyses revealed that sildenafil was related to a lower risk of Alzheimer's disease in subgroups of both males and females. Our findings demonstrated a significant association between sildenafil use and a lower risk of Alzheimer's disease.

Keywords. Public health, Alzheimer's disease, Sildenafil, Big data, Epidemiology informatics

1. Introduction

Alzheimer's disease (AD), a chronic neurodegenerative disease with multiple pathogenesis pathways, is the seventh leading cause of death in the United States. Recent studies estimated that AD could lead to dementia in more than 6 million Americans, most of whom are 65 or older. AD is a progressive brain disorder whose symptoms worsen over time and cannot be stopped or reversed. Despite significant advancements in our understanding of AD diagnosis and treatment, AD patients desperately need novel therapeutics to slow the progression of this life-threatening disease.

Sildenafil, a phosphodiesterase (PDE) inhibitor, is an oral medication approved by the US Food and Drug Administration for erectile dysfunction (ED) and pulmonary atrial hypertension (PAH). Sildenafil treats PAH by relaxing the blood vessels in the lungs to increase blood flow, while it also treats ED by increasing blood flow to the penis during sexual stimulation.

¹ Corresponding Author: Xingyue Huo, E-mail: hxy6879@hotmail.com.

It has been found that the temporal cortices of AD patients have significantly increased PDE5 protein levels. A number of studies proved that PDE inhibitors regulate signaling pathways by increasing cAMP and/or cGMP levels. The PDE5 inhibitors could potentially interrupt the NO/cGMP/PKG/CREB signaling pathway by increasing the levels of cGMP [1-2]. PDE5 inhibition has been proposed as a potential therapeutic approach for treating AD. Repurposing existing drugs could potentially result in more effective and accessible therapies for AD patients [3]. The purpose of the study was to investigate the relationship between sildenafil use and a lower risk of Alzheimer's disease using a large database of commercial healthcare claims.

2. Methods

2.1. Study Design

The study utilized the IBM^{○,R} MarketScan^{○,R} Medicare Supplemental Database from 2016 to 2019 containing information on the majority of commercially insured individuals in the U.S. Sildenafil prescriptions were identified using the National Drug Code. AD, as well as other medical diagnoses, were derived from individuals' medical records and determined by the international classification of diseases 10th revision (ICD-10) code. All study participants were required to adhere to the following requirements: 1) they should have continuous insurance coverage from 2016 to 2019; 2) they were 65 years or older at the start of the study; 3) they have never been diagnosed with mild cognitive impairment (MCI), encephalopathy, or dementia of any type; 4) the AD diagnosis date should be after the date the drug under investigation was prescribed.

The participants in the study who received a prescription for Sildenafil were referred to as the sildenafil exposure cohort, while the participants who did not receive a prescription for any medication were referred to as the control cohort. The study's outcome measured the interval between the start of sildenafil use and the diagnosis of AD. Subjects without AD diagnosis were censored from the cohorts at the end of the study period.

The covariates included the Charlson Comorbidity Index (CCI), age, sex, and the U.S. region. The CCI was categorized based on comorbidities in the patient's medical records. Each comorbidity category has a corresponding weight, and the total of weights yields a patient's overall comorbidity score. A higher score indicates a greater likelihood of higher morbidity and mortality. A score of 0 means that no comorbidities were found. As a result, we divided CCI into four groups: 0, 1, 2-3, and greater than or equal to 4. Age was categorized into groups of 65 to 74 and 75 or older.

2.2. Statistical analysis

The propensity-score matching (PSM) method was used to control the confounding factors. First, a propensity score of sildenafil exposure cohorts was calculated for each patient using multivariable logistic regression, adjusting for sex, age, geographic region, and CCI. Then, we performed greedy PSM and generated the matched groups at a ratio of 1:1 using the nearest neighbor within the caliper matching strategy. We set a maximum distance within matches with a caliper of 0.2 standard deviations to improve

the matching performance. Every patient from the sildenafil cohort was matched with a patient from the non-sildenafil cohort who shared the same gender, age, region, and CCI.

Univariate analysis of the demographic variables was used to identify potential significant variables that could be used in model runs. All variables that had a chi-square value or a t statistic associated to a p value of 0.15 or less were considered as potentially significant and retained for the model analysis. Additionally, PS-stratified Cox proportional hazards models were utilized to perform the hazard ratios (HRs) of developing AD between sildenafil cohorts and non-sildenafil cohort.

All analysis were performed using procedures in SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p-value of < 0.05 was considered as statistically significant.

3. Results

All medical record data was collected from the year 2016 to 2019 IBM® MarketScan® Medicare claims Databases. Overall, 17,125 (32.4%) individuals had at least one sildenafil prescription, while 35,652 (67.6%) had never received one. After performing 1:1 PMS, there were 13,587 individuals in each of the sildenafil cohort and non-sildenafil cohort. Out of the 27,174 participants in the PSM-matched cohorts (Table 1), 5,674 (10.7%) were diagnosed with AD. Sildenafil users had a lower risk of developing AD (5.7%) than non-sildenafil users, who had an AD incidence of 9.5%.

Table 1. Description of Characteristics for Univariate Analysis

Characteristics		No AD diagnosis	AD diagnosis	P-value
		N=47,103(89.3%)	N=5,674 (10.7%)	
Sildenafil	Sildenafil	12,812 (94.3%)	775 (5.7%)	<.0001
	Non-sildenafil	12,291 (90.5%)	1,296 (9.5%)	
Charlson Comorbidity Index Score	0	5,004 (96.5%)	181 (3.5%)	<.0001
	1	5,451 (94.6%)	309 (5.4%)	
	2-3	8,885 (91.8%)	797 (8.2%)	
	>=4	5,763 (88.0%)	784 (12.0%)	
Sex	Male	24,795 (92.5%)	2,015 (7.5%)	<.0001
	Female	308 (84.6%)	56 (15.4%)	
Region	NE	12,142 (91.7%)	1,097 (8.3%)	<.0001
	NC	3,569 (92.1%)	306 (7.9%)	
	South	7,583 (93.3%)	546 (6.7%)	
	West	1,809 (93.7%)	122 (6.3%)	
Age	65-74 yrs	18,110 (95.0%)	963 (5.1%)	<.0001
	>=75 yrs	6,993 (86.3%)	1,108 (13.7%)	

We found that sildenafil was significantly associated with a 60% lower risk of developing AD (HR =0.40; 95% CI: 0.38-0.44; P<.0001) (Table 2) in comparison to a cohort of individuals who did not take sildenafil. Particularly, sex-stratified analyses revealed that sildenafil was related to a lower risk of AD in subgroups of both men and

women. According to a crude Cox regression model, sildenafil is found to be significantly associated with a 62% lower risk of AD in men (HR=0.38; 95% CI: 0.35-0.42; $P<.0001$), a 47% lower risk of AD in women (HR=0.53; 95% CI: 0.31-0.90; $P=0.019$), and a 62% lower risk of AD across all genders (HR=0.38; 95% CI: 0.35-0.42; $P<.0001$). The outcome of the Cox regression model with the adjusted CCI score and age is also reliable.

Table 2. Hazard ratios (HR) and 95% CI in unadjusted model and model after adjusting for age, region, CCI score.

Parameter	Sex=Male				Sex=Female				Sex= All			
	HR	95% CI		P-Value	HR	95% CI		P-Value	HR	95% CI		P-Value
<i>Unadjusted model</i>												
Sildenafil vs. Non-drug exposure	0.38	0.35	0.42	<.0001	0.53	0.31	0.9	0.02	0.38	0.35	0.42	<.0001
<i>Adjusted model</i>												
Sildenafil vs. Non-drug exposure	0.40	0.36	0.44	<.0001	0.47	0.27	0.81	0.01	0.40	0.36	0.44	<.0001
65-74 yrs vs. >=75 yrs	0.38	0.35	0.41	<.0001	0.10	0.04	0.23	<.0001	0.38	0.35	0.41	<.0001
1 vs. 0 (No comorbidity)	1.42	1.18	1.70	0.0002	0.47	0.03	7.48	0.59	1.42	1.18	1.70	0.0002
2-3 vs. 0 (No comorbidity)	2.10	1.79	2.47	<.0001	2.96	0.39	22.33	0.29	2.10	1.79	2.47	<.0001
>=4 vs. 0 (No comorbidity)	3.08	2.62	3.63	<.0001	1.83	0.25	13.66	0.56	3.08	2.62	3.63	<.0001

4. Discussion

We analyzed the association between the sildenafil use and the risk of AD in older adults aged 65 years or older and then found that sildenafil could reduce the risk of AD by 60%. Our study also suggests that sildenafil could be a promising potential candidate drug in the treatment of AD. More randomized clinical trials of sildenafil in patients with AD are warranted in the future.

Several studies have found that PDE5 inhibitors can modestly increase cerebral blood flow at rest in patients with cognitive impairment but did not adequately address the effects of sildenafil in AD [4-5]. In addition, sildenafil is an effective medication for treating ED. As per studies, the risk factors for older men who need sildenafil to treat ED are cardiovascular disease, hypertension, diabetes mellitus, tobacco use, hyperlipidemia, metabolic syndrome, and depression [6]. The recent meta-analysis of the potential role of PDE-5 inhibitors in the treatment of dementia corroborated our results [9].

Therefore, several analyses need to be conducted regarding sildenafil and AD in different study cohorts [7]. Cox regression analyses were successfully used to estimate the hazard rate (HR) for use of ED medications, controlled for multiple time-varying covariates in previous studies [7-8]. In addition, we plan to conduct further analyses to

see if other FDA-approved medications in the PED 5 inhibitor class, such as Tadalafil, may have comparable effects in lowering the risk of Alzheimer's disease.

5. Conclusion

This is the first study that used MarketScan, a nationwide database containing over 30 million insured members annually, to assess the association between sildenafil usage and Alzheimer's disease. Our approach's novelty is based on applying the unique big data resource to test the hypothesis that sildenafil may have protective properties against Alzheimer's disease. Previous retrospective studies used much smaller samples and produced contradicting results [3, 7-8]. Inclusion of the Charlson Comorbidity Index helped with accounting for multiple comorbidity burden in the target population. After adjusting for the relevant confounders, the Cox regression model showed that sildenafil use was significantly associated with a 60% risk reduction of developing Alzheimer's disease.

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