

Dementia and PDE5 inhibitors: A retrospective cohort study of veterans

Vikas Singh

Kansas City VA Medical Center

Rishi Sharma

University of Missouri–Kansas City

Mukut Sharma

Kansas City VA Medical Center

Thomas Wiegmann

Kansas City VA Medical Center

Ram Sharma

Ram.sharma2@va.gov

Kansas City VA Medical Center

Article

Keywords: Phosphodiesterase type 5 (PDE5) inhibitors, Alzheimer dementia (AD) Vascular dementia, senile dementia, and frontotemporal dementia, veteran study, VHA, VA

Posted Date: October 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11010754/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Dementia is an escalating global public health crisis with profound consequences. Repurposing established medications, such as phosphodiesterase type 5 (PDE5) inhibitors, offers a promising avenue for mitigating dementia risk and progression.

Methods

This retrospective cohort study utilized national data from the U.S. Department of Veterans Affairs to examine whether PDE5 inhibitor use was associated with reduced dementia incidence and delayed dementia diagnosis among 878,240 male Veterans with erectile dysfunction (ED). Propensity score matching generated well-balanced exposed (PDE5 inhibitor users) and unexposed control groups. Baseline dementia prevalence was similarly low in both groups.

Results

During longitudinal follow-up, new diagnoses of Alzheimer, frontotemporal, and vascular dementia were significantly lower among PDE5 inhibitor users than among controls, with odds ratios (ORs) of 0.91 for Alzheimer dementia (95% CI, 0.85–0.96), 0.83 for frontotemporal (95% CI, 0.69–1.00), and 0.84 for vascular dementia (95%, CI 0.79–0.89). Time-to-diagnosis analyses and Kaplan–Meier curves further demonstrated that PDE5 inhibitor exposure was associated with substantial delays in dementia onset, ranging from two to three years across several subtypes. Associations persisted across sensitivity analyses.

Conclusions

The observed protective effect may be explained by vascular and neuroprotective mechanisms unique to PDE5 inhibitors. Limitations include reliance on administrative codes, lack of adherence data, and restriction to a male Veteran population with ED, which may limit generalizability. Nonetheless, these findings highlight the potential of PDE5 inhibitors to reduce dementia incidence and delay its onset, warranting further prospective research and possible clinical trials to explore this novel therapeutic strategy.

INTRODUCTION

Dementia represents one of the most significant public health challenges faced by aging societies. Globally, over 55 million individuals currently live with dementia, and this number is projected to surpass 130 million by 2050 as populations continue to age [1, 2]. The disorder imposes profound personal

consequences on patients and families, including progressive cognitive decline, loss of independence, and substantial caregiver burden [3]. Additionally, dementia generates enormous economic costs through increased healthcare utilization, long-term care, and lost productivity. Worldwide, annual costs of dementia care are estimated to exceed one trillion U.S. dollars and are expected to rise substantially in the coming decades [1, 4]. Dementia encompasses a range of neurodegenerative disorders characterized by the progressive decline in cognitive function. Alzheimer's disease (AD) is the most common form, followed by vascular dementia (VaD), Lewy body dementia, and frontotemporal dementia [5, 6]. Currently, there is no cure for dementia, and treatment options are limited to symptomatic relief and modest attenuation of disease progression. Therefore, strategies capable of delaying the onset of dementia by even a few years could yield significant benefits at both the individual and societal levels [7]

Phosphodiesterase type 5 (PDE5) inhibitors were originally developed to treat erectile dysfunction and pulmonary arterial hypertension [8, 9]. This class of drugs including sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra), functions by inhibiting the degradation of cyclic guanosine monophosphate (cGMP) and enhancing nitric oxide mediated signaling pathways [10]. PDE5 Inhibitors have recently emerged as a promising therapeutic agent for many other clinical disorders including neurodegenerative disorders and cognition [11 12, 13, 14, 15]. Preclinical studies have highlighted potential mechanisms through which PDE5 inhibitors may exert beneficial effects in dementia. For instance, in animal models of AD, sildenafil has been shown to improve memory and learning by enhancing synaptic plasticity and reducing amyloid-beta ($A\beta$) plaque burden [16, 17]. Furthermore, PDE5 inhibitors are believed to improve cerebral blood flow, which may be particularly advantageous in conditions like vascular dementia, where vascular insufficiency plays a pivotal role [18, 19].

Recent clinical investigations have begun to translate these preclinical findings into human trials. A small-scale study demonstrated that participants receiving 30 mg PFDE 5 inhibitor AR1001 showed favorable changes in AD-related plasma biomarkers compared to placebo [20]. Although the study was limited by its sample size and lack of longitudinal follow-up, multifaceted mechanism of action targeting both neuronal and vascular properties positions PDE5 inhibitors as a promising addition to the current therapeutic potential to improve both patient outcomes and quality of life in dementia care [21]. The goal of this study is to establish an impact of PDE5 inhibitors use on dementia in a large national cohort of Veterans diagnosed with ED and received care from the Department of Veterans Affairs during the period of years 1998–2024.

METHODS

Data Source and Study Design:

This retrospective cohort study utilized data from the U.S. Department of Veterans Health Administration (VHA) Corporate Data Warehouse (CDW), a national electronic health record and administrative database [22] accessed only through the Veterans Administration Informatics and Computing Infrastructure (VINCI). The Institutional review board (IRB) of the Kansas City Veterans Administration

Medical Center (KCVAMC) reviewed and approved the study and waived the requirement for informed consent because deidentified data were used. The data was collected from approximately 2.5 million male veterans who received care for erectile dysfunction (ED) within the VA healthcare system during the study period of January 1998 through July 2024. Permission to use de-identified data was granted by the KCVAMC-IRB, as well as through the relevant VINCI DART process for receiving data in assigned VINCI space.

Study Population and Exposure Definition:

Patients with a diagnosis of erectile dysfunction were identified using ICD codes. About 2.6 million patients were prescribed a phosphodiesterase type 5 inhibitor (PDE5i), as determined from VA outpatient pharmacy dispensing records. The index date for exposed individuals was defined as the date of their first recorded PDE5i dispensing during the study period. For the control cohort (Veterans without PDE5i exposure), a comparable index date was assigned by randomly selecting a date from the distribution of PDE5i index dates, ensuring temporal alignment and reducing calendar-time bias. Patients were required to have documented VA clinical activity prior to the index date to allow for ascertainment of baseline comorbidities.

Outcome Ascertainment:

Clinical events were identified using ICD-9 and ICD-10 diagnosis codes extracted from inpatient and outpatient encounters. All diagnosis codes were date-stamped within the electronic record. Events occurring prior to the index date were classified as prior prevalent (baseline) conditions and were used to characterize comorbidity burden. Events occurring after the index date were classified as new incident outcomes for outcome analyses.

All cardiovascular outcomes were defined as categorical variables (yes/no) based on the presence of at least one qualifying ICD code.

Covariates:

Baseline demographic and clinical variables included age, BMI, follow-up duration, and selected cardiovascular, mental, and other comorbidities identified via ICD codes prior to the index date. Continuous variables were transformed into ordinal categorical variables with clinically meaningful subcategories to facilitate propensity matching.

Missing Data:

Variables derived from ICD coding were treated as binary indicators (present/absent).

Propensity Score Matching:

As documented in Fig. 1, Propensity score matching was performed using SAS (PROC PSMATCH). Covariates included age, BMI, follow-up duration, and selected baseline groupings of cardiovascular and mental disease ICD codes. A one-to-one greedy nearest neighbor matching algorithm without replacement was applied, resulting in 439,120 individuals per cohort.

Statistical Analysis:

Categorical variables were compared using frequency distributions. Associations were expressed as odds ratios (ORs) with 95% confidence intervals. Continuous variables were evaluated using expanded means tests and are presented side by side.

Exposure Definition and Intention-to-Treat Framework:

Medication exposure was defined as the first outpatient dispensing event. Due to the absence of reliable information on medication duration and adherence, an intention-to-treat framework was employed. Any resulting misclassification of exposure status is expected to be non-differential and to bias results toward the null.

RESULTS

Baseline Characteristics of Cohorts:

To minimize differences between the PDE5 inhibitor-treated group and the non-treated control group, propensity score matching was performed [23]. Table 1 outlines the baseline characteristics of the matched cohorts, including age, race, BMI, follow-up duration, type 2 diabetes, and cardiovascular diseases. Most variables became more balanced between the groups, with odds ratios approaching unity.

Dementia Prevalence:

Baseline dementia diagnoses prior to the index date, representing prevalence, are summarized in Table 2. The baseline prevalence of Alzheimer's disease, frontotemporal dementia, vascular dementia, and senile dementia did not differ significantly between the untreated control group and the PDE5 inhibitor-treated group

Dementia Incidence: The incidence of new dementia diagnoses after the index date is summarized in Table 3. New cases of Alzheimer's disease occurred less frequently in the PDE5 inhibitor-treated group compared to the control group. Similar reductions were observed for frontotemporal dementia and vascular dementia, whereas the incidence of senile dementia did not differ between the groups.

Additional Time-to-Diagnosis Analyses:

In addition to comparisons of incident disease frequency, expanded means analyses were conducted to

evaluate the time from index date to dementia diagnosis among individuals who developed dementia during follow-up. Table 4 demonstrates that the PDE5 inhibitor-treated group had a longer average time to dementia diagnosis than the control group. These findings suggest that PDE5 inhibitor use may be associated with a delayed onset of dementia

Effect of PDE-5 Inhibitor Exposure on Rate of Dementia:

Kaplan-Meier (KM) analysis was used to further evaluate the effects of PDE5 inhibitors on the instantaneous event rate of dementia. Each plot describes cumulative incidence, includes hazard ratios, and enumerates the populations at risk. The analyses demonstrate a significant effect of PDE5 inhibitor use on dementia outcomes, with KM curves showing gradual and progressive separation between treatment groups.

Among dementia subtypes, the effect of PDE5 inhibitors was least notable for frontotemporal dementia (Figure 2) but was similarly pronounced for Alzheimer's disease (Figure 3), senile dementia (Figure 4), and vascular dementia (Figure 5), consistent with a vascular component playing a role in Alzheimer's disease. Despite significant mortality observed in the overall study population, the death rate plot (Figure 6) indicates minimal separation between the two groups, underscoring the differences in dementia outcomes.

DISCUSSION

The present study examined the association between phosphodiesterase type 5 (PDE5) inhibitor exposure and subsequent dementia diagnoses in a large national cohort of veterans with erectile dysfunction. Within this clinically homogeneous population, PDE5 inhibitor exposure was associated with a lower incidence of several dementia subtypes, notably Alzheimer's disease, frontotemporal dementia, vascular dementia, and senile dementia.

Another key observation from these analyses is the consistent delay in time to diagnosis observed across dementia outcomes among individuals receiving PDE5 inhibitors. Specifically, delays in dementia diagnoses ranged from two to three years in several categories. Even modest delays in disease onset can therefore lead to meaningful improvements in quality of life.

The Kaplan–Meier analyses further strengthen the clinical relevance of these findings. Unlike simple frequency comparisons or mean time-to-diagnosis analyses, Kaplan–Meier methods assess the cumulative probability of remaining event-free or the cumulative incidence of diagnosis over time, while accounting for variable follow-up duration and censoring. The persistent divergence in survival curves across several dementia subtypes suggests that the observed associations are not limited to isolated early events or statistical artifacts related to unequal follow-up. Instead, the curves indicate a sustained delay in the clinical manifestation of disease among PDE5 inhibitor users.

From a clinical perspective, even modest extensions in dementia-free survival may have substantial implications. Delaying the onset of symptomatic dementia by several years could prolong independent

living, lessen caregiver burden, and reduce healthcare utilization at the population level. The Kaplan–Meier findings therefore enhance the potential public health significance of these associations and support further prospective investigation of PDE5 inhibitors as candidate neurovascular or disease-modifying therapies. The gradual and progressive, rather than abrupt, pattern of separation in the curves is consistent with a biologically plausible modulation of neurovascular or degenerative processes, rather than isolated short-term effects.

These observations are consistent with experimental studies demonstrating that PDE5 inhibition enhances nitric oxide–cGMP signaling, improves endothelial function, and may increase synaptic plasticity and cerebral perfusion [24, 25]. Improvements in vascular signaling may be particularly relevant for vascular dementia and may influence Alzheimer’s disease through vascular mechanisms [26, 27, 28].

The reduction observed in incidence of vascular dementia may reflect improved endothelial and microvascular function associated with PDE5 inhibition [29, 30, 31]. It is noteworthy that erectile dysfunction itself is increasingly recognized as an early manifestation of systemic vascular disease and endothelial dysfunction [7, 31].

PDE5 inhibitors have been widely prescribed for more than two decades and are generally well tolerated [32]. Common mild and transient adverse effects include headache, flushing, and dyspepsia [33, 34], while serious adverse cardiovascular events are rare when contraindications, such as nitrate therapy, are avoided [35, 36, 37]. Given their long clinical history and favorable safety profile, PDE5 inhibitors could represent attractive candidates for therapeutic repurposing should their protective cognitive effects be confirmed.

Limitations of this study include its observational design, potential residual confounding despite propensity matching, reliance on administrative diagnostic coding, and limited information regarding medication adherence or duration of therapy. Furthermore, the cohort consisted entirely of male veterans with erectile dysfunction and may not be generalizable to other populations [38, 39]. Despite these limitations, the present findings contribute to emerging evidence suggesting a possible association between PDE5 inhibitor exposure and a reduced incidence of several dementia subtypes, as well as a delay in the clinical diagnosis of these disorders.

The dementia prevalence and incidence data refer to the combined overall study population, including both PDE5-treated and untreated cohorts, prior to stratified outcome comparison. Within this large VA erectile dysfunction cohort baseline prevalence was approximately 0.17% for Alzheimer’s disease, 0.19% for vascular dementia, and only 0.014% for frontotemporal dementia. These values are markedly lower than expected prevalence estimates in older adults, where overall dementia prevalence in individuals older than 65 years is commonly reported at 7–14%, with Alzheimer’s disease accounting for approximately 60–70% of cases [40, 41]

The relatively low baseline prevalence likely reflects several characteristics of the study design and source population. Individuals with advanced neurodegenerative disease may have been less likely to

receive PDE5 therapy or to meet cohort inclusion criteria, and the erectile dysfunction population may represent a somewhat healthier and more functional subgroup of aging veterans at study entry. In addition, exclusion of prevalent disease and propensity matching procedures enriched the cohort for individuals initially free of overt dementia, thereby strengthening the assessment of incident neurodegenerative outcomes during follow-up.

In contrast, incident dementia rates during longitudinal follow-up were clinically substantial, with approximately 1.3% developing Alzheimer's disease, 1.35% developing vascular dementia, and 3.4% developing senile dementia. These rates are broadly consistent with recent population-based dementia incidence studies, when adjusted for age, sex distribution (including male predominance in some cohorts), and follow-up length, yield rates that are broadly consistent with prevalence estimates in community-dwelling elderly populations [41]. There is no significant association between PDE5 inhibitor use and the risk of incident dementia. Canadian epidemiologic surveillance data report an overall incidence rate of dementia of 14.3 per 1,000 population aged ≥ 65 years, and increasing sharply to ~ 34.2 per 1,000 population annually among adults older than 85 + years [42, 43]

Sex differences are indeed fundamental in interpreting dementia epidemiology. Women generally demonstrate higher Alzheimer's disease incidence and lifetime risk compared to men, particularly after age 80, while vascular dementia incidence tends to be similar or slightly elevated in men [44, 45]. Approximately two-thirds of Alzheimer's disease cases in community populations occur in women [45]. In male-dominated cohorts, such as VA populations, the overall dementia burden relative to mixed-sex community cohorts is expectedly lower, which is biologically plausible given these epidemiologic patterns.

The comparatively high burden of vascular dementia observed in this cohort is especially noteworthy and consistent with proposed endothelial and cerebrovascular mechanisms of PDE5 inhibitors [46]. PDE5 inhibition enhances nitric oxide signaling, endothelial function, cerebral perfusion, and microvascular circulation—mechanisms that may preferentially influence vascular neurodegenerative pathways [47]. The robust vascular dementia signal supports the hypothesis that part of the observed neuroprotective association may be mediated through vascular and endothelial effects rather than solely through direct anti-Alzheimer mechanisms [46, 47].

In summary, the combination of very low prevalence of baseline dementia and substantial incident dementia during follow-up strengthens the study design by reducing the likelihood of reverse causation and allowing clearer evaluation of new-onset neurodegenerative outcomes following PDE5 exposure. These considerations suggest that the cognitive effects of PDE5 inhibitors should be explored in broader populations, including women. Postmenopausal women with evidence of vascular or microvascular disease may represent a biologically plausible population in which to evaluate these agents. Future prospective studies or clinical trials using longer-acting PDE5 inhibitors, such as tadalafil, could determine whether enhancement of neurovascular signaling can delay the onset or progression of vascular-related cognitive decline. Given the rising global incidence of dementia and its substantial

individual and societal costs, further investigation of existing medications with plausible neurovascular mechanisms is warranted

Declarations

The contents of this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conflict of Interest:

Dr. Vikas Singh, Dr. Rishi Sharma, Dr. Mukut Sharma, Dr. Thomas Wiegmann and Dr. Ram Sharma have nothing to disclose.

Ethical Approval:

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. The study was reviewed and approved as an exempt study by the Kansas City VA Medical Center-Institutional Review Board [IRBNet No. 1830170-1]. All data used in this study were de-identified and permission to use data was granted by KCVAMC-IRB. Patient consent was not needed.

Funding:

No funding or sponsorship was received for this study. This work was supported by resources from the Kansas City VA Medical Center and the Midwest Veterans Biomedical Research Foundation.

Author Contribution

Drs. Vikas Singh and Rishi Sharma participated in drafting and revising the manuscript. Dr. Mukut Sharma critically reviewed, revised the manuscript and helped in data interpretation. Dr. Thomas Wiegmann helped with data extraction, cleaning, statistical analysis or interpretation of data. tools. Dr. Ram Sharma conceptualized and designed study, data collection instruments, initial data evaluation, and critically reviewed and revised the manuscript. All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors have reviewed and approved the final manuscript prior to submission.

Acknowledgement

This work was supported by resources from the Kansas City VA Medical Center and the Midwest Veterans Biomedical Research Foundation

Data Availability

Since all data reside in VINCI assigned secure space accessible to the PI and study staff for analysis. Cumulative datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

References

1. World Health Organization. Dementia. (2021). <https://www.who.int/news-room/fact-sheets/detail/dementia>
2. Tiwari, S., Atluri, V., Kaushik, A., Yndart, A. & Nair, M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int. J. Nanomed.* **14**, 5541–5554 (2019).
3. Landeiro, F., Barrows, P., Nuttall Musson, E., Gray, A. M. & Leal, J. Reducing social isolation and loneliness in older people: a systematic review protocol. *BMJ Open.* **7** (5), e013778 (2017).
4. Wimo, A. et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's Dement.* 2017; 13(1), 1–7. (2017).
5. Prince, M., Bryce, R. & Ferri, C. P. World Alzheimer Report 2011: The benefits of early diagnosis and intervention. Alzheimer's Disease International. (2011).
6. Ballard, C. et al. Alzheimer's disease. *Lancet* **377** (9770), 1019–1031 (2011).
7. Xu, Y., Sachdev, P. S. & Lennon, M. J. Vascular cognitive impairment and dementia drug-development pipeline 2025. *Alzheimer's Dement.* **12**, e70263 (2026).
8. Goldstein, I. et al. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl. J. Med.* **338** (20), 1397–1404 (1998).
9. Montani, D. et al. Phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension. *Adv. Ther.* **26** (9), 813–825 (2009).
10. Toque, H. A. et al. Comparative relaxing effects of sildenafil, vardenafil, and tadalafil in human corpus cavernosum: contribution of endogenous nitric oxide release. *Urology* **74** (1), 216–221 (2009).
11. Samidurai, A., Xi, L., Das, A. & Kukreja, R. C. Beyond Erectile Dysfunction: cGMP-Specific Phosphodiesterase 5 Inhibitors for Other Clinical Disorders. *Annu. Rev. Pharmacol. Toxicol.* **63**, 585–615 (2023).
12. Ribaud, G., Ongaro, A., Zagotto, G., Memo, M. & Gianoncelli, A. Therapeutic Potential of Phosphodiesterase Inhibitors against Neurodegeneration: The Perspective of the Medicinal Chemist. *ACS Chem. Neurosci.* **11** (12), 1726–1739 (2020).
13. Singh, N. K., Singh, P., Varshney, P., Singh, A. & Bhushan, B. Multimodal action of phosphodiesterase 5 inhibitors against neurodegenerative disorders: An update review. *J. Biochem. Mol. Toxicol.* **38** (11), e70021 (2024).

14. Ricciarelli, R. Erectile Dysfunction Drugs as Potential Therapy for Cognitive Decline: Preclinical and Translational Evidence. *Cells* **14** (19), 1505 (2025).
15. Kumar, A., Kim, F., Song, D. K. & Choung, J. J. Polypharmacological Potential of Phosphodiesterase 5 Inhibitors for the Treatment of Neurocognitive Disorders. *Aging Dis.* **15** (5), 2008–2014 (2024).
16. Liu, L. et al. Phosphodiesterase 5 inhibitors as novel agents for the treatment of Alzheimer's disease. *Brain Res. Bull.* **153**, 223–231 (2019).
17. Puzzo, D. et al. Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid-beta load in an Alzheimer's disease mouse model. *J. Neurosci.* **29** (25), 8075–8086 (2009).
18. Venkat, P. et al. Sildenafil treatment of vascular dementia in aged rats. *Neurochem Int.* **127**, 103–112 (2019).
19. Pauls, M. M. et al. The effect of phosphodiesterase-5 inhibitors on cerebral blood flow in humans: A systematic review. *J. Cereb. Blood Flow. Metab.* **38** (2), 189–203 (2018).
20. Greeley, D. et al. A phase 2 randomized, placebo-controlled study on the efficacy and safety of AR1001, a phosphodiesterase-5 inhibitor, in patients with mild-to-moderate Alzheimer's disease. *J. Prev. Alzheimers Dis.* **12** (9), 100337 (2025).
21. Hainsworth, A. H., Arancio, O., Elahi, F. M., Isaacs, J. D. & Cheng, F. PDE5 inhibitor drugs for use in dementia. *Alzheimer's Dement.* **9**, e12412 (2023).
22. US Department of Veterans Affairs, Informatics, V. A. & Computing Infrastructure (VINCI). and. ; Retrieved from. (2021). <https://vincicentral.vinci.med.va.gov/>
23. Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivar. Behav. Res.* **46** (3), 399–424 (2011).
24. Zhang, R. et al. Sildenafil (Viagra) induces neurogenesis and promotes functional recovery after stroke in rats. *Stroke* **33** (11), 2675–2680 (2002).
25. Puzzo, D. et al. Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid-beta load in an Alzheimer's disease mouse model. *J. Neurosci.* **29** (25), 8075–8086 (2009).
26. El-Bakly, W. et al. The efficacy and underlying mechanism of phosphodiesterase- 5 inhibitors in preventing cognitive impairment and Alzheimer pathology: A systematic review of animal studies. *Behav. Brain Res.* **372**, 112004 (2019).
27. Sanders, O. Sildenafil for the Treatment of Alzheimer's Disease: A Systematic Review. *J. Alzheimers Dis. Rep.* **4** (1), 91–106 (2020).
28. Zhang, X. et al. The emerging role of nitric oxide in the synaptic dysfunction of vascular dementia. *Neural Regen Res.* **20** (2), 402–415 (2025).
29. Burnett, A. L. Nitric oxide regulation of penile erection: biology and therapeutic implications. *J. Androl.* **23** (5), S20–S26 (2002).
30. Boolell, M. et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int. J. Impot. Res.* **8** (2), 47–52 (1996).

31. Vlachopoulos, C., Ioakeimidis, N., Terentes-Printzios, D. & Stefanadis, C. The triad: erectile dysfunction–endothelial dysfunction–cardiovascular disease. *Curr. Pharm. Des.* **14** (35), 3700–3714 (2008).
32. Madeira, C. R. et al. Efficacy and safety of oral phosphodiesterase 5 inhibitors for erectile dysfunction: a network meta-analysis and multicriteria decision analysis. *World J. Urol.* ; **39**(3):953–962. (2021).
33. Chebbi, A. et al. Oral drug treatments of erectile dysfunction: A AFU/SFMS systematic review. *Fr. J. Urol.* **35** (12), 102962 (2025).
34. Zhong, K., Hu, H., Xiao, L., Fan, G. & Zhang, L. Vascular aging-driven erectile dysfunction: pathophysiological mechanisms and emerging therapies-a narrative review. *Transl Androl. Urol.* **14** (12), 4033–4047 (2025).
35. Jehle, D. V. K. et al. Benefits of Tadalafil and Sildenafil on Mortality, Cardiovascular Disease, and Dementia. *Am. J. Med.* **138** (3), 441–448e3 (2025).
36. Bhattacharyya, S., Miller, L. E., Rojanasart, S. & Patel, D. P. Association of erectile dysfunction with all-cause and cardiovascular mortality in US men: findings from NHANES 2001–2004 with 16-year follow-up. *Int J Impot Res.* ;10.1038/s41443-025-01218-z. (2025).
37. Fan, Y., Hu, B., Man, C. & Cui, F. Erectile dysfunction and risk of cardiovascular and all-cause mortality in the general population: a meta-analysis of cohort studies. *World J. Urol.* **36** (10), 1681–1689 (2018).
38. Matthews, K. A. et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. *Alzheimers Dement.* **15** (1), 17–24 (2019).
39. Manly, J. J. et al. Estimating the Prevalence of Dementia and Mild Cognitive Impairment in the US: The 2016 Health and Retirement Study Harmonized Cognitive Assessment Protocol Project. *JAMA Neurol.* **79** (12), 1242–1249 (2022).
40. Satizabal, C. L. et al. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl. J. Med.* **374** (6), 523–532 (2016).
41. Desai, R. J. et al. No association between initiation of phosphodiesterase-5 inhibitors and risk of incident Alzheimer's disease and related dementia: results from the Drug Repurposing for Effective Alzheimer's Medicines study. *Brain Commun.* **4** (5), fcac247 (2022).
42. Lindsay, J. et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am. J. Epidemiol.* **156** (5), 445–453 (2002).
43. Public Health Agency of Canada. *Dementia in Canada, including Alzheimer's disease: Highlights from the Canadian Chronic Disease Surveillance System*. Public Health Agency of Canada. (2017). <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/dementia-highlights-canadian-chronic-disease-surveillance.html>.
44. Martinkova, J. et al. Proportion of Women and Reporting of Outcomes by Sex in Clinical Trials for Alzheimer Disease: A Systematic Review and Meta-analysis. *JAMA Netw. Open.* **4** (9), e2124124 (2021).

45. O’Neal, M. A. Women and the risk of Alzheimer's disease. *Front. Glob Women’s Health.* **4**, 1324522 (2024).

46. Bhatia, P. & Singh, N. Tadalafil ameliorates memory deficits, oxidative stress, endothelial dysfunction and neuropathological changes in rat model of hyperhomocysteinemia induced vascular dementia. *Int. J. Neurosci.* **132** (4), 384–396 (2022).

47. Jehle, D. V. K. et al. Benefits of Tadalafil and Sildenafil on Mortality, Cardiovascular Disease, and Dementia. *Am. J. Med.* **138** (3), 441–448e3 (2025).

Tables

Table 1- Baseline Characteristics of matched cohorts

Characteristics		Control (n=439,120)	PDE5 (n=439120)	Odds Ratio	95% CI	P- value
Age	< 50 yrs.	58,216 (13.26%)	59,609 (13.57%)	0.9731	0.9612- 0.9851	<.0001
	>50 yrs.	380,904 (86.74%)	379,511 (86.43%)	0.9731	0.9612- 0.9851	<.0001
Race	White	284,350 (64.75%)	277,701 (63.24%)	1.0679	1.0587- 1.0773	<.0001
	Non-White (Others)	154,770 (35.25%)	161,419 (36.76%)	1.0679	1.0587- 1.0773	<.0001
BMI	< 35	394,230 (89.78%)	391,281 (89.11%)	1.0737	1.0592- 1.0884	<.0001
	>35	448,90 (10.22%)	478,39 (10.89%)	1.0737	1.0592- 1.0884	<.0001
Follow-up period	< 5 yrs.	169,415 (38.58%)	175,729 (40.02)	0.9415	0.9335- 0.9496	<.0001
	>5 yrs.	269,705 (61.42%)	263,391 (59.98)	0.9415	0.9335- 0.9496	<.0001
Type 2 Diabetes	No	334,019 (76.07%)	333,115 (75.86%)	1.0113	1.0015- 1.0213	0.024
	Yes	105,101 (23.93%)	106,005 (24.14%)	1.0113	1.0015- 1.0213	0.024
Base line CVD	No	208,297 (47.44%)	204,530 (46.58%)	1.035	1.0264- 1.0437	<.0001
	Yes	230,823 (52.56%)	234,590 (53.42%)	1.035	1.0264- 1.0437	<.0001

Table 2. Prevalence of dementia prior to index date

Dementia subtypes	Control N=439,120	PDE5 N=439,120	Odds Ratio	95% CI	p-value
Alzheimer dementia	808 (0.184%)	709 (0.161%)	1.16	1.01–1.34	0.038
Frontotemporal dementia	59 (0.013%)	65 (0.0148%)	1.41	0.89–2.21	0.138
Vascular dementia	841 (0.191%)	814 (0.185%)	1.01	0.89–1.14	0.922
Senile dementia	2240 (0.510%)	2209 (0.503%)	0.93	0.85–1.02	0.120

Table 3. Incidence of new dementia diagnosis

Dementia subtypes	Control N=439,120	PDE 5 N=439,120	Odds Ratio	95% CI	p-value
Alzheimer dementia	6564 (1.49%)	5030 (1.14%)	0.91	0.85–0.96	0.001
Frontotemporal dementia	690 (0.157%)	640 (0.145%)	0.83	0.69–1.00	0.0001
Vascular dementia	6601 (1.503%)	5248 (1.195%)	0.84	0.79–0.89	<0.0001
Senile dementia	16,104 (3.667%)	13,578 (3.092%)	1.00	0.97–1.04	0.817

Table-4. Delayed time-to-diagnosis of dementia

Dementia subtypes	Control group N=Days to DX	PDE5 group N=Days to Dx	Delay In days	p-value
Alzheimer dementia	2670	3433	+763	<0.0001
Frontotemporal dementia	2674	3387	+713	0.0003
Vascular dementia	2843	3637	+794	<0.0001
Senile dementia	2829	3762	+933	<0.0001

Figures

Figure 1. Study schema

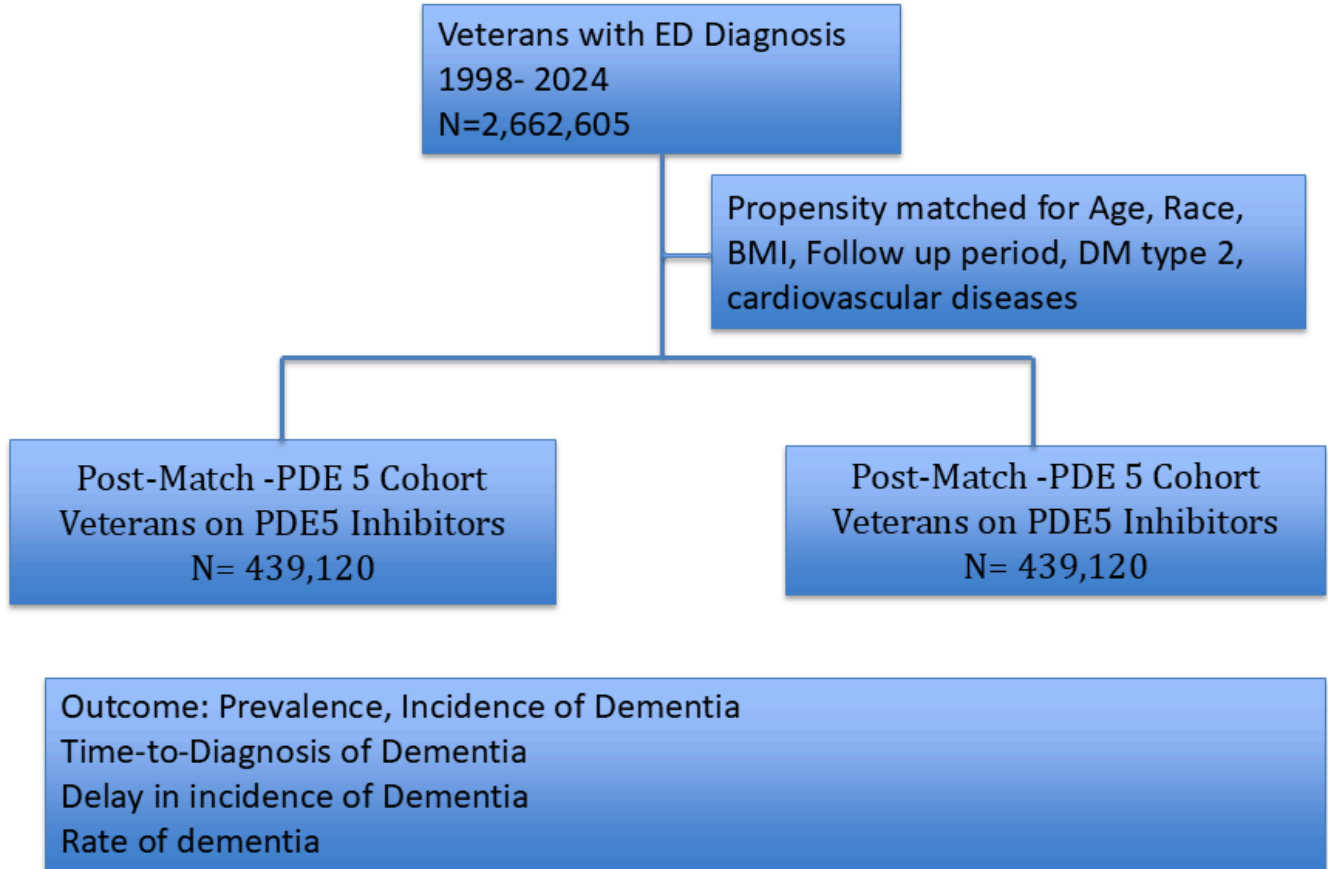
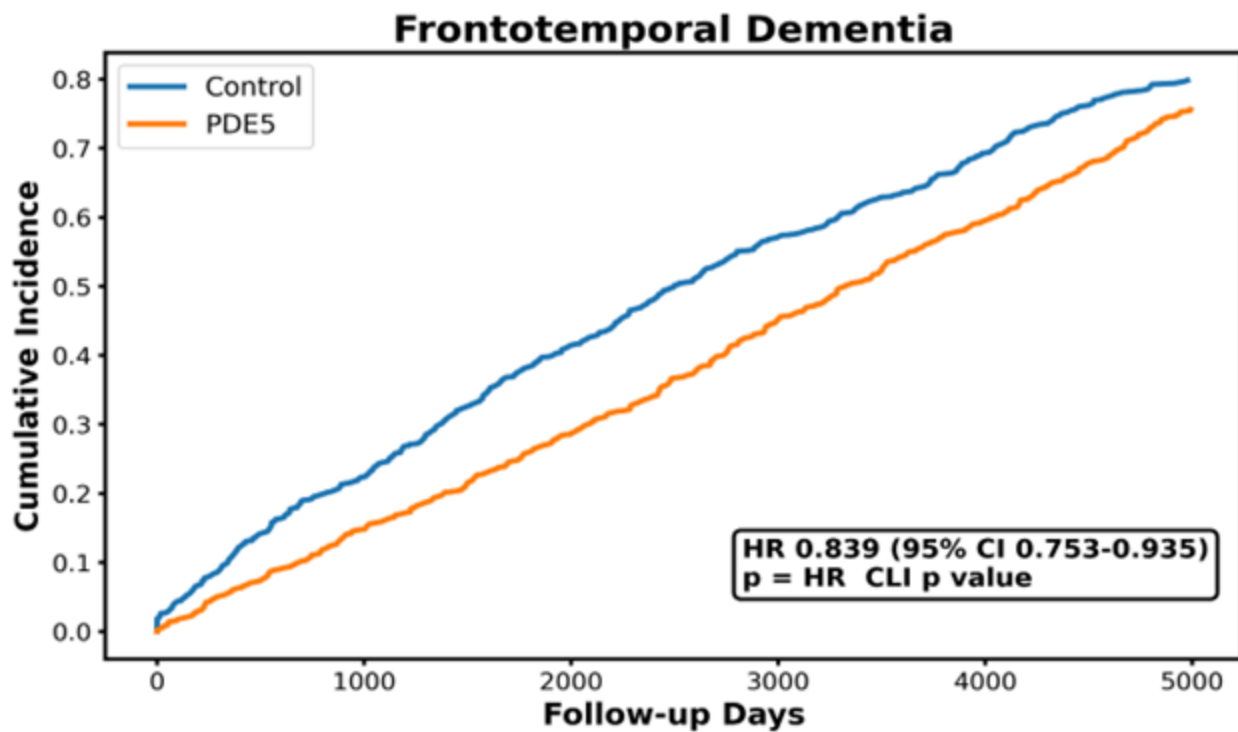


Figure 1

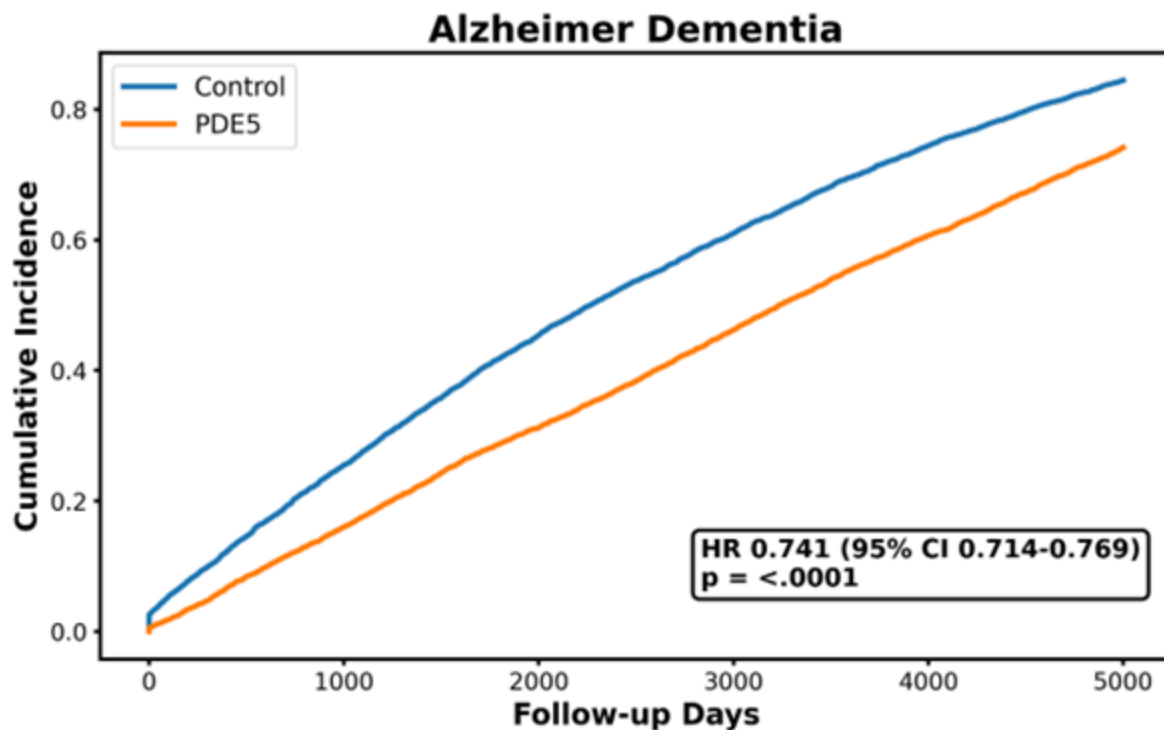
See image above for figure legend



At Risk	0	1000	2000	3000	4000	5000
Control	645	512	390	288	206	135
PDE5	614	522	436	339	251	151

Figure 2

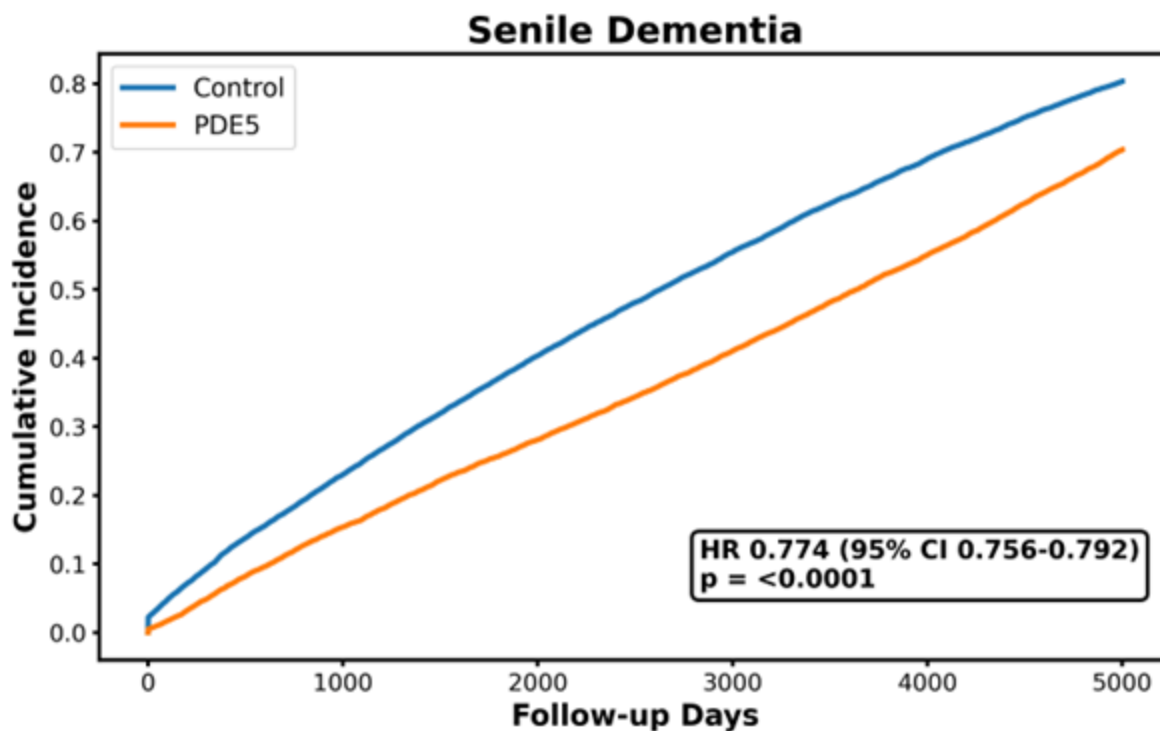
Kaplan–Meier curves for Frontotemporal dementia



At Risk	0	1000	2000	3000	4000	5000
Control	4010	3263	2545	1915	1335	860
PDE5	3650	3125	2596	2053	1540	1048

Figure 3

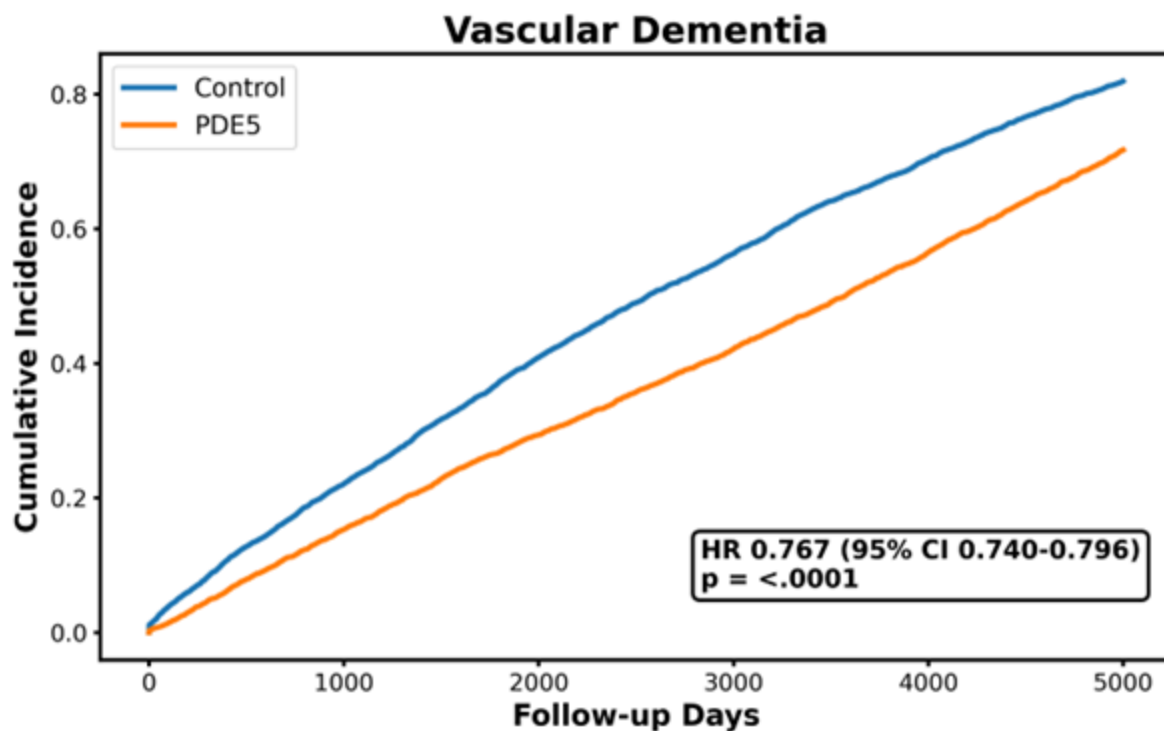
Kaplan–Meier curves for Alzheimer dementia



At Risk	0	1000	2000	3000	4000	5000
Control	6359	5402	4480	3586	2696	1899
PDE5	6396	5530	4736	3913	3074	2210

Figure 4

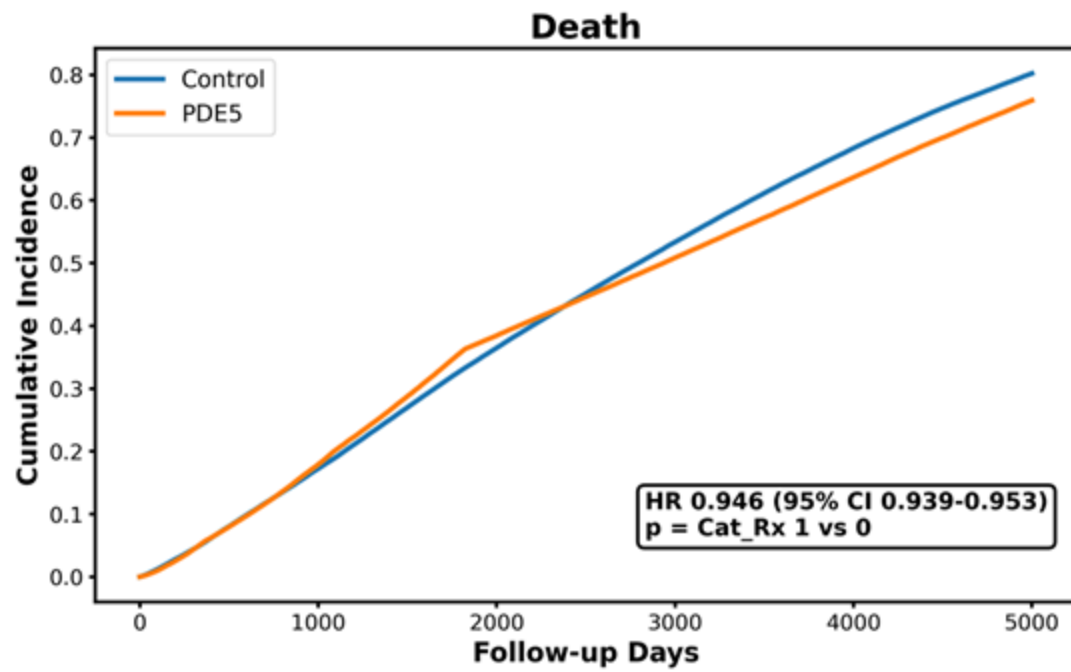
Kaplan–Meier curves for Senile dementia



At Risk	0	1000	2000	3000	4000	5000
Control	4174	3426	2707	2085	1477	944
PDE5	3737	3194	2678	2191	1678	1134

Figure 5

Kaplan–Meier curves for Vascular dementia



At Risk	0	1000	2000	3000	4000	5000
Control	8978	7974	6974	5974	4974	3974
PDE5	8670	7669	6669	5669	4669	3669

Figure 6

Kaplan–Meier curves for Overall Death