Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer's Disease

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Abstract

Despite a large body of research examining the associations between medication use and dementia, the issue remains unresolved. This thesis uses administrative healthcare data to examine two drug classes, proton pump inhibitors (PPIs) and benzodiazepines, and dementia risk using a methodological sensitivity analysis approach to better understand why the evidence remains equivocal, and whether these drugs do increase the risk of dementia. Cox regression models were used to model risk using a population level cohort. Subgroup analysis was used when needed to reduce indication bias. Finally, high dimensional propensity score matched cohorts were used to reduce unmeasured confounding.

We found that while PPI users had modestly higher risk of dementia, this increased risk was due to higher rates of baseline comorbid conditions that are also risk factors for dementia. An analysis of PPI initiators also found that these conditions were predictors of treatment initiation and increased duration of use. After adjusting for the comorbid conditions, the association between PPIs and dementia was null.

Similarly, benzodiazepine users had higher risk of dementia but also higher rates of dementia risk factors at baseline. Adjusting for these conditions reduced the estimated increased risk, although it remained significant. However, this class of drugs is most used in those with depression and anxiety, risk factors for dementia, resulting in potential indication bias. When this bias was reduced by examining cohorts of depressed persons, or of those with anxiety no increase in dementia risk was found.

The pharmacoepidemiological research into dementia risk associated with prescription drugs is messy. Insufficiently controlling for the noise present in non-randomized and observational data can lead to detecting signals of uncertain validity. It is hoped that this systematic approach will raise the bar for future research in this area, and that future researchers would, before publishing alarming findings, assess more closely whether they have truly controlled for confounding, reduce the risk of bias, and that their study design can answer the question they are trying to ask.

Table of Contents

Chapter 1: Introduction

What if that tablet you take every morning to control your heartburn will also cause you to develop Alzheimer's disease when you are 65? Perhaps that capsule you take to help you sleep at night also causes dementia? Would you still take them? These are not adverse effects listed on the handout you got from the pharmacy, but you may have come across a story on the evening news informing you that this is something you should worry about. Maybe your doctor read a news article commenting about a new study showing your heartburn medication increases your chances of dementia by 44%[1,2] and wants to stop prescribing it, but you worry that if you do, your gastroesophageal reflux disease could lead to throat cancer. You ask your healthcare professional to do some research for you only for them to get back to you saying they read 20 studies and don't know the answer as the evidence is equivocal. It turns out that many drugs have been associated with increased risk of dementia, including the sodium-glucose cotransport (SGLT-2) inhibitors,[3] metformin,[4] and antidepressants.[5] This dissertation will examine whether the risk of dementia is altered by the use of proton pump inhibitors (PPIs) and by benzodiazepines.

Dementia exacts a huge toll on the individual and their support network. In Canada, a typical case of dementia carries an economic cost to society of about $67,200 per year, with an annual aggregate cost of over $40 billion.[6] This includes the costs of medical care, hospitalization and other direct costs which account for about 46% of the total burden; the indirect economic costs attributable to effects on informal care givers, including the considerable time devoted to caring for someone with dementia are responsible for 54% of the total burden.[6]

In addition to the economic burden, both to the health care system and to caregivers, there is a large mental and emotional burden on both the individual with dementia, as well as for their spouse, family, friends, and all those who love and care for them.[7,8] An individual diagnosed with dementia has to come to terms with their terminal diagnosis, the knowledge that their symptoms won't get better, and the possible future loss of autonomy and independence. Family and friends will, over time, watch as the person they love and care for slowly changes into a different person. Providing care is physically and emotionally taxing, stressful and often invisible to the outside world.[8] However, not that all experiences of caregiving are negative, spending more time together and showing (or, for the patient, receiving) care can provide positive emotions and bonding.[7]

The history of drug safety research is marked by significant missteps, resulting in improvements in regulatory oversight and stricter requirements for pre-approval studies. Thalidomide, a sedative hypnotic from the 1950s, was approved based on drug safety studies conducted in animals. It was later marketed for morning sickness despite not being studied in pregnancy, resulting in 10,000 infants dying shortly after birth or being born with severe birth defects.[9] This event cemented the importance of doing safety studies in humans, which was not the standard for many regulatory agencies at the time. Diethylstilbestrol (DES), an estrogenic compound, was first studied in the 1940s to reduce risk of miscarriage and marketed for this use.[10-12] At the time, it was thought that the fetus was not exposed to drugs taken by the mother, so the effects on the fetus were not studied. Even after being shown to not be effective, it continued to be prescribed. Research later revealed that it increased the risk of cervical, vaginal, and breast cancer in female offspring in later life, but by then 5 to 10 million pregnant people had already taken it.[12] Phenolphthalein was used for over a century as an non-prescription remedy for constipation, only being withdrawn in 1997 due to being carcinogenic.[13] Cisapride, a gastric motility agent, was withdrawn after being on market for 9 years due to causing arrhythmias and cases of sudden cardiac death.[13] Nefazodone, an antidepressant introduced to Canada in 1994, was withdrawn in 2003

due to case-reports of hepatoxicity.[13] Fenfluramine, an appetite suppressant, was available for 27 years before it was withdrawn due to causing cardiac valve problems. These examples demonstrate the importance of pre- and post-approval research and surveillance. While a conventional randomized controlled trial (RCT) would have discovered the effects of thalidomide, provided they followed the mother and child to birth, many of the above dangers would require longer follow-up than usual (e.g., up to 15 years to detect the vaginal and cervical cancer caused by DES), or very large cohorts for rare events such as hepatoxicity (nefazodone) and valve di[14]sease (fenfluramine). Unfortunately, this doesn't regularly happen due to their high cost, complexity, the difficulty in retaining subjects across multiple years, and the fact that it is not required. This is why post-market surveillance and pharmacoepidemiological studies are vital in identifying drug safety concerns.

Whether prescription drugs can increase the risk of dementia is one of those questions that conventional randomized controlled studies are not well suited for. In this case, it is not because dementia is rare, it affects 8.5% of Canadians over the age of 65[15] and over 37% of those 85 and older[16], rather it is because of the long asymptomatic prodromal phase of most dementias. Aside from vascular dementia, which can develop immediately after a major cerebrovascular accident and account for 20-30% of all dementias, [17] the non-vascular dementias develop slowly over the course of decades, far longer than a typical RCT.[18,19] This requires the use of epidemiological methods similar to those used to demonstrate the link between tobacco smoke and cancer[20], or asbestos and mesothelioma[14].

Fortunately, as the administration of the healthcare system became increasingly computerized over the past decades, there are now medical, hospital, and prescription databases with decades of data available to answer these questions. These developments have greatly aided the field of pharmacoepidemiology, where there now exist data repositories containing all medical, hospital, and prescription drug data for millions of people across entire regions over multiple decades of their lives. The advent of this era of "big data" allows researchers to quickly (compared to an RCT), cheaply (again,

compared to an RCT) look for rare adverse effects and detect adverse events that take long periods of time to develop and become apparent.

Unfortunately, developing study designs that make use of this data while also avoiding methodological biases and appropriate control for confounding can be difficult. For example, immortal time bias, where person-time is inappropriately categorized, is a frequent source of bias and can be challenging even for seasoned epidemiologists to spot.[21] Other biases including indication bias, selection bias, protopathic bias, and time-lag may be easily missed by pharmacoepidemiologists who are experts in research methodology but are lacking in knowledge of the medical context. For example, an epidemiologist could find that people with a history of taking selective serotonin reuptake inhibitors (SSRIs) are at higher risk of suicide. Without knowing that SSRIs are an antidepressant and taken by depressed people who are already at increased risk of suicide could lead to calls for all antidepressants to be removed from the market. Choosing an exposure assessment window is a key design decision when addressing causal hypothesis. For example, it is known that Alzheimer's disease develops over decades before symptoms become apparent and a diagnosis can be made.[18,19] The biologically relevant exposure period where something can alter the risk of dementia is therefore many years prior to diagnosis. While this is well established in the cancer literature, there is a lot of drug-dementia research where the exposure assessment window immediately precedes diagnosis by one to three years. These types of errors appear in many published pharmacoepidemiology studies looking at the effects of drugs on dementia risk. [22-26] The availability and affordability (in comparison to an RCT) of accessing and analyzing big datasets, the publish-or-perish system present in academia, and the ability to fish through the data looking for significant findings has led to an explosion of research sometimes resulting a mountain of conflicting evidence. This is true for both benzodiazepines and PPIs, where dozens of papers have been published, and new articles appear regularly. Unfortunately, it is often poorer quality, low sample number

observational studies that receive the most attention as these are the most likely to reach sensational findings.[27]

In the research contained in this dissertation, we have used what I call a methodological sensitivity approach where various modelling approaches are used to answer different facets of the same question. In doing this, we hope to address the different potential biases in several ways to see how robust any association we might find is between dementia and PPIs or benzodiazepines. This interest in PPIs was sparked by two papers,[22,23] published shortly after beginning my doctoral program which reported an increase of over 40% in dementia rates among PPI users. This paper, which was heavily reported on in the news, had several major design flaws that we felt needed to be addressed. Appendix A contains an annotated bibliography of the previously PPI-dementia studies describing the wide array of diverse study designs, data sources, and results. When this thesis was first envisioned, I hoped to be able to provide a meta-analysis of these results and compare that to my eventual results. This was dropped from consideration due to the heterogeneity of designs and statistical methods, as the bibliography makes clear, in addition to the difficulty in combining results from observational studies. We chose benzodiazepines as they are widely used in depressed and anxious people, both of which are risk factors for and potential early symptoms of dementia and thus would be affected by significant indication and protopathic bias. Another major shortcoming seen in the existing literature was the use of inappropriate exposure assessment periods that missed the biological relevant exposure window for dementia. The widespread use of both classes of drugs makes studying the safety of both drug classes of vital importance. The benefits they can provide when prescribed appropriately also means that claims regarding their potential harms could prevent individuals from treatments that could potentially improve their quality of life. Patients and physicians need to know whether these drugs are safe, and if not, what level of risk could they pose, as sometimes a risk is justified by benefit. The aim of this

research is to identify if these drugs are actually associated with an increased risk of dementia, and if so, to quantify it accurately to allow a risk-benefit calculation to be made.

A sandwich thesis format has been used for this thesis containing three research papers and two chapters of background material. Chapter 2 provides a short review of what we know about the dementia disease process, the epidemiology of dementia, types of dementia, and treatments. Chapter 3 covers the methods used in the dementia-PPI and dementia-benzodiazepine papers in more detail than could be contained in the word limits required for journal publication. Chapter 4 contains the PPI-dementia paper while Chapter 5 is focused on understanding what it is about PPI users that might explain the correlation between PPI use and dementia. Chapter 6 contains an analysis on the association between benzodiazepine use and dementia. The concluding chapter summarizes what has been learned and the potential implications of this work.

Chapter 2: Dementia

Dementia is a collective term for various conditions that affect the brain and can cause impairment of memory and cognitive ability including such domains as judgment, the ability to make decisions, plan, and communicate effectively.[17,28] It is primarily a disease of aging, infrequently occurring in younger persons with some exceptions, such as familial Alzheimer's disease associated with genetic mutations, persons with Down's syndrome, or as a product of chronic traumatic encephalopathy.[29,30]

In addition to memory and cognitive deficits, individuals may also experience behavioral and psychological symptoms, including personality shifts, irritability, restlessness, as well as feelings of depression and anxiety.[17,31-34] Some forms of dementia may also cause movement disorders and parkinsonian symptoms.[32,35] Together, the symptoms of dementia impair a person's self-care capabilities and hinder activities of daily living, leading to disability.[34,36] The process is irreversible and terminal, with median survival time after diagnosis between 3.3 to 11.7 years.[37]

This introduction will review what is known about the pathophysiology of dementia, epidemiology, risk factors, and the potential to prevent a portion of cases by acting on modifiable risk factors.

The Pathophysiology of Dementia

Alzheimer's disease is the most prevalent form of dementia, making up approximately 50-75% of cases, while vascular dementia (VaD) is the second most common, accounting for roughly 20-30%. [17]Other forms, such as dementia with Lewy bodies, Parkinson's disease dementia, and fronto-temporal dementia, make up the remaining cases.[17] Vascular dementia is caused by cerebrovascular disease and is considered a non-neurodegenerative condition as the disease does not continue to progress unless

there are further hypoxic insults.[28] Non-vascular dementias (Alzheimer's, Lewy bodies, Parkinson's and fronto-temporal dementias) are considered neurodegenerative and are progressive and irreversible.[28] Non-vascular dementias are also similar in that the disease process is poorly understood, and they all feature abnormal aggregation of specific proteins in the brain.[28] The reported prevalence of these subtypes varies widely in research due to different study methods, population diversity, temporal factors, and the inherent challenge of distinguishing between them. It's also common for individuals diagnosed with one type of dementia to have mixed dementia,[28,38] most often a vascular dementia occurring with a non-vascular dementia

VaD arises from brain tissue hypoxia, which may occur due to hemorrhagic or ischemic stroke, from transient ischemic attacks, or other events which reduce cerebral blood flood. [17] These hypoxic events cause damage and lead to the disruption of synaptic connections and the death of nerve cells. Consequently, cardiovascular and cerebrovascular diseases are significant risk factors for VaD. Brain damage manifests as small widespread lesions from microvascular damage or as large lesions from major infarcts.[39] VaD can have an abrupt onset following events like a stroke, either hemorrhagic or ischemic, or it may develop gradually due to transient ischemic attacks or atherosclerosis. Although no current treatments can restore lost healthy brain tissue, therapeutic strategies focused on stopping or minimizing the risk of further infarcts can halt or slow down disease progression in the early stages.

Non-vascular dementias are less well understood, but they share the common feature of abnormal protein accumulations. Alzheimer's disease was first described by Dr. Alois Alzheimer in 1906 after he observed distinctive plaques in the brain of a deceased patient with dementia.[39,40] These plaques, sometimes referred to as senile plaques, consist of beta-amyloid protein, which originates from the amyloid precursor protein (APP) found in the membranes of nerve cells.[41] The amyloid hypothesis suggests that after APP is cleaved by secretases, amyloid beta is released and aggregates to form these characteristic plaques, and this results in the Alzheimer's dementia.[42] However, the exact role of these

plaques in Alzheimer's disease is unclear, as there is a weak correlation between plaque quantity and dementia severity.[42,43] Alzheimer's disease also features neurofibrillary tangles composed of tau protein that form within neurons.[41] Tau assists in transporting cellular components, and the tangles may disrupt this process, potentially contributing to the pathological process. It remains unclear whether these protein abnormalities are causally related or simply correlated with dementia, ultimately the disease process leads to the loss of neuronal connections and cell death.

The term "dementia with Lewy bodies" encompasses both Lewy body dementia (LBD) and Parkinson's disease dementia, which is a form of dementia that evolves as a secondary condition to Parkinson's disease.[44] These disorders share symptoms and may stem from a similar disease process.[35] LBD often presents with parkinsonian movement disorders early on, while individuals with Parkinson's disease have a heightened risk of developing dementia. Both conditions are associated with abnormal structures known as Lewy bodies, composed of alpha-synuclein protein aggregates found within the neuronal cell bodies and neurites.[45] The primary distinction between the two lies in the sequence of symptom onset; Parkinson's disease dementia is diagnosed when the movement disorder occurs before cognitive decline.[44] It's also possible for LBD to coexist with Alzheimer's disease (AD) as mixed dementia. Differentiating AD from LBD can be based on early symptoms: LBD typically manifests with movement issues first, followed by memory problems, whereas AD starts with memory impairment.[35] LBD may also involve more pronounced autonomic dysfunctions and hallucinations. Additionally, alpha-synuclein's involvement in AD is suggested by the presence of Lewy bodies in many cases.[35]

Fronto-temporal dementia (FTD) is typically diagnosed earlier in life than the other dementias, most commonly between the ages of 45 and 65.[46] Unlike AD and LBD, FTD is primarily associated with damage to the cortical rather than deep-brain structures or the hippocampus. This leads to pronounced behavioral, emotional, and language disturbances, with lesser effects on memory and cognitive functions.[33,35] However, it can also cause damage to parts of the brain involved in movement and result

in Parkinsonian symptoms. Abnormalities in the tau protein may also contribute to the development of FTD.[17,33]

Diagnosis

Non-vascular dementias are insidious in their progression. The pathophysiological process that results in dementia may begin 10 to 20-years before symptoms of dementia become evident.[18,19] The early, latent phase is asymptomatic and does not result in obvious cognitive deficits, although some studies using intensive neurocognitive testing have shown subtle differences in baseline ability in non-demented persons who later became demented.[19,47] Additionally, advances in blood-based biomarker detection and new imagining technologies make it possible to now diagnose the disease long before clinically observable symptoms appear.[48]

In the prodromal phase, individuals begin to experience early symptoms of dementia, and may be diagnosed with mild cognitive impairment (MCI), a condition where cognitive ability appears on the continuum between the normal cognitive changes that occur due to aging and the development of frank dementia.[49] The effect of other comorbid chronic conditions such as depression, infectious diseases including urinary tract infections, and use of many types of drugs commonly taken by older adults, especially those with anticholinergic of sedative side effects, can make a differential diagnosis difficult.[50] As a result, not all individuals diagnosed with MCI will continue to deteriorate, with some reverting to normal cognitive status. However, their risk of dementia is high, with 10 to 15% of people with MCI progressing to dementia per year,[49] and the conversion rate at 6 years is up to 80%.[51]

As the neurodegenerative process progresses symptoms rise to meet the diagnostic criteria for dementia. Due to the loss of neurons and the limited ability of the brain to regenerate them, especially later in life, this process is functionally irreversible. Cognition and memory will continue to decline, and

activities of daily living become more difficult leaving individuals to need more assistance, eventually leading to disability and death.

Treatment

Once diagnosed, treatment options are limited. The two main classes of drugs used for treating dementia, cholinesterase inhibitors and the N-methyl-D-aspartate receptor (NMDA) inhibitor memantine. [52,53] Cholinesterase inhibitors attempt to enhance cholinergic neurotransmission as the cholinergic system is disrupted in Alzheimer's, and other dementia[54] NMDA receptors are widespread throughout the CNS, and they may have a role in mediating neuroexcitatory cell death when overactive. By blocking the NMDA ion channel, memantine may reduce or block this damage, but the mechanism by which it alleviates dementia symptoms is unclear.[55] Both classes of drugs have been shown to have effects on cognition in dementia, but with very small effect sizes, no effect on neuropsychiatric symptoms, and high rates of side effects.[56] A 2018 meta-analysis looking at cholinesterase inhibitors reported a pooled effect estimate at 3 months of an increase of 1.08 and 1.10 points (out of 30) at 12 months on the Mini Mental State Exam (MMSE) for patients with Alzheimer's disease and vascular dementia. For context, the MMSE is a short exam that tests if patients can correctly answer a serious of 30 questions and tasks, each worth one point for a total of 30 points, such as drawing a clock face with the hands pointing to a specific time and counting down from 100 in multiplies of seven.[57] A difference of 2 to 3 points is considered the minimal clinically important difference for moderate to severe Alzheimer's.[58,59] The effect for persons with Parkinson's dementia/dementia with Lewy bodies was higher, at 2.11 at 6 months.[58] The effect of memantine for dementia was lower, with a pooled difference compared to placebo of 0.65 and 0.40 at 3 and 6 months, and a non-significant difference at 12 months.[58] At best, they appear to modestly slow the rate of decline, however, this is a temporary improvement and they do not alter the course of the disease or repair the damage already done.[60]

There is hope that new biological agents could act as disease-modifying therapies, such as monoclonal antibodies that bind to the amyloid aggregates that create amyloid plaques, or against phosphorylated tau which forms neurofibrillary tangles.[61] These antibodies bind to their target proteins, helping the immune system target and clear the aggregates, hopefully improving symptoms and potentially stopping disease progression. The monoclonal antibody aducanumab was the first anti-amyloid antibody approved for clinical use, and was approved for use based on its ability to reduce the amount of amyloid plaques seen on PET scans.[62] This approval was controversial as two phase 3 clinical studies had conflicting results regarding clinical benefit and both were stopped early due to failing a futility analysis.[61,62] However, a post-hoc analysis of the pooled data was used by the drug manufacturer to apply for, and obtain FDA approval. This approval was controversial as the FDA advisory committee established to review the data had concluded there was insufficient evidence to support this and raised safety concerns.[63,64] Biogen, the manufacturer of aducanumab, later decided to pull the drug from the marked. Lecanemab, another anti-amyloid antibody, was approved in 2023 and appears to modestly slow cognitive decline, but not reverse it.[61] Further research is ongoing and needed to determine the role of these biological agents in dementia treatment, and possibly prevention.

Drugs used in the treatment of mental illness, such as antidepressants, antipsychotics, anxiolytics and sedatives are sometimes used to address the psychological and behavioural symptoms.[65] There is little evidence to suggest that antidepressants are beneficial in treating depressive symptoms of dementia and could cause harm, particularly first-generation antidepressants (e.g., tricyclic antidepressants) although they may help specific patients. [65,66] Antipsychotic agents are one of the most commonly used agents in treating the behavioural symptoms, especially agitation, despite providing no significant benefit and increasing the risk of falls, cognitive impairment, and may increase the risk of cerebrovascular mortality.[67] Benzodiazepines and Z-drugs (e.g. zopiclone) are used to treat sleep disturbances and agitation. While this is not uncommon, their use is not recommended either as they

can also acutely impair cognition and memory, lead to daytime sleepiness, increase the risk of falls and should be avoided.[68,69]

There are currently nearly 200 hundred clinical trials looking at over 140 different small molecules, antibodies, vaccines and other drugs as potential treatments for dementia, mostly Alzheimer's dementia.[66] These include entirely new molecules and previously approved drugs being studied for the use in dementia. In 2023 there were thirty-six molecules in phase 3 trials, with over half looking at potential disease modifying agents.[66] However, the history of AD drug trials is mostly that of failure and only time will tell if any end up being useful.[56,70]

Epidemiology of Dementia

Estimates of the prevalence of dementia can vary substantially due to several factors including diverse methodologies, sources of data, different populations being studied, and by variations in the diagnostic criteria used and who is making the diagnosis. Rate estimates can be obtained from cross-sectional studies, longitudinal cohort studies, or by using administrative data or medical records.

A cross-sectional approach involves examining an appropriately chosen cohort at one point in time using questionnaires or interviews along with clinical and neurological examinations to determine dementia status. Prospective longitudinal studies involve creating a cohort of healthy (non-demented) individuals and periodically assessing members for dementia over time, using similar techniques as a cross-sectional study. Examples of such prospective studies include the Adult Changes in Thought (ACT) study centred at the University of Washington, and the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) in Germany.[22,71] For both cross-sectional and cohort study types, investigators will typically train research staff on the diagnostic criteria and on how to conduct standardized interviews to increase the reliability of their diagnosis. These studies both require considerable time and resources to

conduct and thus tend to be limited in size. Longitudinal studies also must deal with subjects being lost during follow-up.

Administrative health care data can also be used to conduct population-wide studies. These are much less time and resource intensive and loss during follow-up is less of an issue. However, they do have limitations. Case-finding is dependent on individuals actively seeking medical care from a physician and then being diagnosed with a dementia. This method thus will miss individuals who do not interact with the health care system. The diagnoses recorded in this data are made by many different physicians, each using their own clinical judgement, and thus the accuracy of a diagnosis (or non-diagnosis) can affect the results. Variation in the quality and the breadth of data collected, and different patient populations can make combining results across data sources to determine long-term trends or global averages of dementia prevalence less reliable.

Age based Dementia Prevalence:

The Canadian Alzheimer's Society, using the Canadian Study on Health and Aging, estimated that in 2014 the prevalence of dementia in those aged 65-74 was 2.8%, for those 75-84 it was 11.6%, and for those 85 and over it was 37.1%. Estimated rates by age are similar in the United States, at 5.0% for those between 71 and 79, 24% for 80-89, and 37% for those 90 years of age and older.[72] Similar numbers have been reported in the United States and Western Europe.[36]

Changing Trends in Prevalence:

A recent meta-analysis looked at studies examining changes in dementia prevalence over time used prospective cohort studies with similar methodologies to mitigate for varying diagnostic criteria over time and excluded studies using administrative or medical records data. They reported that the total number of people living with dementia is stable or declining in European countries and the US despite an aging population.[73] This is due to a decrease in the age-specific prevalence of dementia, which

counteracts the rising number of persons at risk.[73] In other words, although there are more older persons, the age at which they develop dementia has also risen. The balance between how much the older population has grown and the change in age-specific rates in each location will determine how the absolute number of persons with dementia changes. Possible reasons for this include the declining rates of smoking, increasing awareness of the benefits of exercise, better treatment for diabetes and cardiovascular disease (risk factors for dementia), better access to education and possibly other factors.[73] Fewer studies that mitigate for the changes in diagnostic criteria were found for non-Western countries. Among those included was a Japanese study that suggested dementia prevalence may be increasing, while a Nigerian study found stable prevalence rates.[73]

A separate systematic review reported much the same findings when using cohort studies.[74] They also looked at medical record-based studies and found that many reported significant increases in dementia in a number of countries, including Canada. However, they also found some record-based studies reporting a stable or decreasing incidence and prevalence rates. As previously mentioned, while record-based studies generally have much larger sample sizes, they are limited in that they only contain data on people who sought medical care, diagnostic criteria have changed over time, as has awareness of dementia among patients and providers. Diagnostic criteria change over time, making looking at long term trends more difficult. Additionally, different researchers using the same data may apply definitions to what defines a records-based diagnosis, making combining prevalence studies using these sources of data challenging.

Risk Factors and Prevention

“Prevention is the best medicine”, as the saying goes. This is doubly true for dementia, as it is the only effective “medicine” available for reducing risk. It has been reported that potentially modifiable risk factors are responsible for up to half of all Alzheimer’s dementia cases, and that eliminating these risk

factors would result in substantially lower rates of dementia.[39,75,76] However, we have known about the risk factors for many other health problems such as cardiovascular disease, lung cancer, influenza and COVID infections, but getting people to modify their behaviours is the more difficult part.

The single biggest risk factor for dementia is age. A commonly cited rule of thumb states that the prevalence of dementia roughly doubles for every 5 years above the age of 65.[77] There are also genetic factors that contribute to risk, mostly for early-onset dementia, also known as familial dementia. This form of the disease is rare, with a prevalence of about 5 per 100,000 persons and is usually linked to mutations on one of three genes, *APP*, *PSEN1* and *PSEN2*. *APP* (which codes for amyloid precursor protein) is found on chromosome 21, the gene duplicated in people with trisomy 21 (Down's syndrome). The increased dose of *APP* in people with Down's syndrome is possibly responsible for their increased risk of Alzheimer's type pathology and the earlier age of onset.[29] The more common genetic risk is carried by the APOE gene, specifically the APOE-4 allele. People homozygous for APOE-4 have about a ten times increase in the risk of dementia over their lifetime.[78]

Conditions across our lifespan appear to affect our risk of developing dementia, even those present during the gestational period.[39] Smaller birth size and head circumference, which are indicators of the intrauterine environment during gestation, are associated with reduced cognitive capacity and brain reserve later in life and an increased risk of dementia.[39,79] Early life stressors, such as the death of a parent, may increase the risk of dementia, possibly due to stress which exposes the young, developing brain to high levels of cortisol.[80] Another risk factor is lower educational attainment, which has been consistently shown to increase the risk of dementia[81,82] with one meta-analysis reporting a 72% (pooled effect size 1.72 (95% CI 1.25, 1.96) increase risk compared to those with higher attainment.[39] Hypertension, cardiovascular disease and diabetes significantly increase the risk of dementia.[81,82] The evidence suggests that effective treatment of hypertension could mitigate this risk.[83] The effect of treatment for diabetes on dementia risk is uncertain. Untreated diabetes reduces life expectancy,

resulting in a reduced chance of a person living long enough to develop dementia, so better treatment could actually increase the number of people with diabetes who develop dementia.[83] Depression in midlife or earlier also increases the risk of dementia.[82,84] A systematic review that looked at the effect of antidepressant treatment of depression on dementia risk concluded that treatment did not reduce this risk, and may even increase it.[85] However, comparing treated vs untreated depressed persons may be problematic as mild to moderate depression is more likely to be untreated than those with severe depression. While longitudinal studies have shown an association between late life depression and dementia, it probably represents an early symptom of depression and not a risk factor itself.[31,39,83,84,86]

Significant other risk factors include smoking, excessive alcohol consumption, hearing impairment, social isolation/loneliness, and traumatic brain injury.[81-83] There are studies suggesting a role for obesity, but whether that is due to the increase in risk of diabetes rather than obesity alone is not known. A decrease in BMI in later life is a predictor of dementia, although this might be a case of reverse causation as loss of appetite and decreasing weight can be symptoms of dementia.[39]

As the field of pharmacoepidemiology has advanced, and large, detailed, population-level electronic data become more available, the study of the effects of drugs on dementia risk has exploded. This makes sense, as it is possible that treating some of the conditions (with drugs) that are risk factors for dementia could lower or eliminate that risk. On the other hand, we also need to know if these drugs may increase the risk of dementia themselves. Unlike other risk factors such as age or our size at birth, use of medication is something we have control over. However, the results of drug-dementia studies have often been contradictory or inconclusive.

For example, a recent meta-analysis looking at the effect of metformin, an anti-diabetic agent, on the risk of dementia found that 11 studies showed a reduced risk, four that were inconclusive, and two that showed an increase in risk.[4] However, the reviewers noted that 15 of the 17 studies had a time-lag bias

as they had not properly controlled for the stage of diabetes, and eight of the studies had immortal time bias where patient time was inappropriately allocated. There is also a report that discontinuing metformin results in a risk reduction.[87]

The use of hormone replacement therapy to treat menopausal symptoms is another group of drugs that has been examined closely with contradictory results. A systematic review published in 2023 identified six clinical trials and 32 observational studies that looked at the link between HRT and dementia. Of the six RCTs, two showed an increased risk of dementia and 4 found no significant effect.[88] The pooled effect estimate indicated an increase in the risk of dementia with a relative risk of 1.38 (95% CI 1.16, 1.64). However, of the 32 observational studies, 12 showed a decreased risk in HRT users, one showed an increase in risk, and 14 had no significant finding, with a pooled relative risk of 0.78 (95%CI 0.64, 0.95).

Two other classes of drugs that have received significant attention are the proton-pump inhibitors (PPIs) and benzodiazepines. Many research papers examining these drugs have been published with widely varying conclusions. Reasons for these discrepancies include different study designs, sources of data, different methods of finding cases, different populations and age groups being studied, varying levels of controlling for confounding, and the presence of bias in the methods. These two classes of drugs are the subject of this thesis and will be discussed more fully in the following chapters.

Chapter 3: Methods

Introduction

This chapter is included to supplement the methods sections for two of the papers included in this thesis; Chapter 4, Signal and Noise: Proton-pump-inhibitors and the risk of dementia?; Chapter 5, Clearing the Confounding Confusion: Benzodiazepines and the Risk of Dementia?

Sources of data

All three studies included in this thesis used administrative data from the Manitoba Population Research Data Repository which is maintained and housed at the Manitoba Centre for Health Policy (MHCP), a unit of the Rady Faculty of Health Sciences at the University of Manitoba. All information for my description of the data comes from the MCHP Manitoba Population Research Data Repository Data Descriptions webpage (http://mchp-appserv.cpe.umanitoba.ca/dataDescriptions.php), MCHP concept dictionary (https://mchp-appserv.cpe.umanitoba.ca/search.php) and the Meta-data Dictionary (only available through internal access).The repository contains a wealth of administrative health, registry, census, and survey data. Manitoba has a universal healthcare program and funds the provision of healthcare to Manitobans. The data generated during the normal operations of these programs is collected by the provincial government. This includes things such as physician billing claims, prescription claims submitted to the Drug Program Information Network to process Pharmacare reimbursement, and hospital discharge abstracts. This data is gathered and sent to the repository on an ongoing basis after being deidentified by Manitoba Health, Seniors and Long-Term Care to comply with healthcare privacy laws and regulations. The repository also contains data from the Employment and Income Assistance program, the Manitoba Justice system, provincially run elementary and high schools, the University of Manitoba, and other provincially run programs.

For this work, ethics approval was granted by the Health Research Ethics Board at the University of Manitoba. The Health Information Privacy Committee (HIPC), now known as the Provincial Health Research Privacy Committee approved our use of personal health data in compliance with the Personal Health Information Act. Original approvals granted access to data from April 1st, 1995, to March 31st, 2017. Later amendments extended years of available data to March 31st, 2021. The starting year was chosen as this is the first year that prescription data is available in the repository. All approvals can be found in the appendix.

Manitoba Health Registry

To access the provincially funded healthcare system, residents of Manitoba must register with Manitoba Health to receive a Provincial Health Identification Numbers (PHIN). Infants born in the province are automatically assigned a PHIN. Each person has a unique PHIN number, which they are assigned for life. People who leave and then re-enter the province are typically reassigned their previous PHIN. This PHIN number is used across the healthcare system and allows us to cross-link individual level data across the different components of the system. Information in the registry includes a person's data of birth, postal code, biological sex, start date of coverage as well as end date, if terminated, and the reason it was cancelled. To comply with privacy regulations (PHIA), the version of the registry contained in the repository is deidentified by a mathematical conversion to what is called a scrambled PHIN.

Drug Program Information Network

The Drug Program Information Network (DPIN) is the computerized provincial drug insurance claim system and community pharmacies are required to submit claims for prescription cost reimbursement through this system. All prescriptions pass through this system even when they are paid by private insurance plans. Thus, this system allows us to analyze prescription drug use across the entire Manitoba population starting from 1995. Only dispensed prescriptions result in a DPIN claim, the system does not

contain information on written but unfilled prescriptions. Since it is only dispensed prescriptions that can impact a patient, these records are a better indication of medication use. However, the difference between prescribing and dispensation data can be important. There are databases that record physician prescribing, commonly obtained from electronic medical record systems, but not dispensations. Examples include the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) (available in the repository), and the Clinical Practice Research Datalink (CPRD) in the UK. These systems record prescriptions written for patients but may not capture the indication for the prescription or if they have been dispensed. In some cases, EMR based prescriptions can be linked to dispensation data. For the purposes of this study dispensed prescription represent a better indication of medication use.

The DPIN system captures information on almost all prescription drugs dispensed to community dwelling members of the population, with a small number of exceptions. Non-prescription (over the counter, OTC) drugs are rarely entered into the DPIN system as they are not covered by Pharmacare, Manitoba's universal drug benefits program. However, they will occasionally be covered by a third-party insurer in which case they would have to be submitted to DPIN to process the insurance claim electronically. Drugs dispensed from nursing stations in remote Northern communities are not captured. Most long-term care facilities (LTCs) in Manitoba are serviced by community pharmacies, and thus their prescriptions are captured, but about 25% of LTCs are serviced by hospital pharmacies which generally do not process prescriptions through DPIN.

Variables included in the DPIN data included drug identification number (DIN), which are assigned by Health Canada to every marketed prescription drug, date of dispensation, quantity dispensed, duration of prescription (days supplied) which is estimated by the pharmacist entering the prescription based on the instructions written by the physician. These prescription DIN numbers can be crosslinked with the Universal DIN Master file (UDM), a dataset derived from Health Canada's Drug Product Database, to attach information such as anatomical, chemical, therapeutic (ATC) class numbers, generic drug names,

and strength of drug to the prescription record. [89,90] ATC codes were also included as a dimension for calculating high-dimensional propensity (HDPS) scores.

Medical claims

Medical claims data are generated when physicians bill the provincial healthcare system for rendering services to patients. Due to Manitoba's universal healthcare program, physicians submit all claims for reimbursement to the provincial government, meaning the repository contains population-wide medical data. Data elements include the patients scrambled PHIN numbers, the first 3 digits of the International Classification of Disease, version 9 Clinical Modification (ICD-9) code that represents the main reason for the visit, a tariff code containing information on specific procedures or service provided, the date the patient was seen, among other variables. One limitation is that only one ICD code can be used for each physician visit. Patients with complex healthcare needs may present at the doctor's office needing care for more than one diagnosis, thus information is lost. The ICD codes also do not represent a true diagnosis, and it could represent a diagnosis the clinician is investigating. Additionally, many conditions may be included under the umbrella of the first 3 digits, with additional (unavailable) digits needed to differentiate between them. For example, both Type 1 and Type 2 diabetes are included under the ICD-9 code of 250. Up to five digits are now available for medical claims with service dates from the 2015/2016 fiscal year onwards, however these were not used for this research. ICD and tariff codes were used as dimensions in the calculation of HDPS scores.

Data used – Hospital data

Hospital abstracts are generated for every hospital admission in the province, except for the small number of exclusively psychiatric hospitals. Data from those hospitals is stored in a separate database and require special permissions to access which we did not request. Hospital abstracts are high quality data generated from a patient's chart by coders trained to abstract information in a standardized

method, increasing the reliability and consistency of the data. These abstracts contain hundreds of different variables including date of admission, separation, diagnosis, interventions and procedures codes, transfers from other facilities. Prior to April 2004, ICD-9 codes were used to code diagnostic information. After 2004 a switch was made to used ICD-10-CA codes. Abstracts contain up to 16 ICD-9 or up to 25 ICD-10 codes, depending on the period. Diagnoses are only included if they resulted in any medical care or intervention, or if they arose during the hospital stay. Interventions/procedures are entered as Canadian Classification of Health Intervention (CCI) codes. In this study diagnostic codes and admission/separation dates were mainly used to determine diagnoses and diagnosis dates. ICD diagnosis codes and CCI intervention codes were used as separate dimensions when we calculated HDPS scores.

Census data

While individual-level Census data is not available, the repository does include census data summarized at the dissemination area level. Statistics Canada divides the country geographically into a series of increasingly localized units, from provinces to census tracts, down to the smallest unit known as a dissemination area (DA). Originally a DA was the region an individual census taker would cover when conducting the periodic census taking. It represents an area containing between roughly 400 to 600 people. DAs can be linked to individuals by using the Manitoba Health Registry, which contains postal codes and municipal areas for each registered person. These postal codes can then be linked to DAs through the Postal Code Conversion File created and maintained by MCHP. For this thesis, we used census data to find neighborhood-based income quintiles as a proxy measure of socio-economic status. Income quintiles were also used to generate HDPS scores.

Long-Term Care homes

The long-term care (LTC) admissions database was used to determine when an individual was admitted to a care home. The LTC databases contain a wealth of information on individual assessments, pre-existing diagnosis, and level of care needed. For this research we used only admission dates to determine when a patients medication history through DPIN may have been lost to collection. Anybody admitted to a care home during the exposure assessment period was excluded.

Cohort Construction

Stratification

The biggest risk factor for developing dementia is age. Rates of dementia climb rapidly after the age of 60 to 65. Other risk factors are spread across an individual's lifetime, such as educational attainment, diabetes and cardiovascular health in middle age, and social and intellectual engagement later in life. Because the effects of drug use on dementia may differ depending on stage of life, age-based cohorts were created, with exposure measured across the same age-range and follow-up beginning at the same age in each cohort. For the PPI paper, individuals were stratified as:

- Stratum 1: Born between April 1st, 1942, to March 31st, 1952.
- Stratum 2: Born between April 1st, 1932, to March 31st, 1942.
- Stratum 3: Born between April 1st, 1922, to March 31st, 1932.

For the benzodiazepine paper, the strata were:

- Stratum 1: Born between April 1st, 1944, to March 31st, 1954.
- Stratum 2: Born between April 1st, 1934, to March 31st, 1944.
- Stratum 3: Born between April 1st, 1924, to March 31st, 1934.

For both papers, follow-up started on an individual's 55th (stratum 1), 65th (stratum 2), or 75th (stratum 3) birthday. For the PPI paper, this would mean follow-up began between April 1998 and March 2008, while for the benzodiazepine paper follow-up began between April 2000 and March 2010. When the PPI paper was started, our data permissions were only up to 2017 and we wanted to maximize the duration of follow-up to catch enough events to power our analysis. Having limited years of data means there is a trade off between extending the duration of follow-up time and ensuring a sufficient exposure and covariate assessment period. When the benzodiazepine analysis began, we had amended our approvals to include the additional years of data that had become available.

These strata were analyzed independently. They were also used to construct similarly stratified, high-dimensional propensity score (HDPS) matched cohorts. For the benzodiazepine analysis, a sub-analysis was conducted on a group composed of individuals with depression and a group composed of individuals diagnosed with anxiety. This is discussed further in the analysis section (below).

Inclusion/exclusions criteria

To be included in analysis, an individual had to have continuous health care coverage starting from April 1st, 1995, the start of our data approvals and when the DPIN program began, until at least 1 year into follow-up (assessed using the Manitoba Health Registry). This ensured we had as complete a drug and medical history as possible. We used a new-user design, with a one-year washout period in the first year of data to exclude any prevalent users of the drug class under investigation. For the PPI analysis individuals who had a prescription of histamine-2 antagonists in the first year were also excluded.

Individuals who had comorbidities that are associated with a high risk of dementia such as Parkinson's disease, Down's syndrome, schizophrenia, or epilepsy were excluded. For the PPI analysis individuals with a history of liver disease were also excluded as this is a contraindication for PPI use. Individuals with a diagnosis of dementia prior to follow-up were also excluded.

Individuals admitted to an LTC during their exposure assessment period were excluded as we are missing prescription data on about 25% of individual residing in them as some LTCs are serviced by hospital rather than community pharmacies and thus their prescription data in not included in DPIN.

Alzheimer's disease and vascular dementia are the two main types of dementia, accounting for 50-75% and 20-30% of all dementia cases each, respectively. [39], and have different causes. Vascular dementia is the result of cerebrovascular disease, while Alzheimer's (and the other, less common dementias) are associated with abnormal protein accumulations.[39]. It is likely that the effect of drug exposure on the risk of either dementia could differ, possibly increasing the risk of one, and decreasing the risk of the other. However, as we only have the first 3 digits of ICD-9 codes available in medical claims, we are unable to reliable distinguish between these two different types of dementia. To make our outcome of dementia more homogenous for analysis, we tried to exclude vascular dementia as much as possible by excluding individuals with cerebrovascular disease from our cohort.

Exposure Assessment Window

Cumulative drug use was the exposure of interest in these studies. Cumulative exposure was measured in the baseline period prior to follow-up (starting when an individual reaches 55th, 65th, or 75th years of age, depending on strata assignment). For the PPI analysis this ranged from a minimum of three up to a maximum of ten years; for the benzodiazepine analysis it ranged from five to ten years. A DIN list was created for PPIs by selecting for DINs associated with ATC codes beginning with "A02BC" from the UDM. For benzodiazepines, drug DINs associated with the ATC codes starting with N05BA, N05CD (for anxiolytic and sedatives) or N03AE01 (for clonazepam, listed in anti-epileptic drugs) were used. These DIN lists were then linked to DPIN to extract prescription data. Drug use was quantified by using World Health Organization designated daily doses (DDD), which represent the commonly used daily dose of a drug in milligrams. Prescription quantity (tables or capsules dispensed) multiplied by dose (mg) per unit

was divided by the DDD quantity to determine DDDs dispensed. These DDDs represent an approximation of the number of days of treatment per prescription.

As part of the sensitivity analysis for the PPI papers, time-varying cumulative PPI use was also quantified. Prescriptions dispensed were summed in each 6-month period of follow-up and added to the growing cumulative sum. Time-varying exposure was not assessed for the benzodiazepine analysis.

Outcome Ascertainment

Cases of dementia were determined by using a previously validated algorithm developed for use with administrative data [91]. The definition chosen had a specificity of 99% (95% CI 98.8,99.4), a sensitivity of 79.3% (95% CI 72.9,85.8), a positive predictive value of 80.4% (95% CI 74.0,86.8), and a negative predictive value of 99% (95% CI 98.7,99.4). For an individual to be categorized as having dementia, they required one or more hospitalizations with an ICD-9 (290.0, 290.1, 290.2, 290.3, 290.4, 331.0, 331.1, 331.5, 331.82) or ICD-10 ((F00.x, F01.x, F02.x, F03.x, G30.x) code for dementia, one or more prescriptions for an anti-dementia drug (ATC codes starting with N06D, which includes acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine; as well as the glutamate antagonist memantine), or three or more medical claims within a 2-year period with an ICD-9 code for dementia (290, 294, 331). Further, each of the three medical claims required at least a 30-day separation between them to avoid including cases of delirium misclassified as dementia. We varied from the validated definition by not including the ICD-9 code for Creutzfeldt-Jakob disease (ICD-9 46.1) or "amnestic disorder in conditions classified elsewhere" (ICD-9 294) and the ICD-10 code for vascular dementia (F01.5). The original validated definition did not include an ICD-10 code for either Creutzfeldt-Jakob disease or amnestic disorder caused by other conditions. Creutzfeldt-Jakob is very rare condition caused by prion disease, and thus has a different etiology from the dementias studied here. Amnestic

disorder caused by other conditions, by definition, is due to other medical conditions including Korsakoff's psychosis.

Comorbidities

Comorbidities were assessed using a combination of medical claims, hospital abstracts and DPIN data using definitions described by Amiche et al.[92]. Comorbidities included asthma, amnestic disorder, cerebrovascular disease, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, dyslipidemia, epilepsy, alcohol/substance use disorders, gastroesophageal reflux disease (GERD), peptic ulcer disease, hypothyroidism, hyperthyroidism, liver disease, Parkinson's disease, schizophrenia, and vascular dementia. Vascular dementia could only be ascertained with the data available through hospital abstracts due to previously mentioned limitations. Most of these comorbidities require two or more medical claims within a 2-year period of each other or one or more hospitalizations to be classified as a diagnosis. Asthma, COPD, and rheumatic disorders also required one or more prescriptions to confirm a diagnosis. These definitions were developed by the Institute for Clinical Evaluative Sciences (ICES), an Ontario based research centre that works with administrative data much like that contained in the Manitoba repository.

High-Dimensional Propensity Score Cohort Construction

The HDPS cohorts consisted of a subgroup of persons included in the standard cohort where users were matched to non-users based on the high-dimensional propensity scores.

User/non-user definitions

Previously, researchers in this area have used several definitions of drug use/non-use in published studies. To mimic this literature, we calculated multiple propensity scores (PS) for each stratum using

similar definitions. We defined non-users, for all calculations, as those with no prior prescription in the three years prior to follow-up of that drug class, while the definition of a user varied.

For the PPI analysis, users (exposed persons) were defined three ways; any use (1 or more dispensed prescriptions), dispensation of 30 or more DDDs, and dispensation of 180 or more DDDs. For the definitions requiring a minimum number of DDDs, any person who received more than 0 but less than the required number of DDDs was excluded from that analysis. Only two definitions were used for the benzodiazepine score calculations: 30 DDDs or greater, and 90 DDDs or greater. Uses were then matched to non-users at ratio of 1:2 for the PPI analysis, and 1:1 for the benzodiazepine analysis, using a caliper of 0.01. Exact matching on sex, income quintile and Charlson Comorbidity index was required.

Five dimensions were used to calculate the HDPS scores, consisting of prescription data, medical claims, and hospitalization abstracts. For the prescription dimension, the ATC codes of each prescription dispensed to an individual in the three years prior to follow-up were used. Medical claims were used to create two dimensions, one based on ICD-9 diagnostic codes, the second using medical tariff codes. Hospital abstracts were used to create the last two dimensions consisting of diagnostic codes and intervention codes. These dimensions were entered into the HDPS macro created by Sebastion Schneeweiss [93] and propensity scores were calculated. Users and non-users were matched by greedy selection with a caliper of 0.01 or less.

Standardized differences in covariates were used to assess the success of HDPS balancing of confounding factors. Comorbid conditions and prescription drug use were determined using the same algorithm as in the non-HDPS models, but only used date from the three years of data prior to follow-up similar as this was also used to create the dimensions for the HDPS model. A standardized difference of 0.10 between users and non-users was considered well balanced.

Analysis.

Survival analysis was performed using Cox proportional hazards regression to analyze the relationship between cumulative drug exposure and the risk of dementia with a variety of approaches to minimize the risk of confounding, selection bias, and lag-time bias. The biggest risk factor for dementia is age, with the risk for dementia increasing in a non- linear fashion after the sixth decade of life. By using age as the timescale, the non-parametric baseline-hazard function accounts for this non-linear risk. Individuals within a stratum and across different exposures were thus compared to each other at the same age. Time was divided into 6-month steps from the beginning of follow-up. Each stratum was modelled independently from the others and reported separately.

Individuals were classified as either non- users (zero exposure) or divided into different categories of users based on cumulative DDDs dispensed up to the beginning of follow-up. These categories were determined by looking at the distribution of cumulative DDDs and choosing levels that would divide the user cohort into three roughly equal sized groups that represent short, intermediate, and long-term use. For the PPI analysis, these levels were 1-30 DDDs (1-30 days of standard doses), 31-180 DDDs (>1 month to 6 months), and >180 DDDs (>half a year). For benzodiazepines, the levels were 1-14 DDDs, 15-180 DDDs, and >180 DDDs. Fourteen days of benzodiazepine treatment is also the maximum recommended duration of therapy, although this is frequently ignored in practice. The benzodiazepine analysis also included two subgroup analyses; people with a diagnosis of depression, and a group of people with anxiety. Due to the smaller size of these sub-cohorts, cumulative benzodiazepine exposure among users was divided into only two levels, 1- 30 DDDs, and >30 DDDs.

Covariate selection

Covariates were selected for potential inclusion after testing their association with dementia individually. Variables with a p-value of <0.20 were then entered into a multivariate model and through

a process of manual backward selection retained if they retained significance at a p-value of 0.1 or less. Covariates that are clinically relevant to the analysis, such as sex, cardio-vascular disease, depression/anxiety and diabetes were included in all models.

Modelling

Methodological sensitivity analysis, using several different modelling approaches, was used to examine how the different methods affected the association between drug use and dementia, and to control for different types of bias (selection bias and protopathic bias) and to address unmeasurable confounding (HDPS matched cohorts).

Cox proportional hazard regression models were run in SAS v9.4 using PROC PHREG. Individuals were censored if they died, lost healthcare coverage (generally because they left the province or died) or were diagnosed with cerebrovascular disease or vascular dementia on the date the event occurred. The proportional hazards assumption was checked using Schoenfeld residuals.

Sensitivity analysis using time-varying exposures

As a sensitivity analysis for the PPI project, models using time-varying exposure were used. This involved assessing PPI exposure not just up to baseline, but also during follow-up and updating the cumulative PPI exposure for every six-month time-step. The main motivation for this was the relatively low level of use of PPIs in the early years of our data, and the continuing large upward trend in PPIs use in Manitoba. We also used time-varying covariates (comorbid conditions), updating these variables in a similar manner to exposure. Finally, we combined both time-vary exposure and time-varying covariate data-structures in a third model.

Addressing protopathic bias

In addition to standard models where outcomes are measured starting from the beginning of follow-up, models were run using lag periods to decrease the possible effect of protopathic bias affecting our results and the potential of assessing drug exposure during the prodromal stage of dementia. Protopathic bias is a bias that occurs when the early symptoms of a not yet diagnosed condition result in treatment.[94] Because the treatment precedes the actual diagnosis, a naïve approach to analysis might assume that the treatments are the cause of this outcome. These lag-periods involved censoring any outcomes that occur in a window starting immediately after the beginning of follow-up. For the PPI analysis, this meant an analysis where we excluded any outcomes in the first 5-years of follow-up. Benzodiazepines are used to treat anxiety, agitation, and sleep disturbances which are symptoms of dementia[31] making this drug class more likely to produce protopathic bias. As mentioned in chapter 1, the disease process of non-vascular dementia begins a decade or more before symptoms meet the clinical criteria for a dementia diagnosis. Therefore, we used lag periods of both 5 and 10 years in that analysis.

Addressing selection bias

The benzodiazepine analysis also looked at two subgroups of people, those with depression and those with anxiety. This was done to reduce the effect of selection bias. Selection bias could occur because both anxiety[95,96] and depression[39,84,86] are risk factors for dementia, and not taking this into account could result in incorrectly assuming a causal relationship between persons treated for these disorders with dementia. While depression, anxiety, and antidepressant use were independent variables in the previous models we cannot exclude the possibility that there may be individuals with undiagnosed depression or anxiety. By creating these subgroups we ensure that all users and non-users are similarly at higher risk of dementia.

Reducing unmeasured confounding

The HDPS cohorts were analyzed in a similar manner, but with only drug exposure included as an independent variable. The exception to this were covariates that remained unbalanced after HDPS matching. In this case, these covariates would be included to control for these factors.

Chapter 4: Proton Pump Inhibitors and Dementia

Proton pump inhibitors (PPIs) first became available in Canada in the late 1980s and their use has increased ever since. They are the second most commonly prescribed class of drugs among senior citizens in Canada, the most prescribed class in the UK, and are placed similarly in much the rest of the world.[97,98] They are used to treat a variety of gastrointestinal disorders related to gastric acidity and are highly effective, however, they are also frequently overprescribed, used for longer than necessary, and at higher than necessary doses.[99-102] Two common factors that play into their long term use is a) they have very few bothersome side effects and are well tolerated, and b) rebound hyperacidity can occur when they are abruptly stopped which can cause a temporary return of symptoms leading people to restart their use. This high level of use, and the prolonged exposure that commonly occurs increases the need for long-term safety studies. However, alarmist reporting on the two initial studies that showed an increase in dementia could also have potentially persuaded people with GERD to discontinue therapy to avoid this risk. Unfortunately, GERD is one of the conditions for which long term acid suppression may be required to prevent long term complications such as esophageal cancer. While PPIs are overprescribed and some people may discontinue therapy without incident, others have real need for ongoing treatment. For example, patients with Zollinger-Ellison disease also need to use PPIs long-term, and they need to know whether their treatment is safe.

The initial PPI studies that linked their use to dementia had serious methodological problems, primarily, they looked at PPI use over consecutive 18-month periods and determined if patients developed dementia in the following 18-month period.[22,103] Such a study design would be appropriate for looking at an outcome that develops relatively soon after exposure, unlike dementia which develops over decades. Second, they implicitly assumed the effect of PPIs on the dementia disease process was reversible, as subjects could switch from exposed to non-exposed status over time.

The following manuscript, reproduced in this chapter in full, has been published in the journal Clinical Pharmacology and Therapeutics in October 2022:

> Friesen KJ, Falk J, Chateau D, Kuo IF, Bugden S. Signal and Noise: Proton Pump Inhibitors and the Risk of Dementia? Clinical Pharmacology and Therapeutics. 2023;113(1):152-159.

It examines the effect of PPI use on dementia risk using a population-based approach. It attempts to avoid the mistakes mentioned above by using five- and ten-year lag windows that exclude outcomes occurring during those periods after the start of follow-up. High-dimensional propensity scores were also used to reduce unmeasured confounding. Long follow-up times allowed us to examine the effect of PPI use in middle-age and follow patients long enough to where a dementia outcome could occur, unlike some previous papers who, although including younger persons, lacked the sufficient follow-up time for them to become at risk of developing dementia.

Manuscript: Signal and Noise: Proton-pump-inhibitors and the risk of dementia?

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Abstract:

The association between proton pump inhibitor (PPI) use and dementia remains controversial. This cohort study re-examines this issue, addressing shortcomings identified in previous publications using a population-based and a high-dimensional propensity score matched cohort to follow patients for up to 22 years. Cox regression models using baseline characteristics, a lag period, and time-varying variables were used to examine the risk of dementia by cumulative PPI exposure.

High-dose PPI users (>180 days of use) had significantly higher risk of dementia in crude Cox models. After adjustment for medical diagnoses and prescription drug use these associations disappeared. Among high-dose users starting PPI therapy between 46 and 55 years old, the unadjusted hazard ratio (HR) was 1.55 (95% confidence interval 1.14, 2.10); the adjusted hazard ratio (aHR) was 1.10 (0.80, 1.51). For high-dose users starting therapy between 56-65 years, HR= 1.22 (1.03, 1.44); aHR= 0.99 (0.83, 1.17). High-dose users between age of 66-75 had no association with the risk of dementia. The use of lag models or time-varying parameters similarly found some association with dementia in crude, but not multivariable Cox models.

While high-dose PPI users were more likely to develop dementia, they were more likely to be diagnosed with dementia risk factors such as diabetes and cardiovascular disease, which are risk factors for dementia. Controlling for these conditions using multivariable models or a propensity-score matched cohort eliminated this association.

Signal and Noise: Proton-pump-inhibitors and the risk of dementia?

Introduction:

The association between proton pump inhibitors (PPIs) and dementia has received substantial attention since the publication of two German studies in 2015[22] and 2016[23] which reported a 40% increased risk of dementia in PPI users. Over a dozen papers followed with conflicting and inconsistent results resulting in significant "noise" making it difficult for clinicians to determine the "signal" from this body of research.[24,103-119] (Table 1). Dementia is largely untreatable; our currently available treatments provide minimal benefit, high rates of adverse effects, and can be very expensive.[52,53,120] However, research suggests that 40% of dementias could possibly be prevented or delayed by risk factor modification, meaning that there are things we can do to diminish the burden of this devastating disease.[76,121] Given the widespread use of PPIs and their important role in treating gastrointestinal disorders, it is vitally important to determine if this class of drugs is an actual risk factor as this may change the choices clinicians and patients make in using these drugs.

Randomized controlled trials (RCTs) are the gold-standard in determining the safety and effectiveness of drugs. The large PPI RCTs followed patients for several weeks to months, long enough establish their benefit and safety in short-term treatment. A small number of long-term PPI RCTs (> 1 year) exist, but with sample sizes in the low hundreds they lack the necessary statistical power to asses dementia risk.[25,122-124] Observational cohort studies can leverage millions of person-years of data spanning decades and are a practical alternative to RCTs when assessing long-term safety outcomes, but require proper methods to limit the effects of confounding and bias. While numerous publications have reported on this issue, there remain shortcomings in the evidence to date.

Dementia is a progressive disease with an asymptomatic latent phase of several decades, followed by a prodromal phase of several years where symptoms cannot be differentiated from normal cognitive

changes associated with aging.[46,125] Assessing the effects of PPIs requires looking at the biologically relevant period. If PPIs trigger dementia we need to examine use prior to latent phase onset, if they accelerate its development, we should examine the latent phase. However, several studies lacked sufficient follow-up time to avoid this prodromal period, while several allowed use statuses to vary from being a user to non-user (or vice versa), considering only the most recent exposure window in analyzing outcomes. (Table 1) One method that has been used to avoid this problem is the use of lag-periods, where exposure during the prodromal period is excluded from analysis when follow-up time permits.

Another common shortcoming is categorizing the cohort as either "users" or "non-users". This collapses persons with short-term use with those with years of PPI exposure. While several studies examined duration of exposure, the results were again inconsistent. (Table 2) Two studies found evidence of a dose-response relationship, [112,114], two found increased risk,[103,108] and one found similar risk across levels of use.[106]

The variation is cohort ages and duration of follow-up complicates the comparison of study results, with most focusing on older cohorts (e.g., ≥ 75 years) as this is when dementia risk is highest. However, this excludes the most biologically relevant exposure window. (Table 1) A major reason for this choice is the follow-up periods required to assess the effects of midlife (~45 years) exposure, which necessitates at least 15 to 20 years for a statistically meaningful number of cases to be captured.

There are justifications for the use of many of the analytical approaches used in the literature and deciding on the correct *a priori* is not always clear. To evaluate whether PPIs increase the risk of dementia, or if this association is due to confounding or other types of bias, we used several analytical approaches on a large, population based administrative healthcare database with a longer period of follow-up than any yet published study.

Methods:

Data sources:

Administrative health care data from April 1st, 1995, and March 31st, 2021, were used to conduct an longitudinal cohort study off PPI use and dementia risk. Using the Manitoba Population Research Data Repository, we obtained prescription dispensation data, medical billing records, hospital discharge abstracts, long-term care home admissions data, Canadian census data, and the Manitoba Health Care registry. This population-based repository has been used extensively for health and social research and has been previously described.[126] A de-identified scrambled ID number allows for crosslinking of records across databases in the repository. Ethics approval for this study was obtained from the University of Manitoba Health Research Ethics Board (H2017:404) and the Province of Manitoba's Health Information Privacy Committee (2017/2018-46).

Study Population:

All persons in the province of Manitoba between 46 and 75 years of age on April 1st 1998 (study start date) were eligible for inclusion if they a) had at least 3 years of pre- and a minimum of 1 year post-start date healthcare coverage; b) had no PPI or histamine-2 receptor antagonist prescriptions prior to study start; c) no pre-existing dementia diagnosis; d) did not have a diagnosis of Parkinson's disease, schizophrenia, epilepsy, or Downs's syndrome as these are strong, independent risk factors for dementia; e) no diagnosis of liver disease as this is a contraindication to PPI use; f) did not enter a long-term care home prior to beginning of follow-up as prescription data in long-term care homes is missing for approximately 25% of residents.

From this population, two types of cohorts were developed: a) a population-based cohort including all study subjects meeting inclusion criteria, and b) a propensity score matched cohort derived from the

population-based cohort (discussed further later). For each cohort type, three age-based cohorts were created based on age at study start: cohort 1 (46-55 years, born between April 1, 1943, and March 31, 1952), cohort 2 (56-65 years, born between April 1933 and March 1943), and cohort 3 (66-75 years, born between April 1923 and March 1933). Analyses were run on each age-based cohorts independently for both population and propensity-score based cohorts.

Covariates:

We assessed comorbidities through medical claims and hospital discharge abstracts using International Classification of Disease (ICD) version 9-CA and 10-CM codes, and prescription data using Anatomical, Therapeutic, Chemical classification (ATC) codes with definitions previously reported by Amiche *et al*.[92] Diagnoses screened for inclusion in our final models included hypertension, chronic obstructive pulmonary disease, cardiovascular disease, depression and anxiety (as a combined group), dyslipidemia, gastroesophageal reflux disease, gout, hyperthyroidism, hypothyroidism, peptic ulcer disease, substance abuse (including alcoholism), and autoimmune disorders. While we calculated Charlson Comorbidity Index scores for descriptive purposes, these scores were not used in our modelling approaches. We determined non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants use in the five years before follow-up. NSAIDs were included as they are commonly co-prescribed with PPIs and have been reported to increase the risk of dementia.[127] Antidepressant use has also been suggested as a risk factor for dementia and we felt it important to include. Median neighborhood income quintiles were determined based on postal code and collapsed into two groups, bottom 2 vs upper 3 quintiles, as socioeconomic status is known to affect health outcomes.

Exposure Assessment:

We measured cumulative PPI exposure prior to follow-up using World Health Organization (WHO) defined daily doses (DDDs).[128] PPI use was modelled as a categorical variable with 3 levels: 1-30 DDDs,

31-180 DDDs, and > 180 DDDs. These categories divided users into approximately equally sized groups. Time-varying exposure models used cumulative PPI DDDs up to each event-time using these same levels.

Outcome Assessment:

Individuals with dementia were identified using a validated algorithm (sensitivity 79%, specificity 99%) using hospital, medical, and prescription data.[91] This definition requires one of the following conditions to be met: one or more prescriptions for a dementia-specific medication (donepezil, galantamine, rivastigmine, memantine); a dementia diagnosis in hospital data; or 3 or more medical claims with a diagnostic codes within 2 years of each other, provided at least 30 days exist between claims. We were unable to distinguish between Alzheimer's and other dementias, so we excluded persons with Parkinson's to exclude Parkinson's dementia, and censored individuals with cerebrovascular disease to reduce vascular dementia cases which may have a different pathophysiology.

Statistical Analysis:

Descriptive statistics were used to characterize our cohorts, with standardized differences in the mean used to compare PPI user groups to non-users. The Kaplan Meier estimator was used to look at time (i.e. age) to development of dementia. Cox regression was used to test the association between cumulative PPI use and dementia in each age-based cohort, for both cohort-types, independently. Follow-up time began, for each cohort, at the age at the upper limit of that cohort (Figure 1). For example, follow-up time for cohort 1 (age 46-55) began at age 55 (that cohort's baseline). This made age, one of the strongest predictors of dementia risk, equivalent to follow-up time. This allows the effect of age to be handled by the non-parametric baseline hazard function, rather than adjusting for age as a covariate.[129,130] Medical diagnoses were entered as individual covariates in exploratory single-variable models, including in initial multivariable models if there was an association with the outcome at a p-value of less than 0.2, and remained in the final model if they had a final p-value of 0.10 or less. NSAID

and antidepressant use, diabetes, cardiovascular disease, and income quintile were included in all models. Individuals were followed until dementia, death, lapse of health care registration, moving out of province, or when then end of data was reached, and those without a diagnosis of dementia were censored. Cox modelling assumptions were tested by examining Schoenfeld residuals.

Population-based cohort models:

Cox regression models incorporated exposure and covariates in several ways (Figure 1). Our main model (Model A) used baseline covariates and total cumulative PPI use up to baseline. A baseline model with a lag (Model B) excluded events within the first 5 years of follow-up to minimize prodromal exposures. Three time-varying models were also used. Model C used baseline cumulative PPI use and time-varying diagnoses to account for conditions arising during follow-up. Model D used baseline diagnoses and time-varying PPI use. Model E allowed both diagnoses and exposure levels to vary with time during follow-up.

Propensity-score matched cohort models:

We used HDPS to calculate propensity scores and create a matched cohort from each age-based cohort as another method to control for confounding using the HDPS algorithm and methods developed by Schneeweiss.[93] Previous studies have used various "user" definitions including requiring only 1 or more prescriptions; a minimum of 30 DDDs (or >30 DDDs); and a minimum of 6 months of use. We calculated 3 propensity scores, one for each of these definitions of a "user", and matched on this score, sex, income quintile, and Charlson comorbidity index score (CCI) at a ratio of up to 1:2. PPI users not meeting the second or third definition of user were removed from data prior to HDPS calculation.

These user/non-user matched cohorts were then modeled three different ways: 1) simple Cox regression model (HDPS Model A), 2) using a 5-year lag period (HDPS Model B), and 3) by censoring non-

users if they became users during follow-up (HDPS Model C). We included this last model as matched non-users have a high propensity to use PPI and may become users during follow-up.

Results:

We included 207,380 persons in our final analysis, including 17,764 persons with dementia during follow-up. Using the Kaplan Meier estimator, we found that 25% of our cohort developed dementia by the age of 88 years.

PPI users were more likely to have medical comorbidities at baseline, with higher levels of PPI exposure associated with higher proportions of morbidities in each of the three age cohorts (Tables S1 – S3). The standardized difference between non-users and high-dose users (>180 DDDs) for cohorts 1, 2, and 3 were 0.33, 0.38 and 0.46 for cardiovascular disease, and 0.18, 0.23, and 0.17 for diabetes. These conditions are all dementia risk factors.[131,132]

Table 3 lists the Cox regression results for population-based models A through E. Persons using greater than 180 PPI DDDs were at increased risk of dementia in our main model (model A) for both cohort 1 (crude hazard ratio (cHR) = 1.55 [95% confidence interval 1.14, 2.10]) and cohort 2 (cHR = 1.22 [1.03, 1.44]) but not in our oldest cohort. (Table 3). After adjustment for baseline diagnoses none of the dose groups had a significantly increased risk of dementia, with point estimates ranging from an adjusted HR of 0.82 up to 1.13. Using lag-models (model B) or using time-varying diagnosis models (model C) did not find a significant risk of dementia in any age or dose group.

Extending our exposure window to include PPI use during follow-up (Model D & E with time-varying cumulative exposure), we observed a significant risk in the high dose PPI group prior to covariate adjustment (Table 3). This increase was highest in the youngest cohort (cohort 1) and decreased as cohort age increased (cohort 2 and 3). After adjustment for baseline (model D) diagnoses, only the

highest dose group in cohort 1 had a marginal but statistically significant increased risk (aHR= 1.19 [1.06, 1.33]). This effect disappeared when diagnoses were also modelled as time varying.

HDPS matching reduced covariate imbalance (aside from GERD which was not included in the propensity score model) within 10% of the standardized difference. (Tables S4 - S12). Our matched analysis found statistically significant but minor effects only in cohort 2 (age 56-65) for some comparison groups (Table 4). These effects were not significant, and the point estimate was close to the null when non-users were compared with high-dose users. In contrast, when the criteria to be considered exposed was broadened to include lower dose users there was a modest but statistically significant increase in risk, but only in HDPS cohort 2 for some models. In the other HDPS matched cohorts (HDPS Cohort 1 and 2) PPIs showed no effect on the risk of dementia.

Discussion:

Our crude analysis found PPI users who initiated treatment between the age of 46 and 65 to be at a modestly increased risk of dementia, however this appears to be due to confounding. The highest risk was seen in the highest dose group, those with more than 180 total DDDs of PPIs use, and in those who began using PPIs between the age of 46-55, with a 55% higher risk, compared to a 22% increase for those starting PPI use between the ages of 56-65, and a non-significant 6% risk in our oldest cohort (66-75 years). After adjustment for comorbid conditions, or when analyzed using an HDPS matched cohort, no increase in risk was found in most cohorts and comparison groups.

PPI users had significantly higher rates of many morbidities such as cardiovascular disease, diabetes mellitus, and depression, and were highest in high dose users. These conditions are themselves risk factors, and after controlling for them PPI use was no longer associated with an increased risk.[121] HDPS methods created balanced cohorts, reduced confounding, and found PPI no difference in dementia risk.

Our findings differ from Haenisch and Gomm who found significant dementia risk in PPIs users.[22,23] (Table 1). User status was determined based on the 18 months preceding each outcome assessment. This window falls well within the dementia prodromal period and is not a biologically relevant period. Herghelegiu[105] used an observation period of 3 years but exposure was based on patient recall, they had a small cohort, and outcomes assessed using the Mini-Mental State Exam (MMSE), which is a screening and not diagnostic tool. Tai found significant user/non-user as well as dose-response effects of PPI using a PS matched cohort, but not among their highest dose group. Their analysis used time-in-study, rather than age, as a timescale and included patients from ages 40 to over 70. The Chen user/non-user analysis allowed user status to vary, and users became non-users when they discontinued PPIs.[114] In contrast, we assumed the effect of PPI was cumulative and non-reversible as dementia is a neurodegenerative condition. In both their dose-response and user/non-user analysis they used baseline comorbidities summarized by CCI score, which is designed to predict mortality not dementia risk. As Chen used up to 14 years of follow-up, using baseline comorbidities alone may also be inadequate. A recent study by Choi *et al* found an increased risk in current and past users of PPIs, and a dose-response effect.[119]. However, this study only looked at exposure status in the year before diagnosis at the very end of the prodromal period, and therefore has important limitations in its ability to assess the causal relationship between PPI use and dementia. Lastly, the role of chance findings in the discrepant literature should also be considered given the number of papers published.

Our youngest cohort had the strongest association between high levels of PPI use dementia risk, with increasing cohort age displaying lower crude risk. This was an unexpected finding. In this young cohort, long-term PPI use may be a proxy for poorer baseline health, and sicker individuals see physicians more frequently and have more opportunities to get PPIs prescription renewals. While comorbidities were more common in the older cohorts across exposure levels, the difference between non-users and the

PPI users was greatest in the youngest cohort. Older persons see physicians more frequently for a variety of reasons, and PPI use may not act as strong a proxy for poor general health in this group.

Looking at the viewpoints Bradford Hill listed as useful when assessing causality,[133] we can see that the link between PPIs and the risk of dementia fails on multiple points. Studies finding increased dementia risk typically reported modest risk estimates with lower confidence intervals typically near the null. Further, there is a clear lack of consistency in the PPI-dementia literature. (Table 2) Regarding biological plausibility, another of Hill's considerations, numerous potential biological mechanisms have been suggested but *in vivo* data is lacking, and the etiology of dementia is itself not understood.

Our study has multiple strengths and limitations. We had over 20 years of data allowing us to follow individuals for longer than previous studies, and access to virtually all interactions between our cohort and healthcare providers thanks to universal healthcare system and central data repository We used prescription dispensation data rather than relying on patient interviews or prescriptions found in medical records but not necessarily filled. This allowed us to determine cumulative doses dispensed accurately, allowing us to look for a dose-response relationship. Whereas other studies often combined wide ranges of age into one group or were restricted to older persons (>75 years), we age-stratified our analysis into 3 groups. Limitations include a lack of data on educational status, exercise, ethnicity, apolipoprotein E status, and smoking. We were also unable to distinguish between AD and non-AD dementia. Alzheimer's disease accounts for 50% to 70% of dementias, followed by vascular dementia at 15%. We minimized the heterogeneity of dementia cases by excluding patients with cerebrovascular disease (vascular dementia), Parkinson's disease (Parkinson's dementia). Lastly, the algorithm we used to identify cases of dementia in our data was highly specific at 99% but had a 79% sensitivity, meaning that we likely have undercounted the true number of cases in our population. However, we would expect that if this undercounting were differential between exposure groups, it would bias the results towards showing a higher risk among the highest dose PPI users. Medical comorbidities were highest in

this group, and they likely encounter the medical system more frequently, increasing the probability of physicians diagnosing those with dementia.

The link between PPIs and dementia remains unclear as there is wide variation between studies as to sources of data, cases ascertainment, the duration of study follow-up, and the analytical approaches used, resulting in diverse findings. Our findings add to the evidence that long-term PPI use does not increase dementia risk. While we did find elevated rates of dementia in long-term PPI users compared to non-users, we also found higher rates of diabetes, depression, cardiovascular disease, and other medical conditions which are independent risk factors for dementia and AD, both prior to PPI initiation as well as during follow-up. After using statistical methods to control for this "noise" we determined that the higher rates of cooccurring conditions was responsible for the dementia signal found in our population of PPI users, and not PPI use itself. These results will hopefully increase the confidence in the safety of long-term PPI use with regards to the risk of dementia, which is important as many rely on them to control symptoms of gastric acidity disorders and to prevent their potential long-term complications.

Study Highlights:

What is the current knowledge on the topic?

PPIs are one of the most prescribed classes of drugs in the world. Concern has been raised in previous reports that their use may increase the risk of dementia.

What question did this study address?

This study re-examines this question using over 20 years of data in a large, population-based cohort and using a high dimension propensity score matched cohort stratified by age.

What does this study add to our knowledge?

We found that while long term users of proton pump inhibitors have higher rates of dementia than non-users, they also have higher rates of diabetes, depression, cardiovascular disease and other risk factors for dementia. Controlling for these conditions using multivariable models or a propensity score matched cohort eliminated the association between PPIs and dementia.

How might this change clinical pharmacology or translational science?

While they are many reasons not to overuse PPIs, the balance of evidence suggests that increased risk of dementia should not be considered an important factor in prescribing PPIs to patients with appropriate indications for therapy.

Acknowledgements:

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Specific Authors Contributions:

K.F., S.B, and J.F. wrote the manuscript; K.F., S.B., D.C. and I.K. designed the research; K.F. performed the research and analyzed the data.

Abbreviations:

AD, Alzheimer's dementia; aHR, adjusted hazard ratio; ATC, anatomical therapeutic chemical classification; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DDD, designated daily dose; HDPS, high-dimensional propensity score; HR, hazard ratio; ICD, International Classification of Disease; MMSE, mini-mental state exam; NSAID, non-steroidal

anti-inflammatory drug; PPI, proton pump inhibitors; PS, propensity score; RCT, randomized controlled trial; WHO, World Health Organization.

Figures and Tables

Figure 1: Cohort definitions and description of modelling designs

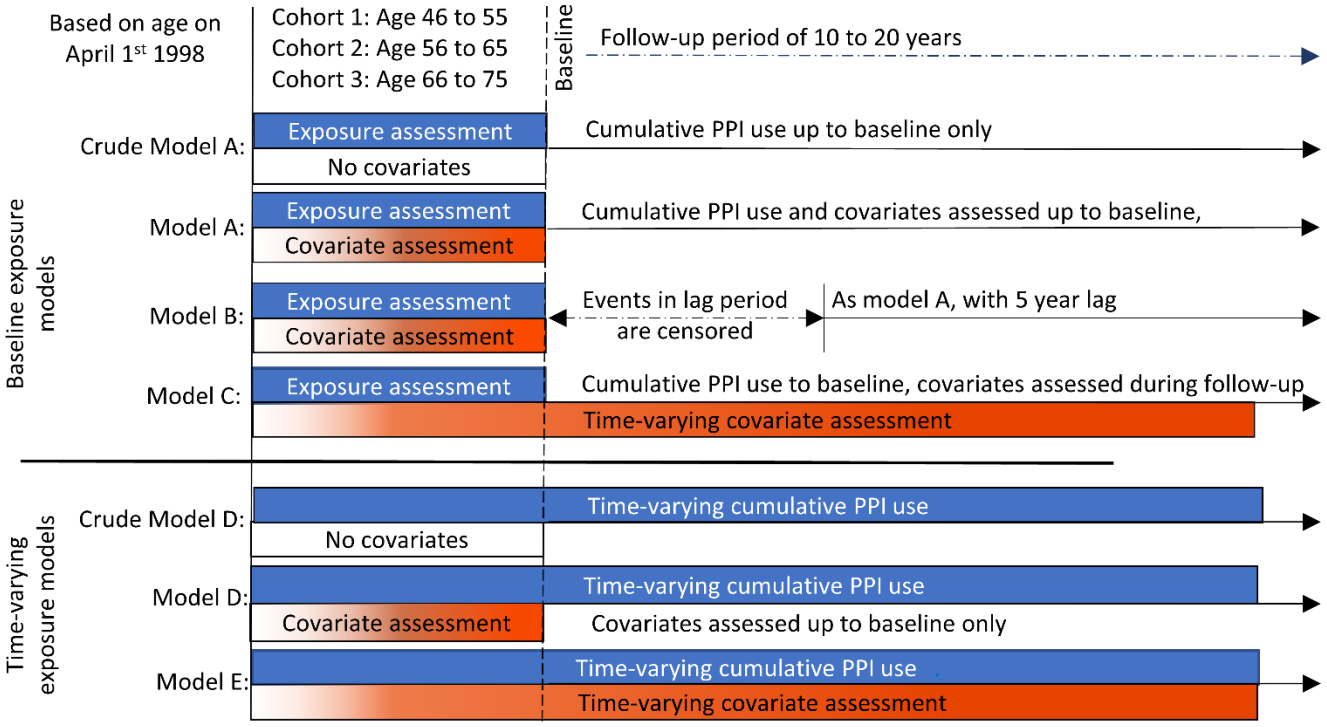

Table 1: Previously published studies looking at the relationship between PPIs and dementia.

Abbreviations: HR, hazard ratio; OR, odds ratio. Significant increase in risk shaded orange, significant decreases shaded blue

					Outcome Measured	
Observational PPI-Dementia Studies					**Alzheimer's Disease**	**Dementia**
Author, Year	**Age**	**Follow Up/Look Back**	**Cohort Size**	**Cases**	**User/Non-User**	**User/Non-User**
Haenisch 2015[22]	>75	Up to 6	3,076	431	HR= 1.44 (1.01–2.06)	HR= 1.38 (1.04–1.83)
Gomm 2016[23]	>75	Up to 7	73,679	29,510	-	HR= 1.44 (1.36-1.52)
Booker 2016[104]	70-90	10	23,912	11,956	-	OR= 0.94 (0.90-0.97)
Herghelegiu 2016[105]	>65	3	148	26	-	OR= 3.67 (2.23 - 19.15)
Tai 2017[106]	>40	Up to 11	15,726	707	-	HR= 1.22 (1.05-1.42)
Taipale 2017[107]	>60	Up to 16	353,576	70,718	OR= 1.02 (1.00-1.04)	-
Gray 2018[108]	>65	10	3,484	827	User/non-user results not reported	
Liao 2018[111]	>65	Not reported	2,140	428	OR= 0.79 (0.63-1.01)	-
Hwang 2018[109]	>60	Up to 7	70,033	1,297	-	HR= 0.99 (0.70-1.39)
Imfield 2018[110]	>65	Up to 15	82,058	41,029	OR= 0.85 (0.82-0.89)	-
Huang 2019[112]	>65	Up to 5	10,533	1,297	No non-user analysis reported	
Cooksey 2020[115]	>55	Up to 15	315,078	37,148	-	HR= 0.67 (0.65-0.67)
Chen 2020[114]	>65	Up to 14	18,800	3,746	-	HR= 1.42 (1.07-1.84)
Wu 2020[117]	>40	Up to 10	5,166	130	-	HR= 0.72 (0.51-1.03)
Torres-Bondia 2020[116]	>45	Up to 14	135,722	1,135	OR= 1.06 (0.93-1.21)	-
Ahn 2022[118]	>40	Up to 10 years	2,698,176	56,576		HR= 1.54 (1.51, 1.580
Choi 2022[119]	>60	Up to 10 years	86,125	17,225	OR= 1.36 (1.26, 1.46)	

Table 2: Observational PPI-dementia studies with results reported by total PPI dose.

Abbreviations: HR, hazard ratio; PS, propensity score; DYD, designated yearly dose, i.e. 365 designated daily doses; CCI, Charlson comorbidity index. Significant increase in risk shaded orange, significant decreases shaded blue

Author, Year	Modelling Method	Low Dose	Medium Dose	High Dose	Highest Dose
Tai 2017[106]	Cox, PS matched	< 28 DDDs	28-48 DDDs	49-83 DDDs	> 84 DDDs
		1.21 (0.94-1.56)	1.32 (1.04-1.68)	1.33 (1.07-1.65)	1.19 (0.95-1.48)
Goldstein 2017[103]	Cox, not matched	Intermittent users		Continuous users	
		HR= 0.84 (0.76-0.93)		HR= 0.78 (0.66-0.93	
Gray 2018[108]	Cox, modelled as a continuous spline	365 DDD (1 DYD)	3 DYD	5 DYD	
		0.87 (0.65-1.18)	0.99 (0.75-1.3)	1.13 (0.82-1.56)	
Chen 2020[114]	Cox, matched on age, sex, CCI	1-30 DDDs	31-180 DDDs	181-365 DDDs	>365 DDDs
		1.09 (0.91-1.37)	1.59 (1.19-1.89)	1.82 (1.22-2.13)	2.02 (1.43-2.31)
Huang 2019[112]	Cox model, PPI users only	Short term	Intermittent users	Continuous users	>365 DDDs
		Reference group	0.91 (0.93-1.17)	0.99 (0.93-1.17)	2.02 (1.43-2.31)
Choi 2022[119]	Logistic model, case control	<30 days	30-90 days	>90 days	
		1.13 (1.07, 1.19)	1.18 (1.10, 1.27)	1.26 (1.16, 1.36)	

Table 3: Population based Cox regression models:

Model A, B, and C model baseline exposure (PPI use from the lower to upper boundary of the starting age categories). Model A is a simple Cox regression model using baseline covariate values. Model B is a lag model where events within the first 5 years of follow-up were censored. Model C allows for diagnoses during follow-up to be incorporated using time-varying values. Model D and E include baseline exposure as well as PPI use during follow-up. Model D uses only baseline diagnoses; model E is time-varying with respect to exposure and diagnoses. Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; DDD, designated daily dose

	Baseline Exposure Analysis				Time-Varying Exposure Analysis		
Stratum 1	Main Model		Model B	Model C		Model D	Model E
Start Age 46-55	Crude HR	aHR	aHR	aHR	Crude HR	aHR	aHR
≤ 30 DDD	1.16 (0.85, 1.59)	0.99 (0.72, 1.35)	1.00 (0.72, 1.38)	0.94 (0.69, 1.29)	0.99 (0.80, 1.22)	0.91 (0.74, 1.13)	0.86 (0.70, 1.07)
31-180 DDD	1.20 (0.87, 1.65)	0.94 (0.68, 1.30)	0.96 (0.68, 1.34)	0.92 (0.66, 1.26)	1.09 (0.93, 1.29)	1.00 (0.84, 1.18)	0.91 (0.77, 1.08)
>180 DDD	1.55 (1.14, 2.10)	1.10 (0.80, 1.51)	1.13 (0.81, 1.57)	1.08 (0.79, 1.47)	1.41 (1.27, 1.58)	1.19 (1.06, 1.33)	1.07 (0.95, 1.20)
Stratum 2							
Start Age 56-65	Crude HR	aHR	aHR	aHR	Crude HR	aHR	aHR
≤ 30 DDD	1.25 (1.06, 1.46)	1.13 (0.97, 1.33)	1.15 (0.97, 1.36)	1.07 (0.91, 1.25)	1.10 (0.98, 1.23)	1.05 (0.94, 1.18)	1.00 (0.90, 1.12)
31-180 DDD	1.13 (0.96, 1.33)	1.00 (0.85, 1.18)	1.05 (0.88, 1.24)	0.95 (0.81, 1.12)	1.03 (0.94, 1.13)	0.97 (0.88, 1.07)	0.90 (0.82, 1.00)
>180 DDD	1.22 (1.03, 1.44)	0.99 (0.83, 1.17)	1.07 (0.90, 1.28)	0.95 (0.80, 1.12)	1.15 (1.08, 1.23)	1.02 (0.95, 1.09)	0.93 (0.87, 1.00)
Stratum 3							
Start Age 66-75	Crude HR	aHR	aHR	aHR	Crude HR	aHR	aHR
≤ 30 DDD	1.02 (0.91, 1.15)	0.97 (0.86, 1.08)	0.91 (0.80, 1.05)	0.93 (0.83, 1.05)	1.07 (0.99, 1.16)	1.02 (0.94, 1.11)	0.99 (0.91, 1.07)
31-180 DDD	0.89 (0.80, 1.00)	0.82 (0.73, 0.92)	0.83 (0.73, 0.94)	0.78 (0.70, 0.88)	0.96 (0.89, 1.03)	0.91 (0.85, 0.98)	0.86 (0.80, 0.93)
>180 DDD	1.06 (0.96, 1.18)	0.94 (0.84, 1.04)	0.92 (0.81, 1.04)	0.89 (0.80, 0.99)	1.09 (1.04, 1.15)	0.99 (0.94, 1.04)	0.91 (0.87, 0.96)

Table 4: High Dimensionalal Propensity score (HDPS) matched Cox regression models: PPI non-users were matched using HDPS scores to three non-exclusive comparison groups; all PPI users, PPI users with more than 30 DDDs of exposure, and PPI users with more than 180 DDDs of exposure. Model A is a standard baseline model, model B is a lag model where all events within the first 5 years of follow-up were excluded, and model C where non-users who started PPI treatment during follow-up were censored on the date of their first prescription. Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; DDD, designated daily dose

PS Matched Analysis

Matching Groups	HDPS Model A	HDPS Model B (5 Year Lag)	HDPS Model C (Censor Future Users)
HDPS Stratum 1 (Start age 46-55)	aHR	aHR	aHR
Users: Non-Users	1.16 (0.91, 1.50)	1.17 (0.9, 1.52)	1.30 (0.96, 1.76)
>30 DDD: Non-Users	1.06 (0.78, 1.46)	1.08 (0.77, 1.50)	1.02 (0.70, 1.48)
>180 DDD: Non-Users	1.23 (0.76, 1.98)	1.20 (0.73, 1.97)	1.14 (0.64, 2.02)
HDPS Stratum 2 (Start age 56-65)			
Users: Non-Users	1.20 (1.05, 1.38)	1.28 (1.11, 1.47)	1.13 (0.96, 1.32)
>30 DDD: Non-Users	1.17 (0.99, 1.39)	1.28 (1.07, 1.53)	1.16 (0.94, 1.42)
>180 DDD: Non-Users	1.04 (0.79, 1.36)	1.10 (0.83, 1.46)	0.91 (0.67, 1.25)
HDPS Stratum 3 (Start age 66-75)			
Users: Non-Users	0.89 (0.82, 0.98)	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)
>30 DDD: Non-Users	0.87 (0.78, 0.97)	0.87 (0.77, 0.98)	0.87 (0.77, 0.98)
>180 DDD: Non-Users	0.96 (0.82, 1.12)	0.90 (0.75, 1.07)	0.90 (0.75, 1.07)

Supplemental tables:

Supplemental tables S1 – S3 Notes:

Notes for supplemental tables S1 – S3: Drug use was quantified using defined daily dose. PPI use is the total cumulative dose up to baseline. For NSAIDs and antidepressants, use in the 5 years pre-baseline was determined. Income quintiles are divided into two groups, those in the lowest two income quintiles versus those in the third and higher income groups. Substance abuse includes alcoholism and abuse of drugs.

Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; CCI, Charlson comorbidity index scores; Std Diff, standardized difference in means/proportions from non-user group

Table S1: Baseline characteristics for cohort 1, age 46-55, by cumulative PPI dose

Age 46-55	Non-users (n= 93,088)		1-30 DDDs (n = 2,467)			>30 to 180 DDDs (n = 2,454)			>180 DDDs (n = 2,297)		
	N	%	n	%	Std diff	n	%	Std diff	n	%	Std diff
Cardiovascular disease	4,458	4.8	253	10.3	0.21	255	10.4	0.21	329	14.3	0.33
Diabetes mellitus	7,829	8.4	263	10.7	0.08	289	11.8	0.11	319	13.9	0.18
GERD	929	1.0	248	10.1	0.40	526	21.4	0.68	931	40.5	1.11
Substance abuse	2,305	2.5	92	3.7	0.07	123	5.0	0.13	142	6.2	0.18
Autoimmune disorders	2,553	2.7	156	6.3	0.17	150	6.1	0.16	203	8.8	0.26
Hypertension	23,077	25.8	827	33.5	0.17	822	33.5	0.17	946	41.2	0.33
COPD	4,517	4.9	218	8.8	0.16	253	10.3	0.20	337	14.7	0.33
Depression	19,200	20.6	893	36.2	0.35	976	39.8	0.43	1,031	44.9	0.54
Dyslipidemia	12,592	13.5	508	20.6	0.19	502	20.4	0.19	546	23.8	0.27
Hypothyroidism	3,719	4.0	142	5.8	0.08	174	7.1	0.14	176	7.7	0.16
Peptic ulcer disease	267	0.3	134	5.4	0.31	203	8.3	0.40	191	8.3	0.40
Income quintile (>3)	63,291	69.0	1,675	67.9	-0.02	1,611	65.7	-0.07	1,532	66.7	-0.05
Antidepressant use											
>1 month	4,440	4.7	169	6.9	-0.23	176	7.2	-0.34	154	6.7	-0.59
>0.5 year	1,859	2.0	89	3.6		80	3.3		105	4.6	
>1 year	7,853	8.4	336	13.6		445	18.1		646	28.1	
NSAIDs											
>1 month	13,098	14.4	454	18.4	-0.14	411	16.8	-0.26	358	15.6	-0.39
>0.5 year	3,993	4.3	143	5.8		140	5.7		152	6.6	
>1 year	8,707	9.4	385	9.4		408	16.6		495	21.6	
CCI level											
1	16,686	17.9	597	24.4	-0.32	622	25.4	-0.37	625	27.2	-0.45
2	4,340	4.7	237	9.6		225	9.2		216	9.4	
≥3	2,048	2.2	114	4.6		152	6.2		176	7.7	

Table S2: Baseline characteristics for Cohort 2, age 56-65, by cumulative PPI dose: See table S1 notes.

	Non-users (n = 55,461)		1-30 DDDs (n = 1,696)			>30 to 180 DDDs (n = 1,769)			>180 DDDs (n = 1,844)		
Age 56-65	**n**	**%**	**n**	**%**	**Std diff**	**n**	**%**	**Std diff**	**n**	**%**	**Std diff**
Cardiovascular disease	6,107	11.0	339	20.0	0.25	389	22.0	0.30	471	25.5	0.38
Diabetes mellitus	7,323	13.2	303	17.9	0.13	288	16.3	0.09	406	22.0	0.23
GERD	675	1.2	201	11.9	0.44	395	22.3	0.69	729	39.5	1.08
Substance abuse	1,160	2.1	62	3.7	0.10	63	3.6	0.09	73	4.0	0.11
Autoimmune disorders	1,672	3.0	80	4.7	0.09	119	6.7	0.17	156	8.5	0.24
Hypertension	22,037	39.7	900	53.1	0.27	870	49.2	0.19	1,091	59.2	0.40
COPD	3,117	5.6	135	8.0	0.10	200	11.3	0.21	296	16.1	0.34
Depression	9,092	16.4	484	28.5	0.29	546	30.9	0.35	710	38.5	0.51
Dyslipidemia	11,254	20.3	480	28.3	0.19	523	29.6	0.22	595	32.3	0.28
Hypothyroidism	2,748	5.0	128	7.6	0.11	145	8.2	0.13	160	8.7	0.15
Peptic ulcer disease	206	0.4	77	4.5	0.27	151	8.5	0.40	164	8.9	0.41
Income quintile (>3)	35,200	63.5	1,093	64.5	0.02	1,131	63.9	0.01	1,134	61.5	-0.04
Antidepressant use											
>1 month	2,257	4.1	86	5.1	-0.22	121	6.8	-0.27	100	5.4	-0.49
>0.5 year	905	1.6	44	2.6		36	2.0		78	4.2	
>1 year	3,413	6.2	201	11.9		225	12.7		383	20.8	
NSAIDs											
>1 month	6,891	12.4	272	16.1	-0.17	264	14.9	-0.33	217	11.8	-0.30
>0.5 year	2,657	4.8	99	5.8		107	6.1		112	6.1	
>1 year	6,304	11.4	250	14.7		296	22.0		405	22.0	
CCI level											
1	12,163	21.9	462	27.2	-0.38	510	28.8	-0.47	532	28.9	-0.56
2	4,756	5.6	213	12.6		258	14.6		268	14.5	
≥3	2,825	5.1	162	9.6		183	10.3		260	14.1	

Table S3: Baseline characteristics for cohort 3, age 66-75, by cumulative PPI dose: See table S1 notes.

Age 66-75	Non-users (n = 41,529)		1-30 DDDs (n = 1,398)			>30 to 180 DDDs (n = 1,569)			>180 DDDs (n = 1,808)		
	n	**%**	**n**	**%**	**Std diff**	**n**	**%**	**Std diff**	**n**	**%**	**Std diff**
Cardiovascular disease	7,765	18.7	401	28.7	0.24	494	31.5	0.30	702	38.8	0.46
Diabetes mellitus	6,371	15.3	252	18.0	0.07	325	20.7	0.14	393	21.7	0.17
GERD	592	1.4	156	11.2	0.41	303	19.3	0.61	657	36.3	1.00
Substance abuse	572	1.4	33	2.4	0.07	31	2.0	0.05	39	2.2	0.06
Autoimmune disorders	1,495	3.6	92	6.6	0.14	120	7.7	0.18	165	9.1	0.23
Hypertension	21,666	52.2	891	64.0	0.24	1,024	65.3	0.27	1,283	71.0	0.39
COPD	2,918	7.0	169	12.1	0.17	207	13.2	0.21	296	16.4	0.30
Depression	6,148	14.8	348	24.9	0.26	452	28.8	0.34	561	31.0	0.39
Dyslipidemia	7,873	19.0	360	25.8	0.16	429	27.4	0.20	612	33.9	0.34
Hypothyroidism	2,614	6.3	144	10.3	0.15	142	9.1	0.11	230	12.7	0.22
Peptic ulcer disease	173	0.4	78	5.6	0.31	167	10.7	0.46	203	11.2	0.47
Income quintile (>3)	23,734	57.2	840	60.1	0.06	927	59.1	0.04	1,046	57.9	0.01
Antidepressant use											
>1 month	1,871	4.5	90	6.4	-0.18	103	6.6	-0.23	126	7.0	-0.41
>0.5 year	886	2.1	38	2.7		56	3.6		85	4.7	
>1 year	2,718	6.6	149	10.7		183	11.7		318	17.6	
NSAIDs											
>1 month	4,908	11.8	196	14.0	-0.09	231	13.6	-0.08	192	10.6	-0.20
>0.5 year	2,216	5.3	89	6.3		89	5.7		140	7.7	
>1 year	5,822	14.0	242	14.4		242	15.4		359	19.9	
CCI level											
1	9,962	24.0	367	26.3	-0.27	446	28.4	-0.39	504	27.9	-0.44
2	4,970	12.0	219	15.7		256	16.3		326	18.0	
≥3	3,569	8.6	205	14.7		273	17..4		334	18.5	

Supplemental Tables S4-S12: Notes:

Drug use was quantified using defined daily dose. PPI use is the total cumulative dose up to baseline. For NSAIDs and antidepressants, use in the 5 years pre-baseline was determined. Income quintiles are divided into two groups, those in the lowest two income quintiles versus those in the third and higher income groups. A standardized difference of greater than 10% (0.10) is considered a significant difference (*) between groups. Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; CCI, Charlson comorbidity index scores; Std Diff, standardized difference in means/proportions; NR, not reportable due to counts of 5 or less persons.

Table S4: Baseline characteristics for HDPS cohort 1 (age 46-55) matching PPI users to non-users:

Age 46-55	Ever-Users Matched to Never Users				
	Non-Exposed n = 11,621		Exposed n = 6,300		Std diff
	n	%	n	%	
Cardiovascular disease	694	6.0	399	6.3	0.015
Diabetes mellitus	1,001	8.6	547	8.7	0.002
GERD	121	1.0	737	11.7	0.447
Autoimmune disorders	368	3.2	246	3.9	0.040
Hypertension	3,018	26.0	1,611	25.6	-0.009
COPD	562	4.8	340	5.4	0.025
Depression	2,534	21.8	1,434	22.8	0.023
Dyslipidemia	1,319	11.4	729	11.6	0.007
Hypothyroidism	414	3.6	222	3.5	-0.002
Income quintile (>3)	7,945	68.4	4,232	67.2	-0.026
Antidepressant use					
>1 month	708	6.1	432	6.9	-0.063
>0.5 year	341	2.9	232	3.7	
>1 year	2,004	17.2	1,148	18.2	
NSAIDs					
>1 month	1,868	16.1	1,064	16.9	-0.047
>0.5 year	657	5.7	378	6.0	
>1 year	1,840	15.8	1,068	17.0	
CCI level					
1	2,961	25.5	1,626	25.8	-0.027
2	1,014	8.7	565	9.0	
≥3	365	3.1	223	3.5	

Table S5: Baseline characteristics for HDPS cohort 1 (age 46-55) matching persons using >30 DDDs of PPIs to non-users:

Age 46-55	>30 DDDs Matched to Never Users				
	Non-Exposed n = 7,505		Exposed n = 4,078		Std diff
	n	%	n	%	
Cardiovascular disease	483	6.4	274	6.7	0.011
Diabetes mellitus	677	9.0	366	9.0	-0.002
GERD	91	1.2	663	16.3	0.553
Autoimmune disorders	270	3.6	165	4.0	0.023
Hypertension	2,052	27.3	1,075	26.4	-0.022
COPD	416	5.5	236	5.8	0.011
Depression	1,728	23.0	976	23.9	0.021
Dyslipidemia	875	11.7	489	12.0	0.010
Hypothyroidism	266	3.5	150	3.7	0.007
Income quintile (>3)	5,064	67.5	2,714	66.6	0.023
Antidepressant use					
>1 month	442	5.9	285	7.0	-0.070
>0.5 year	228	3.0	151	3.7	
>1 year	1,492	19.9	853	20.9	
NSAIDs					
>1 month	1,279	17.0	665	16.3	-0.023
>0.5 year	420	5.6	242	5.9	
>1 year	1,352	18.0	735	18.0	
CCI level					
1	1,930	25.7	1,069	26.2	-0.024
2	665	8.9	365	9.0	
≥3	274	3.7	163	4.0	

Table S6: Baseline characteristics for HDPS cohort 1 (age 46-55) matching persons using >180 DDDs of PPIs to non-users:

Age 46-55	>180 DDDs Matched to Never Users				
	Non-Exposed n = 3,533		Exposed n = 1,889		Std diff
	n	%	n	%	
Cardiovascular disease	260	7.4	144	7.6	0.010
Diabetes mellitus	351	9.9	188	10.0	0.001
GERD	50	1.4	433	22.9	0.697
Autoimmune disorders	158	4.5	90	4.8	0.014
Hypertension	1,033	29.2	550	29.1	-0.0027
COPD	214	6.1	128	6.8	0.029
Depression	913	25.8	489	25.9	0.001
Dyslipidemia	444	12.6	251	13.3	0.021
Hypothyroidism	146	4.1	67	3.5	-0.030
Income quintile (>3)	2,406	68.1	1,272	67.3	-0.016
Antidepressant use					
>1 month	213	6.0	128	6.8	-0.050
>0.5 year	127	3.6	80	4.2	
>1 year	866	24.5	466	24.7	
NSAIDs					
>1 month	582	16.5	295	15.6	-0.045
>0.5 year	204	5.8	127	6.7	
>1 year	689	19.5	377	20.0	
CCI level					
1	945	26.7	506	26.8	0.030
2	310	8.8	172	9.1	
≥3	123	3.5	75	4.0	

Table S7: Baseline characteristics for HDPS cohort 2 (age 56-65) matching PPI users to non-users:

Age 56-65	Ever-Users Matched to Never Users				
	Non-Exposed n = 8,066		Exposed n = 4,421		Std diff
	n	%	n	%	
Cardiovascular disease	873	10.8	538	12.2	0.042
Diabetes mellitus	1,137	14.1	609	13.8	-0.009
GERD	67	0.8	521	11.8	0.462
Autoimmune disorders	30	0.4	21	0.5	0.016
Hypertension	3,118	38.7	1,695	38.3	-0.007
COPD	406	5.0	236	5.3	0.014
Depression	1,198	14.9	697	15.8	0.025
Dyslipidemia	1,320	16.4	685	15.5	-0.024
Hypothyroidism	362	4.5	174	3.9	-0.027
Income quintile (>3)	5,200	64.5	2,843	64.3	-0.003
Antidepressant use					
>1 month	190	2.4	243	5.5	-0.070
>0.5 year	397	4.9	117	2.6	
>1 year	963	11.9	610	13.8	
NSAIDs					
>1 month	1,040	12.9	629	14.2	-0.051
>0.5 year	458	5.7	750	17.0	
>1 year	1,314	16.3	265	6.0	
CCI level					
1	2,308	28.6	1,283	29.0	-0.024
2	1,065	13.2	589	13.3	
≥3	555	6.9	325	7.4	

Table S8: Baseline characteristics for HDPS cohort 2 (age 56-65) matching persons using >30 DDDs of PPIs to non-users

Age 56-65	>30 DDDs Matched to Never Users				
	Non-Exposed n = 5,493		Exposed n = 2,977		Std diff
	n	%	n	%	
Cardiovascular disease	644	11.7	375	12.6	0.027
Diabetes mellitus	801	14.6	413	13.9	-0.020
GERD	51	0.9	466	15.7	0.554
Autoimmune disorders	30	0.5	20	0.7	0.016
Hypertension	2,103	38.3	1,137	38.2	-0.002
COPD	312	5.7	186	6.2	0.024
Depression	875	15.9	483	16.2	0.008
Dyslipidemia	899	16.4	490	16.5	0.003
Hypothyroidism	250	4.6	125	4.2	-0.017
Income quintile (>3)	3,543	64.5	1,901	63.9	-0.013
Antidepressant use					
>1 month	263	4.8	166	5.6	-0.065
>0.5 year	141	2.6	78	2.6	
>1 year	724	13.2	444	14.9	
NSAIDs					
>1 month	725	13.2	399	13.4	-0.027
>0.5 year	319	5.8	174	5.8	
>1 year	958	17.4	547	18.4	
CCI level					
1	1,637	29.8	895	30.1	-0.028
2	741	13.5	408	13.7	
≥3	399	7.3	234	7.9	

Table S9: Baseline characteristics for HDPS cohort 2 (age 56-65) matching persons using >180 DDDs of PPIs to non-users

Age 56-65	>180 DDDs Matched to Never Users				
	Non-Exposed n = 2,546		Exposed n = 1,382		Std diff
	n	%	n	%	
Cardiovascular disease	321	12.6	181	13.1	0.015
Diabetes mellitus	416	16.3	220	15.9	-0.011
GERD	23	0.9	309	22.4	0.710
Autoimmune disorders	15	0.6	12	0.9	0.033
Hypertension	1,056	41.5	578	41.8	0.007
COPD	165	6.5	97	7.0	0.021
Depression	425	16.7	243	17.6	0.024
Dyslipidemia	463	18.2	237	17.1	-0.027
Hypothyroidism	111	4.4	55	4.0	-0.019
Income quintile (>3)	1,602	62.9	870	63.0	0.001
Antidepressant use					
>1 month	132	5.2	71	5.1	-0.085
>0.5 year	81	3.2	54	3.9	
>1 year	363	14.3	233	16.9	
NSAIDs					
>1 month	311	12.2	159	11.5	-0.037
>0.5 year	133	5.2	78	5.6	
>1 year	510	20.0	290	21.0	
CCI level					
1	788	31.0	440	31.8	-0.036
2	306	12.0	170	12.3	
≥3	186	7.3	109	7.9	

Table S10: Baseline characteristics for HDPS cohort 3 (age 66-75) matching PPI users to non-users

Age 66-75	Ever-Users Matched to Never Users				
	Non-Exposed n = 6,797		Exposed n = 3,843		Std diff
	n	%	n	%	
Cardiovascular disease	1,224	18.0	726	18.9	0.023
Diabetes mellitus	1,011	14.9	567	14.8	-0.003
GERD	69	1.0	420	10.9	0.428
Autoimmune disorders	24	0.4	26	0.7	0.045
Hypertension	3,520	51.8	1,943	50.6	-0.025
COPD	404	5.9	255	6.6	0.028
Depression	805	11.8	516	13.4	0.048
Dyslipidemia	1,018	15.0	548	14.3	-0.020
Hypothyroidism	368	5.4	209	5.4	0.001
Income quintile (>3)	4,043	59.5	2,317	60.3	0.017
Antidepressant use					
>1 month	361	5.3	252	6.6	-0.092
>0.5 year	183	2.7	132	3.4	
>1 year	715	10.5	467	12.2	
NSAIDs					
>1 month	831	12.2	488	12.7	-0.020
>0.5 year	453	6.7	245	6.4	
>1 year	1,109	16.3	637	16.6	
CCI level					
1	1,947	28.6	1,114	29.0	-0.031
2	1,112	16.4	635	16.5	
≥3	786	11.6	474	12.3	

Table S11: Baseline characteristics for HDPS cohort 3 (age 66-75) matching persons using >30 DDDs of PPIs to non-users

Age 66-75	>30 DDDs Matched to Never Users				
	Non-Exposed n = 4,680		Exposed n = 2,626		Std diff
	n	%	n	%	
Cardiovascular disease	849	18.1	500	19.0	0.023
Diabetes mellitus	709	15.1	405	15.4	0.008
GERD	55	1.2	376	14.3	0.507
Autoimmune disorders	23	0.5	16	0.6	0.016
Hypertension	2,432	52.0	1,357	51.7	-0.006
COPD	296	6.3	175	6.7	0.014
Depression	602	12.9	355	13.5	0.019
Dyslipidemia	720	15.4	383	14.6	-0.022
Hypothyroidism	265	5.7	130	5.0	-0.032
Income quintile (>3)	2,756	58.9	1,565	59.6	0.014
Antidepressant use					
>1 month	243	5.2	165	6.3	-0.074
>0.5 year	141	3.0	99	3.8	
>1 year	537	11.5	326	12.4	
NSAIDs					
>1 month	597	12.8	308	11.7	-0.038
>0.5 year	302	6.5	174	6.6	
>1 year	757	16.2	450	17.1	
CCI level					
1	1,401	29.9	788	30.0	-0.032
2	785	16.8	443	16.9	
≥3	529	11.303	321	12.2	

Table S12: Baseline characteristics for HDPS cohort 3 (age 66-75) matching persons using >180 DDDs of PPIs to non-users

Age 66-75	>180 DDDs Matched to Never Users				
	Non-Exposed n = 2,405		Exposed n = 1,333		Std diff
	n	%	n	%	
Cardiovascular disease	476	19.8	277	20.8	0.025
Diabetes mellitus	367	15.3	198	14.9	-0.011
GERD	30	1.2	260	19.5	0.627
Autoimmune disorders	10	0.4	9	0.7	0.035
Hypertension	1,335	55.5	730	54.8	-0.015
COPD	154	6.4	93	7.0	0.023
Depression	319	13.3	191	14.3	0.031
Dyslipidemia	404	16.8	206	15.5	-0.037
Hypothyroidism	144	6.0	87	6.5	0.022
Income quintile (>3)	1,441	59.9	790	59.3	-0.013
Antidepressant use					
>1 month	128	5.3	90	6.8	-0.100
>0.5 year	68	2.8	54	4.1	
>1 year	329	13.7	194	14.6	
NSAIDs					
>1 month	258	10.7	141	10.6	-0.055
>0.5 year	157	6.5	99	7.4	
>1 year	435	18.1	260	19.5	
CCI level					
1	731	30.4	402	30.2	-0.032
2	397	16.5	227	17.0	
≥3	266	11.1	158	11.9	

Chapter 5: Predictors of PPI Use and Persistence

In chapter 4, the proton-pump inhibitor (PPI) – dementia risk analysis found that people who use these drugs tend to have higher rates of various comorbidities at baseline, including a number that are associated with an increased risk of dementia such as cardiovascular disease, diabetes, and depression. Ultimately, careful controlling for these associations and other timing factors suggested that there does not appear to be an important increase in risk of dementia with PPI use. It also appears that those exposed to higher cumulative doses of PPIs appeared to have higher rates of these risk factors than people exposed to lower doses. This could be one explanation for why so many studies have found an association between dementia and the use of this drug class. There is a correlation between PPI use and other dementia risk factors which results in confounding.

This chapter contains an analysis designed to look further into the demographic characteristics of PPI users, comorbidities correlated with starting PPI therapy, and at factors associated with increased cumulative exposure using a population-based cohort and 24 years of administrative health data. Understanding the associated characteristic of long-term PPI users may provide greater insight into potential confounding in observational studies. The results may also provide insight into the characteristics of long-term PPI users and provide some guidance for deprescribing initiatives.

Manuscript: Predictors of PPI Use and Persistence: Population-based analysis of PPI utilization and characterization of PPI users

Cover page

Title: Predictors of PPI Use and Persistence: Population-based analysis of PPI utilization and characterization of PPI users

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Kevin Friesen accepts full responsibility for the conduct of this study and guarantees it was conducted ethically.

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K.F., S.B, and J.F. wrote the manuscript; K.F., S.B., D.C. and I.K. designed the research; K.F. performed the research and analyzed the data.

Abstract:

Background: Much has been written about the potential long-term effects of proton -pump inhibitors (PPI) with many conflicting findings. Less discussed are characteristics of PPI users and factors associated with persistent use. This information could illuminate why PPI use has been inconsistently associated with negative outcomes, especially when confounding is inadequately controlled.

Methods:

Administrative health care data was used to identify PPI users and non-users, potential indications for use, comorbid conditions, and socioeconomic indicators in persons aged 45 and over in Manitoba, Canada. Utilization trends were described using descriptive statistics. Logistic regression was used to describe factors associated with PPI initiation, while Kaplan-Meier methods and Cox regression was to examine persistence and factors associated with long-term use.

Results:

Between 1996 and 2020, 340,029 persons received a dispensation of PPIs. Rates increasing from 31.2 to 221.8 users/1000 person-years over this period. PPI use among person diagnosed with gastro-esophageal reflux disease (GERD) or peptic ulcer disease (PUD) increased from 50.1% to 90.0% and 57.4% to 90.0% respectively ($p<0.0001$). The median (IQR) duration of use was 90 days (90, 552). Among those filling more than 1 prescription, median (IQR) use was 340 days (116, 1816). Diabetes, cardiovascular disease, and cerebrovascular disease were associated with a higher likelihood of starting and continuing to use PPIs.

Conclusion:

PPI use has increased over 600% since 1996, with most persons diagnosed with PUD or GERD now prescribed these drugs. Despite PPI use being recommended for short-term use for their common

indications, longer term use is common. Individuals who are dispensed PPIs tend to have higher rates of significant medical comorbid conditions, and these are also associated with a longer duration of use. This association may be one reason why many studies have found associations between PPI use and negative long-term outcomes. More methodologically rigorous studies may reduce or eliminate the safety signals found in observational studies that fail to adequately control for confounding.

Introduction

Proton pump inhibitors (PPI) are a class of drugs that decrease gastric acidity by blocking the action of the hydrogen-potassium ATPase pump in the stomach. They are used to treat peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), and to prevent damage to the gastric mucosa from the use of non-steroids anti-inflammatory drugs (NSAIDS). These drugs are highly prescribed and were the second most commonly prescribed class of drugs among seniors in Canada and most prescribed class in the United Kingdom.[97,98] Research suggests that PPIs are being overused, prescribed for inappropriate indications, and used for longer and at higher doses than medically necessary.[99-102] This has led to calls for more rational prescribing practices and to deprescribe these drugs in patients without a definitive indication, decreasing the dose with an aim to stop treatment if possible for patients whose symptoms have resolved, and using the lowest dose necessary.[134]

Previous studies have investigated factors associated with initiating and persisting with PPI therapy. This has often been done as part of drug utilization research, or in studies looking into rates of inappropriate prescribing.[99,135-139] These studies have primarily focused on indications for use such as GERD, PUD, dyspepsia, the use of NSAIDS, use of anti-platelets and other drugs that increase the risk of a gastrointestinal bleed, as well as age, sex, income, educational status, and geography. However, there is a lack of published data on users' comorbid conditions such as cardiovascular disease, depression, and diabetes and whether these factors are associated with rates of use and persistence with therapy.

Considering the high rates of PPI prescribing and the frequency of long-term use, significant amounts of research into their long-term safety has been done using observational studies. These have shown inconsistent results regarding the risks of pneumonia, osteoarthritis, dementia, mortality, chronic kidney disease*, Clostridium difficile* infection, and cancer among PPI users.[140-144] The randomized controlled trials (RCTs) conducted for drug approval were generally of short duration (4 to 12 weeks) with an

outcome of peptic ulcer healing or *H. pylori* eradication.[145] As almost all PPIs are no longer under patent, the probability of a large, long-term randomized PPI study is low, and we are left with observational studies which are prone to various forms of bias and confounding. Furthermore, RCTs are also not well suited to determine the risk of rare safety outcomes as this requires very large sample sizes with increased cost and difficulty.

The aim of this study is to examine trends in the utilization of PPIs over a 25-year period from 1996 to the end of 2020 and more fully describe the characteristics of PPI users. We will examine the medical comorbidities associated with increased odds of initiating PPI therapy, quantify persistence with treatment, and look at the characteristics associated with extended duration of use. This will enhance our understanding of people who persist with treatment long-term to better understand this patient population and the potential implications for future safety and utilization studies.

Methods

Data sources

We obtained access to data from the Manitoba Population Research Data Repository for the period from January 1996 until the end of December 2020. Databases included prescription dispensation records from the Province of Manitoba's universal Pharmacare program, which contains data on virtually every prescription dispensed to Manitoba residents; medical billing claims; and hospital discharge abstracts. This data repository has been used extensively in previous research and has been described elsewhere.[146,147] Approval to access the data was obtained from the Manitoba Health Information Privacy Committee, and ethics approval from the University of Manitoba Health Research Ethics Board.

Utilization:

All PPI prescriptions for persons 45 years of age and older dispensed between January 1996 to December 2020 were extracted from the Drug Program Information Network (DPIN) using Anatomical Chemical Therapeutic (ATC) codes starting with "A02BC" or "A02BD". Prescriptions for H_2RA agents were similarly extracted using ATC codes beginning with "A02BA". We determined annual rates of PPI and H_2RA use summarized by the annual numbers of users and prescriptions per thousand persons in the population, as well as summarizing PPI use by molecule. For the purposes of the utilization analysis we did not exclude prevalent users.

Incident user characterization:

A new user analysis was conducted for three reference years during the study period (1999, 2009, and 2019) to examine if their characteristics changed over time. New users were defined as those with a PPI prescription in one of these index years, and with no PPI prescriptions in the three previous years to exclude prevalent users. For PPI users, the first PPI prescription in the index year was chosen as index date. Non-users were those who had no PPI prescriptions in that, or the three previous years, and were assigned a randomly chosen date within the index year. Medical claims and hospital discharge abstracts from the three years pre-index date were used to assess medical morbidities using definitions developed by Amiche *et al.*[148] Rates of PUD and GERD were calculated within both groups. NSAID use was assessed in the 120 days prior to, and up to 90 days post-index date. Characteristics associated with an increased likelihood of receiving a PPI dispensation were quantified using logistic regression by comparing incident users to non-users.

Duration of therapy:

Kaplan-Meier analysis was used to characterize persistence of PPI use among incident PPI-users over the age of 45. Incident use was defined in this analysis as an individual's first ever receipt of a PPI dispensation in our data. Persons with a prescription prior to the age of 45, or within the first 2 years of our data were excluded to remove prevalent users. Persistence was defined as ongoing receipt of PPI prescriptions, with no more than a 90-day gap between the end of the last prescription (defined as the dispensation date plus the days of treatment supplied) and a subsequent dispensation. This large gap was chosen to capture the persistence of all regular users and semi-regular users. As part of a sensitivity analysis a stricter definition of persistence, allowing no more than a 30-day gap. We accounted for early fills (stockpiling) by extending the duration of the subsequent prescription by the number of days of overlap. Persons admitted to hospital for 60 days or less were assumed to have continued PPI therapy provided they continued treatment post-discharge. Individuals were censored if they were hospitalized for longer than 60 days, their health coverage lapsed (due to moving out of province or upon death), or at the end of study data.

Predictors of Persistence:

Cox proportional hazards regression was used to examine characteristics associated with persistence with PPI therapy. Cohort membership, persistence and censoring were defined as in the Kaplan-Meier analysis. Baseline characteristics, including age, sex, and medical diagnoses, NSAID use, and *H pylori* eradication therapy were included in the model as covariates, with discontinuation of PPI use being the outcome modelled. Medical diagnoses were determined using the same definitions as above. We also used prescriptions for amoxicillin (A), clarithromycin (C), metronidazole (M), and tetracycline (T) in the 7 days prior to, or up to 90 days after their first PPI prescription to identify persons undergoing *H pylori* eradication therapy. Eradication therapy was defined as receiving prescriptions for the combinations of

A&M, A&C, A&C&M, C&M, or M&T (along with a PPI). To ensure that sufficient data was available to determine baseline characteristics, we excluded persons who started PPI treatment prior to Jan 1998, and those who had less than 3 years of pre-PPI health coverage.

Results

Utilization:

A total of 11,340,418 prescriptions for PPIs were dispensed to 340,029 unique users over the age of 45 between January 1st, 1996, to December 31st, 2020. PPI user rates per thousand persons rose steadily across the entire study period, from 31.2 users to 221.8 users/1000 person-years, equating to an increase of over 600%. (Figure 1). Rates of H_2RA use dropped 62% from 1996 to 2019, from 65.2 to 24.6 users/1000 persons, and then down to 7.0 users/1000 persons in 2020.

Omeprazole was the first PPI on the Canadian market and remains the most widely used PPI accounting for 35.5% of all PPI prescriptions.[149] (Figure 2). The use of rabeprazole has slowly increased, and it accounted for 24.9% of all PPI prescriptions in 2020, followed by pantoprazole at 22.7%.

Incident User Analysis:

The numbers of persons starting PPIs for the first time rose throughout our study period, from a total of 9,692 new users in 1999 to 22,898 in 2019. (Table 1) PPI use among individuals with GERD or PUD increased significantly. In 1999, 50.1% of those with diagnosed GERD were prescribed a PPI, this grew to 90% by 2019 ($p<0.00001$). Among those with PUD, the proportion treated increased from 57.4% to 92.0% ($p<0.00001$). While PPI use increased in individuals with an identified indication, the number of users with no known indication grew significantly. In 1999, 25.8% of new users had a diagnosis of GERD, this dropped to 18.3% in 2019 ($p< 0.001$), and PUD diagnoses in users dropped from 15.1% to only 2.0% in 2019 ($p< 0.001$). Rates of NSAID co-prescribing among new users also declined over this same time

frame, from 23.5% to 18.3% ($p< 0.001$). Increasingly, PPIs are being prescribed to individuals without a recorded indication, from 46.1% in 1999 to 64.2% in 2019.

NSAID use, GERD and PUD were the strongest predictors of receiving a PPI prescription, with the odds ratios rising over time. (Table 2) A diagnosis of alcoholism, cardiovascular disease, and cerebrovascular disease each more than doubled the odds an individual was prescribed a PPI, while other comorbid conditions increased the odds to a lesser extent.

Persistence Assessment:

Of the 246,586 incident PPI use episodes, 100,854 users (40.9%) filled only one prescription, and 41.4% of these had PPI dispensations of eight weeks or less. The median (IQR) duration of PPI use was 90 days (30, 552) using our primary definition that allowed gaps up to 90 days between prescriptions, while under our 30-day gap definition it decreased to 60 days (30, 224). The 75^{th} percentile for duration of use was 552 days, meaning 25% of incident PPI users continued use past 1.5 years. After excluding users who filled only 1 prescription the median duration rose to 340 days (116, 1,816). Duration of use increased with rising age, the median duration of use was 60 days (30, 271) in those 45-54, rising to 257 days (49, 1,252) in those ≥85 years of age. (Table 3)

Characteristics of Long-term Users

Cox regression looking at predictors of continued PPI use, like the Kaplan-Meier analysis, found increasing age at the start of PPI therapy was associated with an increased chance of persistence (a decreased risk of stopping therapy). (Table 3). Diagnoses of diabetes, cardiovascular disease, cerebrovascular disease, autoimmune disorders were also associated with an increased risk of ongoing treatment. (Table 4) Users who received eradication therapy with their first PPI prescription were twice as likely to stop use as those who did not. NSAID therapy, despite being associated with an increase in

the odds of starting PPI therapy (Table 1), did not have a significant effect on the likelihood of continuing treatment.

Discussion

The prevalence of PPI use in the 45 plus population rose by over 600%, from 3% in 1996 to over 22% in 2020. Our findings parallel what has been reported previously. Rates of PPI use are high in much of the world, ranging from 15.5% in Iceland, 18% in Catalonia, and almost 30% France,[150-152] and are higher in the older population with 32% of Canadians over 65, 25.6% of US Medicare enrollees and over 33% of Australians above 65 filling PPI prescriptions.[98,136,150,152,153] Their use has surpassed and eclipsed rates of H_2RA use, which were previously considered the standard of care for gastric acid-related conditions. Omeprazole, the first PPI marketed, continues to account for the plurality of PPI prescriptions, with rabeprazole and pantoprazole use becoming more common towards the end of the study period. The use of H_2RA declined steadily over the study period, dropping 62% between 1996 and 2019. A further, much sharper drop was seen in 2020 and is likely related to a mass recall of ranitidine and a subsequent worldwide shortage of famotidine.[154] While the COVID-19 pandemic could account for some of the sharp drop, a similar drop was not seen for PPI prescriptions.

We found that long-term PPI use is common, with an average duration of almost a year among those who filled 2 or more prescriptions. Australian researchers have reported similar findings, with a median duration among those who filled 2 or more prescriptions exceeded 500 days.[136] We also found that duration of use rose with increasing age, from a median of 60 days in those 45-54 years to 257 days in those 85 years and older. Icelandic researchers noted a similar association with rates of use beyond one year of 13% in those 19-39 years, increasing to 36% of those over 80.

The number of individuals initiating PPI therapy without an indication for their prescribing, such as NSAID use, GERD or PUD, increased from 46% in 1999 to 64% in 2019. Of course, it is possible that these

individuals did have a valid indication, but it was simply not recorded, a finding that has been reported elsewhere.[151] In our data, each medical claim can include only a single diagnostic code. Given the high disease burden in this cohort, it is possible that the visit may have been coded to a different diagnosis, and the PPI prescription may have been a secondary reason for the visit.

With many drugs used to treat chronic conditions, such as statins for hypercholesterolemia, and bisphosphonates for osteoporosis, a large proportion of those starting treatment do not persist with treatment.[155,156] This occurs even though benefits from these drugs accrue only after extended use. However, with PPIs, the recommendation is for short-term therapy for most indications. Given this, it is encouraging that over 40% of new PPI users filled only a single prescription, and 41% of these used PPIs for 8 weeks or less. However, among those who filled two or more prescriptions we found considerable persistence with 50% of users continuing therapy for close to a year and 25% for almost 5 years. One possible reason for this could be rebound hyperacidity and a return of the original complaint, something that can occur after as little as four weeks of PPI therapy.[157]

Persons initiating PPI treatment had higher rates of many chronic medical conditions when compared to non-users. Many of these same conditions were also associated with increased persistence (a decreased likelihood of stopping treatment) (Table 4). This suggests that persons prescribed PPIs are, even prior to beginning therapy, at higher risk for many negative outcomes such as myocardial infarction, stroke, dementia, and even death. And those users more likely to continue treatment are at a higher risk independent of PPI use. This does not necessarily mean that there are no long-term safety issues with PPIs. It does confirm the importance of accurately assessing and properly modelling medical morbidities when conducting PPI safety studies to reduce the risk of confounding bias.

Limitations in our analysis include a lack of data on non-prescription use of both PPIs and H_2RAs, both of which have been available for most of the study period. Our persistence results may underestimate how

long persons continue using PPIs as individuals may switch from prescription to non-prescription products. We also only examined new PPI users when analyzing factors associated with initiation and persistence. Strengths of this analysis include using a population-based cohort where we had access to all prescription and medical data for the entire province, and 25 years of data to analyze. The health care system in our province provides universal health care to all residents, and all prescriptions are reported to a central database.

The rate of PPI use is high, having risen continuously since their introduction to the prescription drug market. Individuals prescribed these drugs have, in general, higher rates of medical comorbidity, and are at increased risk of bad medical outcomes independent of PPI use. Ongoing research will hopefully begin to resolve what has become a large and conflicting body of PPI safety research, but researchers must ensure they design their analysis carefully to control this confounding. Regardless of the outcome of the safety research of others, we know from this and other studies that significant numbers of people use these drugs for longer than recommended, and possibly for inappropriate reasons. The best way to prevent adverse PPI outcomes is to use these drugs for the shortest time necessary, and only when indicated.

Figure 1:Annual rates of PPI and H2RB use over time: Number of unique users of histamine-2 receptor blockers (H2RB) and proton pump inhibitors (PPI) per thousand population from 1996 to 2020f

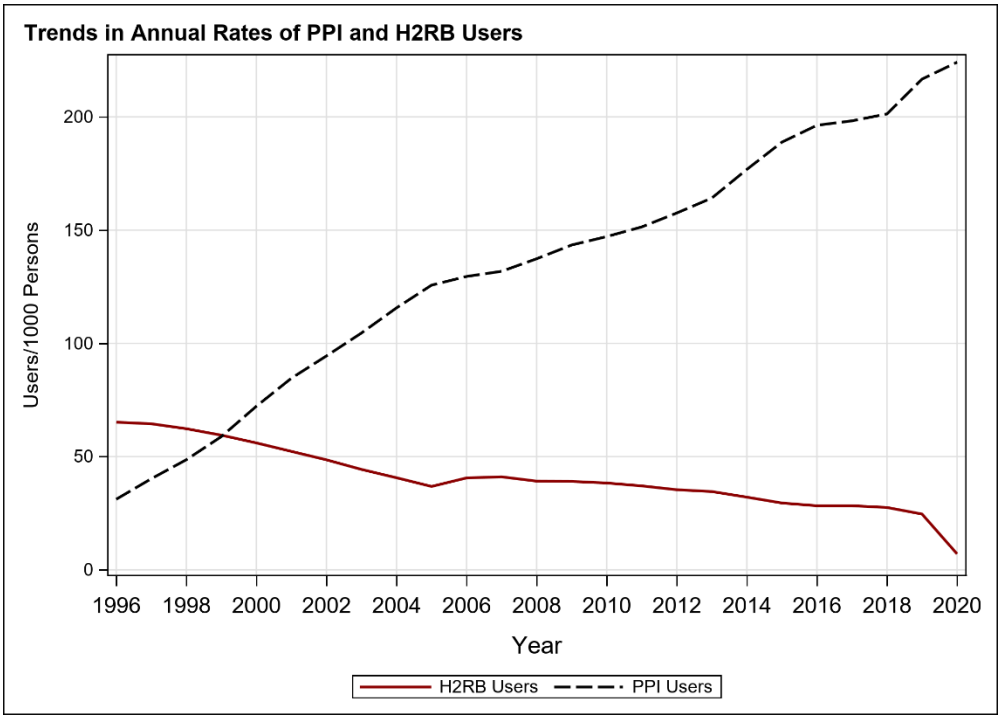

Figure 2: Trends in PPI use by molecule: Prescription counts by proton pump inhibitor molecules

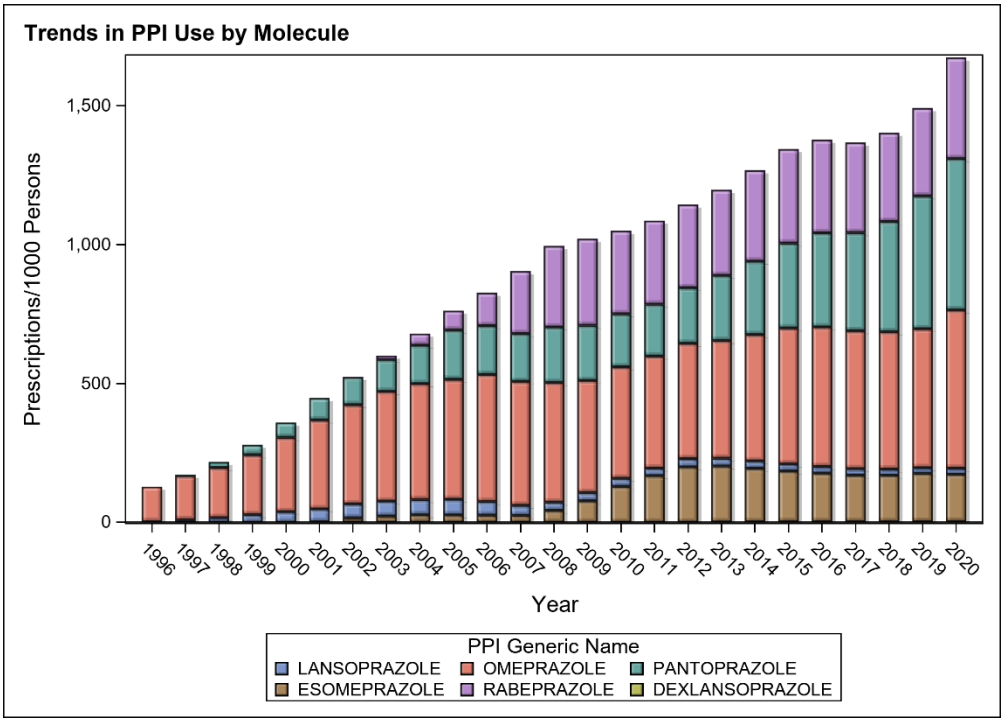

Table 1: Rates of non-steroidal anti-inflammatory drug (NSAID) co-prescribing, gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) among new-users of proton-pump inhibitors

Index year	1999 n (%)	2009 n (%)	2019 n (%)
Incident users	9,692	12,558	22,898
NSAID users	2,276 (23.5)	2,622 (20.9)	4,192 (18.3)
GERD cases	2,503 (25.8)	3,143 (25.0)	4,183 (18.3)
PUD cases	1,467 (15.1)	538 (4.3)	451 (2.0)
Any indication	5224 (53.9)	5601 (44.6)	8194 (35.8)

Table 2: Predictors of proton-pump inhibitor initiation: Logistic regression was used to calculate the odds ratios (and 95% confidence intervals) to begin PPI use based on baseline characterstics. Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; GERD, gastroesphageal reflux disease; PUD, peptic ulcer disease; SLE, systemic lupus erythematosus

Index year	1999	2009	2019
NSAID use	1.88 (1.78, 1.98)	2.47 (2.35, 2.59)	3.46 (3.33, 3.60)
GERD	9.20 (8.73, 9.70)	12.89 (12.29, 13.51)	16.47 (15.74, 17.24)
PUD	7.91 (7.39, 8.47)	9.74 (8.68, 10.94)	16.96 (14.66, 19.63)
Female sex	1.16 (1.11, 1.21)	1.23 (1.19, 1.28)	1.22 (1.19, 1.26)
Age (log age)	2.41 (2.15, 2.70)	2.82 (2.56, 3.12)	2.25 (2.07, 2.43)
Alcoholism	1.28 (1.05, 1.56)	3.04 (2.53, 3.65)	2.60 (2.24, 3.03)
Cardiovascular disease	1.87 (1.76, 1.98)	1.83 (1.71, 1.95)	2.03 (1.92, 2.14)
Cerebrovascular disease	1.20 (1.05, 1.38)	3.14 (2.58, 3.82)	2.37 (2.06, 2.74)
Depression	1.46 (1.38, 1.54)	1.40 (1.33, 1.47)	1.49 (1.43, 1.55)
Diabetes mellitus	1.16 (1.08, 1.24)	1.37 (1.30, 1.45)	1.57 (1.51, 1.62)
Epilepsy	1.10 (0.82, 1.46)	1.31 (1.01, 1.71)	1.32 (1.08, 1.61)
Parkinson's disease	1.06 (0.82, 1.35)	1.45 (1.15, 1.83)	1.29 (1.07, 1.55)
Rheumatoid arthritis	1.49 (1.27, 1.75)	1.67 (1.45, 1.94)	1.48 (1.32, 1.67)
SLE	2.67 (1.98, 3.61)	3.00 (2.30, 3.92)	1.97 (1.57, 2.47)

Table 3: Proton-pump inhibitor persistence: Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles of duration of proton-pump inhibitor use by age at initiation. Results are reported in days.

	Percentile		
Age Group	**25th**	**50th**	**75th**
45-54	30	60	271
55-64	30	86	463
65-74	30	95	669
75-84	30	130	1012
≥85	49	257	1252

Table 4: Factors associated with discontinuation of proton-pump inhibitor therapy: Cox regression was used to analyze factors associated with increased duration of PPI use. The outcome in this analysis was discontinuing PPI therapy. Hazard ratios below 1.0 are associated with a decreased risk of stopping therapy (i.e., increased likelihood of persisting with PPI therapy). Factors associated with decreased duration of use, such as antibiotic eradication therapy, have hazard ratios above 1.0. Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; GERD, gastroesphageal reflux disease; PUD, peptic ulcer disease; SLE, systemic lupus erythematosus.

	Maximum allowed gap between prescription periods		
	90 Days		**30 Days**
	All Users	**Users with >1 PPI prescription**	**All Users**
	Hazard ratio (95% confidence intervals)		
NSAID use	1.04 (1.03, 1.05)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
Rheumatoid arthritis	0.83 (0.80, 0.85)	0.86 (0.82, 0.90)	0.86 (0.83, 0.89)
SLE	0.79 (0.74, 0.85)	0.81 (0.75, 0.89)	0.85 (0.80, 0.90)
Eradication therapy	1.96 (1.93, 1.98)	1.65 (1.62, 1.69)	2.11 (2.08, 2.14)
Peptic ulcer disease	0.78 (0.76, 0.81)	0.90 (0.87, 0.94)	0.78 (0.76, 0.80)
GERD	0.77 (0.76, 0.79)	0.83 (0.81, 0.85)	0.82 (0.81, 0.84)
Diabetes mellitus	0.82 (0.81, 0.83)	0.84 (0.82, 0.85)	0.81 (0.80, 0.82)
Cardiovascular disease	0.85 (0.84, 0.86)	0.89 (0.87, 0.90)	0.85 (0.84, 0.86)
Cerebrovascular disease	0.79 (0.76, 0.82)	0.87 (0.83, 0.91)	0.76 (0.74, 0.79)
Parkinson's disease	0.81 (0.77, 0.86)	0.90 (0.84, 0.97)	0.77 (0.73, 0.81)
Epilepsy	0.80 (0.75, 0.85)	0.85 (0.78, 0.92)	0.75 (0.70, 0.80)
Age Group (reference group 45-54 years)			
55-64	0.89 (0.88, 0.90)	0.91 (0.90, 0.93)	0.88 (0.87, 0.89)
65-74	0.85 (0.84, 0.86)	0.89 (0.87, 0.90)	0.83 (0.82, 0.84)
75-84	0.80 (0.79, 0.81)	0.88 (0.87, 0.90.)	0.75 (0.74, 0.76)
>85	0.69 (0.67, 0.70)	0.85 (0.83, 0.88)	0.60 (0.59, 0.61)

Chapter 6: Benzodiazepines and Dementia

Benzodiazepines are a class of GABAergic drugs used to treat anxiety and sleep disorders. GABA, and the GABA receptors are the main inhibitors of neuronal firing in the central nervous system. [158] Benzodiazepines thus act to inhibit activation of many neuronal circuits, which is thought to be how they exert their effects on anxiety and induce sleepiness. Their inhibitory effects can also affect cognition and memory recall, particularly at higher doses and in older people who are more susceptible to these effects. These effects mimic some of the symptoms of dementia and some researchers have speculated that the cognitive effects of these drugs could increase the risk of actual dementia.[158] However, the effects of benzodiazepines are reversible and end organ toxicity has not been previously associated with this class of drug. Neurotoxicity is, in fact, more associated the neurotransmitter glutamate, which is the main excitatory neurotransmitter in the central nervous system.

Benzodiazepines can increase the risk of delirium, and again this risk is highest in older patients in poorer medical health.[159] This could be misdiagnosed as dementia, particularly if the offending agent is not discontinued quickly and the delirium does not abate. In fact, this is one reason our algorithm used to identify cases of dementia requires that multiple medical claims with a diagnosis of dementia must be separated by at least 30 days to avoid this type of misclassification.

These issues make examining the potential effect of benzodiazepines on dementia more complicated than looking at some other classes of drugs such as PPIs. Furthermore, benzodiazepines are used to treat anxiety and insomnia, both of which frequently co-occur with depression. Depression, and to a lesser extent anxiety, are independent risk factors for dementia themselves. This means any examination of benzodiazepines as dementia risk factors need to beware of potential indication bias. Sleep-wake cycle disturbances and mood disorders are also early symptoms of dementia and can appear in the prodromal period. This creates the potential for protopathic bias to affect results.

In this chapter we conduct another methodological sensitivity analysis to try to tease out the real risk associated with benzodiazepines. In one approach, restricted cohorts containing only persons who had depression (or only people who had anxiety) were used to control for indication bias. To deal with protopathic bias a lag period was used, where any dementia diagnoses during the first years after the start of follow-up were censored. Lastly, depression, especially severe depression, is frequently treated with antidepressant medications. It has been suggested by some that antidepressants are also a risk factor for dementia, although the evidence is equivocal, and that potential relationship is also clouded by the above stated biases. To control for this potential confounder, antidepressant use was quantified, and we included it in our multivariable models.

This paper has been reviewed and approved by my coauthors and is ready to be submitted for publication upon completion of this thesis.

Manuscript: Clearing the Confounding Confusion: Benzodiazepines and the Risk of Dementia?

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Guarantor of Article:

Kevin Friesen accepts full responsibility for the conduct of this study and guarantees it was conducted ethically.

Abstract:

Objective:

To examine the relationship between long-term benzodiazepine exposure and the risk of dementia.

Design:

A retrospective cohort study using administrative health data followed 3 age-based strata for up to a maximum of 22 years to examine the risk of dementia due to benzodiazepine use by comparing incident users to those never exposed. Each stratum was analyzed as a whole, then restricted to persons with depression or anxiety, and finally using high dimension propensity scores (HDPS)-matched cohorts.

Setting:

We used administrative data on subjects receiving standard medical care in Manitoba, Canada.

Measurements:

Prescription data was used to quantify benzodiazepine using cumulative defined-daily-dose (DDD). Comorbidities and cases of dementia were determined using medical and hospital data. Cox regression was used to examine the relationship between cumulative benzodiazepine exposure and dementia outcomes.

Results:

Dementia risk in high-dose users of the youngest strata was elevated compared to non-users (adjusted HR (aHR) 1.33; 95% CI 1.05-1.68), absolute increase < 0.8%). Little to no difference was found in the middle (aHR 1.17; 1.02-1.33) and oldest strata (aHR 1.02; 0.93-1.11). Restriction to persons with depression or anxiety eliminated the association. No association was found using HDPS-matched comparison groups.

Conclusions:

Older benzodiazepine users did not have an increased risk of dementia. A modest relative increase in dementia risk was seen in the high-dose benzodiazepine users of our youngest stratum and a small increase in the middle stratum. This association appears to be driven by the confounding due to higher rates of diabetes, cardiovascular disease, depression, and anxiety among users. Using restriction or HDPS to better control for confounding effects eliminates the association. While benzodiazepines do not appear to be a significant risk factor for dementia, tolerance, dependency and adverse effects caution against their long-term use.

Introduction

Dementia is one of the most common and feared conditions associated with aging. While there are approved medical treatments for dementia, the efficacy of these agents appears modest at best.[17,70] While studies of amyloid-beta plaque-clearing antibodies are ongoing, the failure of multiple similar agents to show clinically significant benefits in past studies should temper our expectations.[56,70] Given the absence of very effective treatments, prevention in the form of avoidance of modifiable risk factors such as predisposing medications remains a key priority to reduce the burden of dementia. Benzodiazepines, drugs used to treat anxiety, insomnia, panic attacks, and sometimes seizure disorders, have received significant attention in this regard.[160] Benzodiazepines temporarily impair cognition and memory, and these effects are more pronounced in older people.[161] Because this impairment can resemble dementia some have suggested that benzodiazepine use may contribute to its development. This paper seeks to critique and evaluate the association between benzodiazepines and dementia in hopes of providing greater clarity to clinicians.

Several studies have been published addressing this question. [162-164] The results of three large studies published in the last three years are informative in representing the diversity of reported results. Tseng et al looked at over a quarter million individuals over ten years and found increased dementia risk for short-acting (hazard ratio (HR)= 1.98, 95% confidence interval (CI) 1.89, 2.07) and long-acting benzodiazepines (HR= 1.47, 95% CI 1.37, 1.58).[165] Osler and Jørgensen looked at over 235,000 people and found a protective effect (odds ratio (OR) = 0.72 (95% CI 0.67, 0.76) after 2 years of follow-up, and no effect after 2 to 20 years (OR= 0.97 (95% CI 0.91, 1.04))[166]. And, a 2022 study by Gerlach et al using a cohort of over half a million persons examined exposure over 10 years and examined outcomes for 5 years after and found a clinically insignificant increase in dementia risk of 5% (HR= 1.05 (95% CI 1.02-1.09)).[167] While there are many possible explanations for these discrepancies, three factors confound the study of benzodiazepine use and dementia: protopathic bias, lag-time bias, and indication bias.

Protopathic bias occurs when the symptoms of an undiagnosed disease prompt a prescription to treat it. As the disease progresses, eventually a correct diagnosis is made. A naïve approach to looking at what caused the disease might assume that because the exposure occurred prior to diagnosis, it could have caused it. With benzodiazepines and dementia, protopathic bias can occur when sub-clinical dementia symptoms such as agitation and sleep disturbances prompt a physician to prescribe benzodiazepines.

Lag-time bias occurs when an event or exposure takes place before diagnosis, meaning it is in the correct temporal order, but biologically speaking there has not been enough time for the drug to cause the outcome. Longitudinal studies suggest that the neurodegenerative process that causes dementia begins 10 to 20 years or more before a diagnosis is made.[168] There is also a prodromal phase lasting several years where subclinical symptoms of dementia begin to appear but do not meet the threshold needed for an accurate diagnosis.[40] Thus, exposures near the date of diagnosis are outside of the biologically relevant exposure window. Protopathic and lag-time bias can be addressed by excluding exposures that occur too close to the date of diagnosis in a case-control study, or by excluding outcomes that occur immediately after exposure when examined in a cohort study.

Indication bias, on the other hand, occurs when the indication for a drug, meaning what it is used to treat, is itself a risk factor for an outcome. We need to consider that benzodiazepines are indicated as treatments for anxiety, which is frequently comorbid with depression, and both have been described as risk factors for the development of dementia.[95,96,169]

Based on these considerations, we conducted an observational study using up to 20 years of administrative health care data to follow benzodiazepine users and non-users. Using a large, population-based dataset we conducted a range of analyses to mitigate the biases and evaluate the effect of benzodiazepines on dementia risk.

Data sources:

Data used in this analysis was obtained from the Manitoba Population Research Data Repository, maintained by the Manitoba Centre for Health Policy. This data has been used extensively for health, education, social and justice research and has been described elsewhere.[126] Access to data from April 1st 1995 to March 31st 2021 was obtained after receiving ethics approval from the University of Manitoba Health Research Ethics Board (H2017:404) and from the Province of Manitoba's Health Information Privacy Committee (2017/2018-46).

Databases used for this project include prescription drug data, hospital discharge abstracts, medical billing claims, Canadian census data, and long-term care admissions data. Manitoba has a universal health care system for all residents, with all encounters between individuals and the medical system and all prescriptions filled by community pharmacies captured in the centralized data system.

Cohort construction:

Inclusion criteria:

All individuals in the Province of Manitoba between the ages of 46 and 75 on April 1st, 2000 were eligible for inclusion in this study provided they had health care registration from April 1st, 1995, or earlier. This was to ensure that we had sufficient data to screen for prior benzodiazepine use, prior dementia diagnosis, or for exclusion from the study.

Three cohorts were constructed and analyzed separately based on date of birth (Figure 1):

- Stratum 1 was born between April 1st, 1944, and March 31st, 1954, with entry at age 46, follow-up beginning on the 55th birthday.
- Stratum 2 was born between April 1st, 1934, and March 31st, 1944, with entry at 56, follow-up beginning on the 65th birthday.

- Stratum 3 was born between April 1st, 1924, and March 31st, 1934, with entry at 66, follow-up beginning on the 75th birthday.

Exclusion criteria:

Individuals with a baseline diagnosis of dementia, Parkinson's disease, schizophrenia, epilepsy, or Downs's syndrome were excluded from the study as these are strong, independent risk factors for dementia. If they received a diagnosis for one of these conditions during follow-up they were censored. Persons who entered a long-term care home prior to beginning of follow-up were also excluded as prescription data is not included in the data repository for approximately 25% of care homes.

Prevalent users of benzodiazepines, defined as those who filled any benzodiazepine prescriptions prior to April 1st, 1996 (in the first year of our data), or prior to stratum entry age were excluded to produce an incident user/non-user population.

Exposure and covariate assessment windows:

Exposures and medical diagnoses were determined using data from a minimum of five, and up to ten years preceding, up to the beginning of follow-up. Follow-up for each stratum began as indicated above and continued until the end of our data (March 31st, 2021), a diagnosis of dementia, loss of health care coverage, or if a censoring event occurred. Demographic details were assessed at the beginning of follow-up. All individuals had a minimum of 5 years and a maximum of 15 years of data available prior to follow-up. This meant that, barring being censored or developing dementia during follow-up, we were able to follow each cohort member for at least 11 years, up to and a maximum of 21 years, depending on when their individual follow-up time began.

Drug exposure assessment:

Drug exposure was assessed using dispensation data and categorized using anatomical, therapeutic, chemical (ATC) codes to identify users of benzodiazepines (ATC codes beginning with N05BA, N05CD or N03AE01). In addition to our exposure of interest, we also identified users of z-type drugs such as zopiclone and zaleplon (ATC codes starting with N05CF), antidepressants (N06A), and antipsychotic drugs (N05A) to include in our models as potential confounders. These drugs are commonly either prescribed alongside or as alternatives to benzodiazepines and may have their own effects on dementia risk. All data available prior to the beginning of follow-up was used to assess cumulative exposure, as measured using the ATC defined daily dose (DDD) method, by multiplying the number of dosage units dispensed by the strength of each dose unit, then divided by the DDD for that drug.

Medical diagnoses:

We ascertained medical diagnoses using medical claims, hospital discharge abstracts, and prescription data using definitions previously described by Amiche *et al*. [92] These diagnoses included hypertension, chronic obstructive pulmonary disease, cardiovascular disease, depression and anxiety (as a combined group), dyslipidemia, hyperthyroidism, hypothyroidism, substance abuse (including alcoholism), and autoimmune disorders. We also calculated Charlson Comorbidity Index scores for descriptive, but not analytical purposes.

Demographic variables:

We used individuals' postal codes listed in the Manitoba Health Care Registry to determine geographic location (rural vs urban). As we do not have data on an individual's personal income, we used postal codes and data from the Canadian Census to determine neighborhood-based median income as a proxy, expressed as quintiles. The Registry was also the source for sex and date of birth.

Outcome assessment:

A validated algorithm with a sensitivity of 79% and specificity of 99% was used to identify individuals with dementia.[91] This definition requires one of the following conditions to be met: one or more prescriptions for a dementia-specific medication (donepezil, galantamine, rivastigmine, memantine); a dementia diagnosis recorded in hospital discharge abstracts; or 3 or more medical claims with a diagnostic code within 2 years of each other, provided at least 30 days exist between claims. Due to limitations in the number of digits recorded for ICD codes in our medical claims data we cannot distinguish Alzheimer's dementia from other dementias. To minimize the heterogeneity in our outcomes we excluded persons with Parkinson's disease (to exclude Parkinson's dementia), vascular dementia (identified using hospital data) and cerebrovascular disease (to reduce possible vascular dementia cases).

Analysis:

We analyzed our data with Cox regression models using a population-based cohort and a high dimensional propensity score (HDPS)[93] matched cohort created independently out of each stratum. Each cohort was modelled separately.

The population-based cohorts were based on all persons eligible for inclusion in each stratum to estimate the risk of dementia in benzodiazepine users compared to non-users. To reduce confounding by indication, we conducted a sub-group analysis using only individuals with a diagnosis of depression at baseline (depression cohort) and a sub-group analysis of using only individuals with a diagnosis of anxiety at baseline (anxiety cohort).

HDPS was used to reduce unmeasured confounding by creating a 1:1 matched cohort of users and non-users. Individuals were matched on propensity score (with a caliper of 0.1) and sex without

replacement. We generated two scores independently using two different definitions of exposure: a) cumulative benzodiazepine dose of greater than 30 DDDs or b) cumulative exposure greater than 90 DDDs (high dose). Note that these are not mutually exclusive groups as those meeting definition b) would also meet a). The unexposed group consisted of those with no exposure to benzodiazepines up to baseline. The dimensions included in the HDPS calculation were a) all ICD -9 diagnostic codes and medical tariff codes from medical claims from the three years prior to follow-up, b) all ATC codes for drugs dispensed in the three-years prior to follow-up, and c) all ICD-9 and ICD-10 diagnosis and procedure codes from hospital discharge abstracts for admissions in the three-years prior to follow-up. The HDPS macro created by Schneeweiss *et al* was used to calculate propensity scores.[93] It selects covariates for entry into the logistic model based on the association of covariates to both exposure and outcomes. Up to 500 covariates could be selected to use in the logistic model created for each age-group and exposure definition.

Statistical analysis:

Summary statistics and standardized differences were used to contrast the characteristics of benzodiazepine users and non-users in both the population-based and the HDPS matched cohorts. Multivariable Cox regression models were used to investigate the risk of dementia based on benzodiazepine use status. All individuals within a stratum began follow up at the same age; age 55 for stratum 1, age 65 for stratum 2, and age 75 for stratum 3, allowing follow-up time to be congruent with age. Age is the single biggest risk factor for dementia and increase with age in a non-linear manner. Using age as the time scale allowed age to be modelled by the non-parametric baseline hazard function in the Cox model and we did not need to include an age covariate in our models. Individuals within strata were all born within 10 years of each other, allowing us to minimize the effects of period effects.

For the population-based cohorts, exposure to benzodiazepines was categorized into one of four mutually exclusive levels: no use, >0 and ≤ 14 DDDs, >14 and ≤ 90 DDDs and >90 DDDs. For the Depression-1 cohort (stratum 1, only depression), exposure was classified into only 3 levels: no use, >0 and ≤ 30 DDD, >30 DDDs due to the low number of cases in this smaller, younger group.

Covariates were tested individually using a bivariate analysis and considered for inclusion in the multivariable model if they had p-values ≤ 0.20. They were kept in the final model if they retained significance at a p-value ≤ 0.10. All models included sex as well as diagnoses of cardiovascular disease and diabetes as these have been previously identified as risk factors for dementia. Depression and anxiety disorders were likewise included in all models, except for the depression and anxiety cohorts. Schoenfeld residuals were used to assess the proportional hazard assumption. If this assumption was violated for a particular variable it was modelled by including a time-dependent term.

HDPS-matched cohorts were analyzed first using exposure status as the only independent variable, and then including any variables that had an absolute standardized differences of over 0.10 between exposed and non-exposed groups.

Lag-models were used to account for the prodromal period that precedes a dementia diagnosis and to reduce potential protopathic bias. These models excluded any individuals who had survival times of less than a) 5 years, or b) 10 years from the beginning of follow-up.

Results

Population-based cohort

Our analysis identified 16,557 cases of incident dementia among 233,612 Manitobans aged 56 years of age and older. Rates of dementia increased with age. In stratum 1 (birth year 1944-54), we identified 1,561 cases among 114,315 persons (1.4%), stratum 2 (birth year 1934-44) had 4,867 cases among

69,317 persons (7.0%), and stratum 3 (born 1924-34) had 10,129 cases among 49,980 persons (20.3%) during follow-up. Median follow-up time was 15.5, 14, and 11 years, respectively. All subjects could potentially be followed for a minimum of 12 years and a maximum of 22 years after the exposure assessment period (provided they did not experience the outcome or get censored before that time).

Benzodiazepine users were more likely be female and have baseline diagnoses of anxiety, depression, diabetes mellitus, hypertension, and cardiovascular disease. (Supplemental table S1) Users exposed to higher doses were similarly more likely to have comorbid conditions in comparison to those exposed to lower doses. This pattern was also seen in rates of antidepressant, antipsychotic, and z-drug use. Users and non-users had similar geographic distributions (rural vs urban) and income levels.

The proportion of individuals developing dementia was higher among benzodiazepine users compared to non-users, and among those exposed to 15-90 or greater than 90 DDDs than those who used 14 DDDs or less for all strata. (Table 2) The relative difference between non-users and high-dose users was greatest among the youngest strata (strata 1), statistically significant for strata 1 ($z= 4.8$, $p<0.0001$) and strata 2 ($z= 3.16$, $p= 0.002$), and lowest and not significantly different for the oldest strata (strata 3, $z=1.7$, $p=0.09$).

Cox regression models comparing non-users to those exposed to varying levels of benzodiazepines found that for strata 1 and 2, increased exposure to benzodiazepines was associated with an increased risk of dementia in both crude and adjusted analysis. (Table 3) Models adjusted for sex, income, geography, comorbidities, antipsychotic use, and antidepressant use moved the hazard ratios closer to the null. However, most estimates remained statistically significant with a 20% to 30% increase in risk.

Point estimates were highest in the youngest strata (1), lower in strata 2, and null and insignificant in strata 3. Lag models did not have a substantial impact on these results.

Depression and anxiety diagnosis-based cohorts

To deal with confounding by indication, Cox models were re-run in a cohort consisting of individuals with a baseline diagnosis of depression and a cohort of persons with an anxiety disorder. (Table 4). In the depression subgroup, most crude models and all adjusted models showed no significant association between benzodiazepine use and dementia risk. In the anxiety-only subgroup analysis, only strata 2 revealed a significant association between exposure to benzodiazepine use and dementia among users of >30 DDDs.

High-dimensional propensity score matched cohort

Our final analysis used an HDPS-matched cohort to help reduce unmeasured confounding. Cohorts were well balanced except for antidepressant and antipsychotic drug use, so adjusted models included these covariates in the models. (Supplementary table S2). No associations between benzodiazepine use and dementia were found in adjusted models. (Table 5).

Discussion

While rates of dementia were higher in benzodiazepine users when compared to non-users in this study, so were rates of diabetes, hypertension, depression, anxiety, substance/alcohol abuse, and antidepressant/antipsychotic drug use. After adjustment for these factors, the association between benzodiazepine use and dementia was greatly reduced. Users exposed to higher cumulative doses of benzodiazepines were similarly more likely to have comorbid conditions compared to those exposed to lower doses. (Supplementary table S1). Similarly, null findings were found when using a HDPS-matched cohort design.

These results are consistent with many of the larger (>50,000 subjects) studies where patients were followed for 10 or more years. Baek et al followed over 600,000 people for a mean of 10.5 years (a 5-year lag window followed by 5.5 years to gather outcomes), and using an active comparator approach found no evidence of a causal link.[170] Richardson et al used a case-control design to evaluate over 300,000 people with a median lookback window of 11 years (4-year lag and 7 years exposure assessment) and found no increase in risk. Tapiainen looked at over 350,000 people for an average of 13.7 years (5-year lag and 8.7 years exposure assessment) and did not find an effect.

A common characteristic of benzodiazepine-dementia studies is the use of older cohorts, typically restricted to individuals 65 years or older. A French study followed a cohort of persons 65 years and older, with a mean age of 78.2 for up to 15 years finding a 62% increase in risk (HR= 1.62 (95%CI 1.08, 24.3).[171] A study from the Netherlands, on the other hand, followed people aged 70-78 and found a non-significant decrease (HR= 0.71 (95%CI 0.58, 1.07)) in dementia.[172] While this is an appropriate age to begin looking for cases, it may not be useful in identifying causal risk factors. The pathological processes that lead to dementia can begin 20 or more years prior diagnosis and thus beginning follow up late will miss the biologically relevant exposure period, although they may be able to identify factors that speed dementia progression.[17]

There are several limitations in our analysis. Because our diagnoses were based on administrative data, we were unable to differentiate between the different types of dementia, which may have different etiologies. While Alzheimer's dementia accounts for 60% to 80% of all dementias[17], we attempted to make our outcomes more homogenous by excluding persons with cerebrovascular disease to decrease the number of vascular dementia cases, as well as excluding code-defined vascular dementia. We also excluded persons with Parkinson's disease to limit the number of Parkinson's dementia. However, it is possible due to inaccurate or incomplete coding that some cases of mixed dementia are included in our cohort. As with other studies using administrative data, we cannot be sure that benzodiazepine users

consumed their entire prescription, although multiple dispensations increase the likelihood they have been. We were also unable to control for a number of significant risk factors such as educational history, exercise, smoking, diet, weight, marital status, baseline cognitive function and family history as this information is not unavailable in our administrative data. Ascertainment of medical comorbidities via claims data depends on individuals seeking medical care and being diagnosed, although Canada's system of universal healthcare reduces barriers to seeking medical attention

Strengths of our analysis include the fact that we had a total of 27 years of population-based data and had access to all our cohort's encounters with the health care system, including prescription dispensations. We stratified our cohort by age to assess whether the age at exposure to benzodiazepines modifies any risk they could pose. Our definition of dementia was based on an algorithm validated for use with administrative data and which has a sensitivity of 79% and specificity of 99%. While the sensitivity means we may have missed some cases, this would not be expected to be differential between the exposed and unexposed groups.

There remains no doubt that benzodiazepine use does acutely affect cognitive function in ways similar to some symptoms of dementia.[173] However, unlike dementia, these changes are generally reversible upon discontinuation and any lasting changes appear to be insignificant.[161,174] And while our paper provides evidence that there is not a significant causal link between benzodiazepine use and the development of dementia, this does not diminish the appropriate avoidance of long-term benzodiazepine use in older adults for other important reasons related to their negative effects. These include the increased risk of falls, motor vehicle accidents, dependency, the potential for abuse and addiction.[69] However, this study suggests that when indicated and appropriate, short-term use of benzodiazepines does not need to be feared as a substantive risk for future dementia.

Author contributions:

Kevin Friesen contributed to all parts of preparing this article.

Shawn Bugden contributed to the conceptualization and study design of this paper, numerous critical revisions, and provided funding needed for access to the underlying data.

I fan Kuo, Dan Chateau, and Jamie Falk contributed to the study design, numerous critical revisions and provided important feedback.

All authors gave final approval for this paper to be funded and are willing to be accountable for the accuracy and veracity of all information provided within.

Disclosures/conflicts of interest

No Disclosures to Report.

Data sharing statement

Due to privacy regulations and the sensitivity of medical information the authors are unable to share access to any of the raw data used to prepare this paper

The data has not been previously presented orally or by poster at scientific meetings.

Figure 1: Stratification and study design time flow diagram

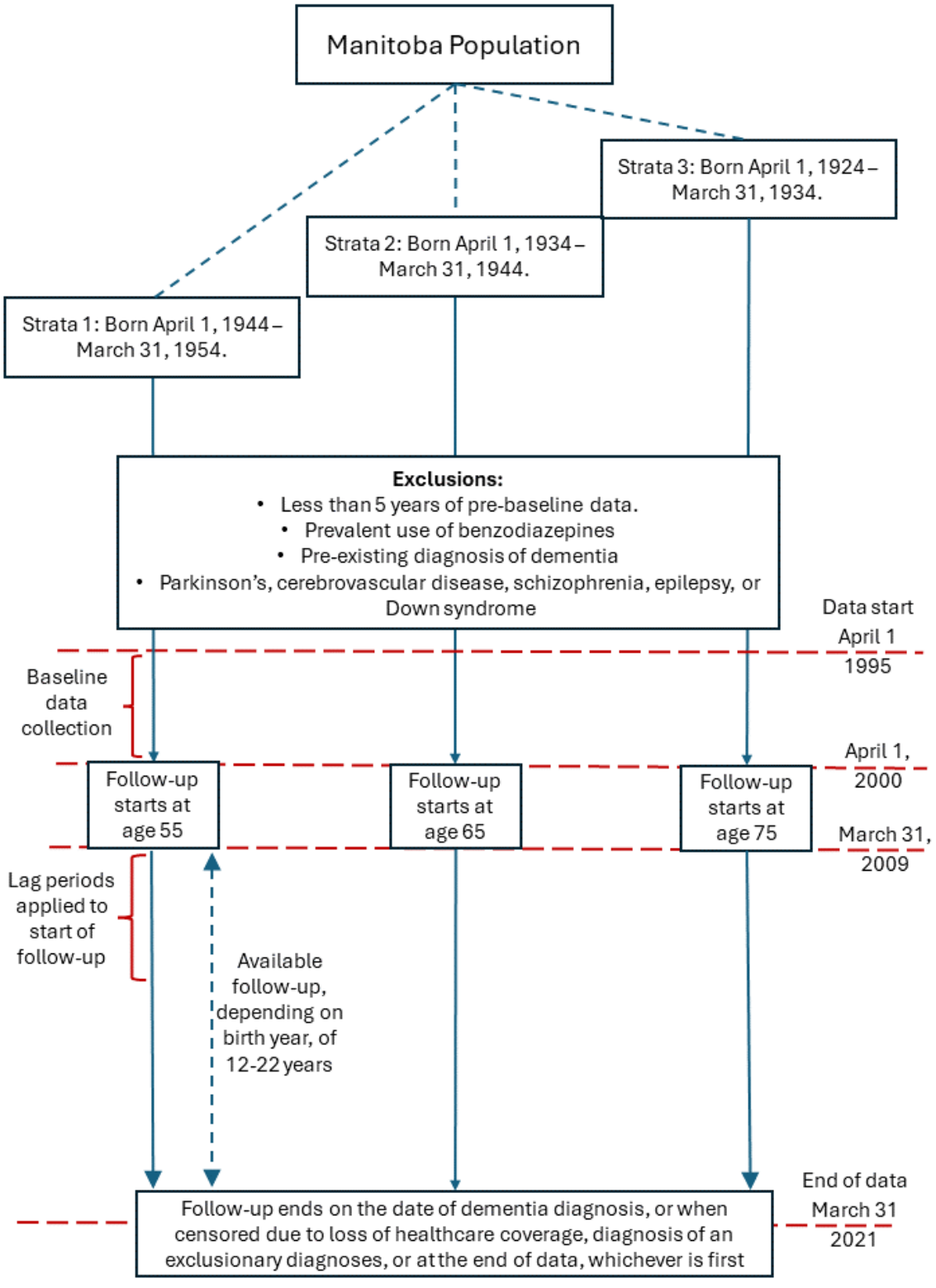

Table 1: Strata and cohort construction

Strata	Date of Birth	Age at start of follow-up	Population Based Cohorts			HDPS-Matched Cohorts	
			Entire population	All depression cohort	All anxiety cohort	Medium dose	High dose
Stratum 1	April 1 1944 to March 31 1954	55	Population 1	Depression 1	Anxiety 1	HDPS medium-dose 1	HDPS high- dose 1
Stratum 2	April 1 1954 to March 31 1944	65	Population 2	Depression 2	Anxiety 2	HDPS medium-dose 2	HDPS high- dose 2
Stratum 3	April 1 1924 to March 31 1934	75	Population 3	Depression 3	Anxiety 3	HDPS medium-dose 3	HDPS high- dose 3

Table 2: Dementia case counts by strata and level of cumulative baseline benzodiazepine use.

Stratum 1: Born 1944-1954

	Base case		5-year lag		10-year lag	
	Cases (n)	%	Cases	%	Cases	%
Non-users	1204	1.3%	1115	1.3%	902	1.1%
<14 DDDs	124	1.4%	112	1.4%	88	1.2%
15-90 DDDs	139	1.8%	128	1.8%	106	1.7%
>90 DDDs	94	2.1%	83	2.1%	58	1.6%
Total cases	1561	1.4%	1438	1.3%	1154	1.2%

Stratum 2: Born 1934-1944

	Base case		5-year lag		10-year lag	
	Cases (n)	%	Cases	%	Cases	%
Non-users	3859	6.8%	3530	7.0%	2617	6.0%
<14 DDDs	355	7.6%	323	7.8%	222	6.3%
15-90 DDDs	388	8.4%	349	8.7%	256	7.6%
>90 DDDs	265	8.2%	229	8.5%	162	7.3%
Total cases	4867	7.0%	4431	7.2%	3257	6.2%

Stratum 3: Born 1924-1934

	Base case		5-year lag		10-year lag	
	Cases (n)	%	Cases	%	Cases	%
Non-users	8040	20.0%	6419	20.4%	3571	16.8%
<14 DDDs	699	20.4%	552	20.9%	326	17.9%
15-90 DDDs	773	21.7%	581	21.9%	318	18.2%
>90 DDDs	617	21.4%	459	22.2%	232	17.5%
Total cases	10129	20.3%	8011	20.6%	4447	17.0%

Table 3: Cox regression results

Dementia risk of dementia by cumulative benzodiazepine exposure vs non-users. Results stratified by year-of-birth categories. Each strata modelled independently. Highlighting = statistically significant.

General population cohorts

Stratum 1: Born 1944-1954

Crude	Base case	5-year lag	10-year lag
≤14 DDDs	1.20 (1.00, 1.45)	1.18 (0.97, 1.44)	1.17 (0.94, 1.46)
15-90 DDDs	1.53 (1.28, 1.82)	1.53 (1.27, 1.84)	1.58 (1.29, 1.94)
>90 DDDs	2.00 (1.62, 2.47)	1.94 (1.55, 2.42)	1.73 (1.33, 2.26)

Adjusted	Base case	5-year lag	10-year lag
≤14 DDDs	1.04 (0.86, 1.26)	1.04 (0.85, 1.27)	1.01 (0.81, 1.27)
15-90 DDDs	1.23 (1.02, 1.48)	1.27 (1.05, 1.54)	1.30 (1.05, 1.61)
>90 DDDs	1.33 (1.05, 1.68)	1.35 (1.05, 1.73)	1.19 (0.89, 1.59)

Stratum 2: Born 1934-1944

Crude	Base case	5-year lag	10-year lag
≤14 DDDs	1.19 (1.07, 1.33)	1.20 (1.07, 1.34)	1.14 (0.99, 1.30)
15-90 DDDs	1.33 (1.20, 1.48)	1.31 (1.18, 1.47)	1.32 (1.16, 1.50)
>90 DDDs	1.46 (1.29, 1.65)	1.40 (1.22, 1.60)	1.39 (1.19, 1.63)

Adjusted	Base case	5-year lag	10-year lag
≤14 DDDs	1.09 (0.97, 1.21)	1.10 (0.98, 1.23)	1.07 (0.93, 1.23)
15-90 DDDs	1.17 (1.05, 1.30)	1.18 (1.05, 1.32)	1.21 (1.06, 1.38)
>90 DDDs	1.17 (1.02, 1.33)	1.15 (1.00, 1.33)	1.20 (1.01, 1.42)

Stratum 3: Born 1924-1934

Crude	Base case	5-year lag	10-year lag
≤14 DDDs	1.02 (0.95, 1.11)	1.01 (0.93, 1.10)	1.07 (0.95, 1.20)
15-90 DDDs	1.15 (1.06, 1.23)	1.09 (1.00, 1.18)	1.07 (0.95, 1.20)
>90 DDDs	1.24 (1.14, 1.34)	1.18 (1.08, 1.30)	1.12 (0.98, 1.28)

Adjusted	Base case	5-year lag	10-year lag
≤14 DDDs	0.95 (0.88, 1.02)	0.96 (0.87, 1.04)	1.04 (0.93, 1.17)
15-90 DDDs	1.02 (0.95, 1.10)	1.00 (0.92, 1.09)	1.02 (0.91, 1.15)
>90 DDDs	1.02 (0.93, 1.11)	1.03 (0.93, 1.14)	1.04 (0.90, 1.19)

Table 4: Depressed subgroup and anxious subgroup analysis

Cox regression results **for depressed cohort and anxious cohort** comparing risk of dementia between benzodiazepine users versus non-users. Individuals with a diagnosis of both would be represented in both analyses. Results are reported by year-of-birth defined strata. Highlighting indicates statistically significant results.

All depressed cohort

Stratum 1: Born 1944-1954

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	1.14 (0.84, 1.54)	1.21 (0.87, 1.67)	1.14 (0.80, 1.62)
>30 DDDs	1.46 (1.10, 1.93)	1.55 (1.15, 2.09)	1.35 (0.96, 1.89)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	1.01 (0.74, 1.38)	1.01 (0.79, 1.54)	1.04 (0.72, 1.50)
>30 DDDs	1.10 (0.81, 1.5)	1.22 (0.88, 1.69)	1.12 (0.77, 1.62)

Stratum 2: Born 1934-1944

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	1.05 (0.85, 1.29)	1.09 (0.88, 1.36)	1.15 (0.89, 1.49)
>30 DDDs	1.22 (1.03, 1.46)	1.15 (0.95, 1.39)	1.16 (0.92, 1.47)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	0.94 (0.77, 1.16)	0.98 (0.78, 1.22)	1.02 (0.79, 1.33)
>30 DDDs	1.03 (0.85, 1.25)	0.97 (0.79, 1.20)	0.98 (0.76, 1.26)

Stratum 3: Born 1924-1934

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	1.06 (0.91, 1.23)	1.07 (0.91, 1.28)	1.14 (0.90, 1.45)
>30 DDDs	1.14 (1.01, 1.29)	1.11 (0.96, 1.29)	1.22 (1.00, 1.5)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	0.99 (0.85, 1.15)	1.03 (0.86, 1.23)	1.09 (0.85, 1.40)
>30 DDDs	0.99 (0.86, 1.13)	1.01 (0.86, 1.18)	1.11 (0.89, 1.39)

All anxious disorder cohorts

Stratum 1: Born 1944-1954

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	0.98 (0.72, 1.32)	1.06 (0.76, 1.46)	1.11 (0.77, 1.60)
>30 DDDs	1.11 (0.83, 1.47)	1.19 (0.88, 1.61)	1.11 (0.78, 1.59)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	0.94 (0.70, 1.27)	1.02 (0.74, 1.42)	1.07 (0.74, 1.55)
>30 DDDs	0.98 (0.74, 1.31)	1.05 (0.76, 1.45)	0.99 (0.68, 1.45)

Stratum 2: Born 1934-1944

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	1.02 (0.81, 1.28)	1.03 (0.80, 1.31)	1.00 (0.75, 1.35)
>30 DDDs	1.33 (1.10, 1.61)	1.34 (1.09, 1.65)	1.32 (1.03, 1.69)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	0.99 (0.79, 1.25)	1.00 (0.78, 1.29)	0.99 (0.74, 1.34)
>30 DDDs	1.23 (1.00, 1.51)	1.26 (1.01, 1.57)	1.27 (0.97, 1.66)

Stratum 3: Born 1924-1934

Crude	Base case	5-year lag	10-year lag
≤30 DDDs	0.95 (0.78, 1.15)	0.93 (0.74, 1.16)	0.94 (0.68, 1.30)
>30 DDDs	1.02 (0.88, 1.19)	0.91 (0.76, 1.09)	0.96 (0.74, 1.25)

Adjusted	Base case	5-year lag	10-year lag
≤30 DDDs	0.94 (0.78, 1.14)	0.92 (0.73, 1.15)	0.93 (0.67, 1.28)
>30 DDDs	0.98 (0.84, 1.15)	0.87 (0.72, 1.06)	0.91 (0.69, 1.20)

Table 5: Cox regression results of HDPS matched cohort: Dementia risk contrasting HDPS matched cohorts. Results stratified by year-of-birth categories. Each strata modelled independently. Highlighted cells are statistically significant.

Stratum 1: Born 1944-1954

HDPS matched, >30 DDDs

Crude	Base case	5-year lag	10-year lag
	1.28 (1.02, 1.61)	1.35 (1.06, 1.73)	1.21 (0.92, 1.59)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	1.18 (0.94, 1.49)	1.27 (0.99, 1.62)	1.14 (0.86, 1.5)

HDPS matched, >90 DDDs

Crude	Base case	5-year lag	10-year lag
	1.31 (0.97, 1.77)	1.40 (1.01, 1.94)	1.22 (0.83, 1.78)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	1.21 (0.89, 1.64)	1.31 (0.94, 1.82)	1.14 (0.77, 1.67)

Stratum 2: Born 1934-1944

HDPS matched, >30 DDDs

Crude	Base case	5-year lag	10-year lag
	1.14 (1, 1.3)	1.17 (1.02, 1.35)	1.16 (0.98, 1.37)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	1.07 (0.94, 1.22)	1.1 (0.96, 1.27)	1.11 (0.94, 1.31)

HDPS matched, >90 DDDs

Crude	Base case	5-year lag	10-year lag
	1.1 (0.92, 1.31)	1.1 (0.91, 1.33)	1.09 (0.87, 1.37)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	1.02 (0.86, 1.22)	1.03 (0.85, 1.25)	1.04 (0.83, 1.31)

Stratum 3: Born 1924-1934

HDPS matched, >30 DDDs

Crude	Base case	5-year lag	10-year lag
	1 (0.92, 1.09)	0.97 (0.87, 1.07)	1 (0.87, 1.15)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	0.97 (0.89, 1.06)	0.94 (0.85, 1.04)	0.97 (0.84, 1.12)

HDPS matched, >90 DDDs

Crude	Base case	5-year lag	10-year lag
	0.97 (0.87, 1.09)	0.92 (0.81, 1.05)	0.97 (0.81, 1.17)
Adjusted	**Base case**	**5-year lag**	**10-year lag**
	0.94 (0.84, 1.06)	0.89 (0.78, 1.02)	0.94 (0.78, 1.14)

Supplementary tables and figures

Table S1: Strata 1 baseline demographics and characteristics.

Stratum 1: Born 1944-1954	Non-users n= 93,714		1-14 DDDs n= 8,666			>14 to 90 DDDs n= 7,526			>90 DDDs n= 4,409		
	n	%	n	%	Std diff	n	%	Std diff	n	%	Std diff
Female	43,1	46.0	5,53	63.8	0.36	4,74	63.0	0.35	2,73	61.9	0.32
Higher income*	64,1	68.4	5,60	64.6	-0.08	4,88	64.8	-0.08	2,70	61.4	-0.15
Rural (vs urban)	35,8	38.2	3,36	38.8	0.01	2,77	36.9	-0.03	1,54	35.1	-0.06
Anxiety disorder	7,55	8.1%	2,06	23.8	0.44	2,55	33.9	0.67	2,25	51.1	1.07
Cardiovascular	4,88	5.2%	680	7.8%	0.11	706	9.4%	0.16	495	11.2	0.22
Depression	9,41	10.0	2,39	27.7	0.46	2,77	36.8	0.67	2,24	50.9	0.99
Diabetes mellitus	8,82	9.4%	1,03	12.0	0.08	867	11.5	0.07	659	14.9	0.17
Hypertension	24,5	26.2	2,97	34.3	0.18	2,65	35.3	0.20	1,71	38.9	0.27
Hypothyroidism	3,99	4.3%	559	6.5%	0.10	524	7.0%	0.12	319	7.2%	0.13
Substance abuse	1,81	1.9%	280	3.2%	0.08	256	3.4%	0.09	210	4.8%	0.16
Antidepressant											
≤30 DDD	6,24	6.7%	1,09	12.6	0.62	1,02	13.7	1.03	435	9.9%	1.4
≤180 DDD	5,57	5.9%	1,07	12.3		1,16	15.4		634	14.4	
>180 DDD	6,47	6.9%	1,75	20.3		2,15	28.6		2,20	50.1	
Antipsychotic use											
≤30 DDD	913	1.0%	246	2.8%	0.16	288	3.8%	0.34	344	7.8%	0.62
>30 DDD	354	0.4%	83	1.0%		161	2.1%		298	6.8%	
Zopiclone use											
≤30 DDD	1,92	2.0%	563	6.5%	0.22	876	11.6	0.39	992	22.5	0.66

***Higher income refers to those in the upper 3 income quintiles**

Table S2: Strata 2 baseline demographics and characteristics.

Stratum 2: Born 1934-1944	Non-users n= 56,809		1-14 DDDs n= 4,691			>14 to 90 DDDs n= 4,602			>90 DDDs n= 3,215		
	n	%	n	%	Std	n	%	Std	n	%	Std
Female	26,6	46.9	2,95	63.0	0.33	2,80	60.9	0.28	1,94	60.6	0.28
Higher income*	36,8	64.9	2,91	62.0	-0.06	2,83	61.5	-0.07	1,92	59.8	-0.11
Rural (vs urban)	23,4	41.3	1,99	42.5	0.02	1,85	40.4	-0.02	1,34	41.8	0.01
Anxiety disorder	3,18	5.6%	705	15.0	0.31	1,02	22.2	0.49	1,08	33.7	0.75
Cardiovascular	6,94	12.2	804	17.1	0.14	813	17.7	0.15	745	23.2	0.29
Depression	5,03	8.9%	1,00	21.5	0.36	1,35	29.4	0.54	1,41	43.9	0.87
Diabetes mellitus	8,64	15.2	879	18.7	0.09	829	18.0	0.08	633	19.7	0.12
Hypertension	24,2	42.7	2,48	53.0	0.21	2,42	52.7	0.20	1,86	58.1	0.31
Hypothyroidism	3,13	5.5%	431	9.2%	0.14	407	8.8%	0.13	285	8.9%	0.13
Substance abuse	891	1.6%	119	2.5%	0.07	102	2.2%	0.05	106	3.3%	0.11
Antidepressant											
≤30 DDD	3,68	6.5%	598	12.7	0.52	659	8.8%	0.84	441	13.7	1.16
≤180 DDD	2,84	5.0%	520	11.1		622	8.3%		466	14.5	
>180 DDD	3,23	5.7%	665	14.2		968	12.9		1,11	34.7	
Antipsychotic use											
≤30 DDD	717	1.3%	165	3.5%	0.17	184	2.4%	0.29	207	6.4%	0.46
>30 DDD	255	0.4%	47	1.0%		74	1.0%		157	4.9%	
Zopiclone use											
≤30 DDD	1,17	2.1%	281	6.0%	0.20	504	6.7%	0.23	579	18.0	0.55

***Higher income refers to those in the upper 3 income**

Table S3: Strata 3 baseline demographics and characteristics.

Stratum 3: Born 1924-1934	Non-users n= 40,102		1-14 DDDs n= 3,433			>14 to 90 DDDs n= 3,556			>90 DDDs n= 2,889		
	n	%	n	%	Std	n	%	Std	n	%	Std
Female	20,4	50.9	2,22	64.7	0.28	2,25	63.5	0.26	1,86	64.4	0.28
Higher income*	23,6	59.0	2,00	58.3	-0.02	2,02	56.9	-0.04	1,60	55.6	-0.07
Rural (vs urban)	15,3	38.3	1,35	39.5	0.02	1,34	37.7	-0.01	1,11	38.6	0.01
Anxiety disorder	1,53	3.8%	406	11.8	0.30	592	16.6	0.43	778	26.9	0.68
Cardiovascular	8,39	20.9	951	27.7	0.16	1,05	29.6	0.20	945	32.7	0.27
Depression	3,06	7.6%	607	17.7	0.31	916	25.8	0.50	1,07	37.0	0.75
Diabetes mellitus	7,11	17.7	692	20.2	0.06	671	18.9	0.03	591	20.5	0.07
Hypertension	22,3	55.7	2,22	64.8	0.18	2,40	67.5	0.24	2,00	69.4	0.29
Hypothyroidism	2,81	7.0%	349	10.2	0.11	357	10.0	0.11	330	11.4	0.15
Substance abuse	356	0.9%	51	1.5%	0.06	44	1.2%	0.03	45	1.6%	0.06
Antidepressant											
≤30 DDD	2,52	6.3%	428	12.5	0.49	492	13.8	0.73	392	13.6	0.99
≤180 DDD	1,42	3.6%	323	9.4%		387	10.9		378	13.1	
>180 DDD	1,66	4.2%	390	11.4		542	15.2		794	27.5	
Antipsychotic use											
≤30 DDD	656	1.6%	132	3.8%	0.15	145	4.1%	0.23	165	5.7%	0.35
>30 DDD	216	0.5%	33	1.0%		71	2.0%		98	3.4%	
Zopiclone use											
≤30 DDD	1,06	2.7%	259	7.5%	0.22	427	12.0	0.36	525	18.2	0.52

Table S4: Baseline demographics and characteristics of stratum 1 HDPS medium-dose cohort.

Use of 30 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 1: Born 1944-1954	>30 DDDs Matched to Never Users				
	Non-Exposed n= 7,707		Exposed n= 7,707		
	n	%	n	%	Std diff
Autoimmune disorder	257	3.3%	262	3.4%	0.00
Cardiovascular disease	493	6.4%	472	6.1%	-0.01
COPD	433	5.6%	418	5.4%	-0.01
Depression	2,945	38.2%	3,093	40.1%	0.04
Diabetes mellitus	816	10.6%	812	10.5%	0.00
Dyslipidemia	795	10.3%	750	9.7%	-0.02
Hypertension	2,142	27.8%	2,017	26.2%	-0.04
Hypothyroidism	295	3.8%	297	3.9%	0.00
Peptic ulcer disease	83	1.1%	89	1.2%	0.01
Antidepressant Use					
>30 - 90 DDD	438	5.7%	603	7.8%	
>90 DDD	2,515	32.6%	3,076	39.9%	
Antipsychotic Use					
≤30 DDD	139	1.8%	314	4.1%	
>30 DDD	228	3.0%	450	5.8%	
Charlson Comorbidity Index					
1	1,932	25.1%	1,936	25.1%	
2	687	8.9%	743	9.6%	
>2	430	5.6%	469	6.1%	
Income quintile	4,896	63.5%	4,830	62.7%	-0.02

Table S5: Baseline demographics and characteristics of stratum 1 HDPS high-dose cohort. Use of 90 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 1: Born 1944-1954	>90 DDDs Matched to Never Users				
	Non-Exposed n= 4,250		Exposed n= 4,250		
	n	%	n	%	Std diff
Autoimmune disorder	157	3.7%	166	3.9%	0.01
Cardiovascular disease	297	7.0%	285	6.7%	-0.01
COPD	248	5.8%	251	5.9%	0.00
Depression	1,848	43.5%	1,937	45.6%	0.04
Diabetes mellitus	501	11.8%	496	11.7%	0.00
Dyslipidemia	402	9.5%	408	9.6%	0.00
Hypertension	1,185	27.9%	1,156	27.2%	-0.02
Hypothyroidism	164	3.9%	152	3.6%	-0.01
Peptic ulcer disease	54	1.3%	58	1.4%	0.01
Antidepressant Use					
>30 - 90 DDD	244	5.7%	324	7.6%	
>90 DDD	1,628	38.3%	1,973	46.4%	
Antipsychotic Use					
≤30 DDD	92	2.2%	215	5.1%	
>30 DDD	180	4.2%	331	7.8%	
Charlson Comorbidity Index					
1	1,133	26.7%	1,137	26.8%	
2	411	9.7%	411	9.7%	
>2	275	6.5%	292	6.9%	
Income quintile	2,615	61.5%	2,599	61.2%	-0.01

Table S6: Baseline demographics and characteristics of stratum 2 HDPS medium-dose cohort.

Use of 30 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 2: Born 1934-1944	>30 DDDs Matched to Never Users				
	Non-Exposed n= 5,232		Exposed n= 5,232		
	n	%	n	%	Std diff
Autoimmune disorder	207	4.0%	184	3.5%	-0.02
Cardiovascular disease	682	13.0%	682	13.0%	0.00
COPD	354	6.8%	309	5.9%	-0.04
Depression	1,436	27.4%	1,519	29.0%	0.04
Diabetes mellitus	791	15.1%	797	15.2%	0.00
Dyslipidemia	792	15.1%	755	14.4%	-0.02
Hypertension	2,269	43.4%	2,143	41.0%	-0.05
Hypothyroidism	226	4.3%	229	4.4%	0.00
Peptic ulcer disease	72	1.4%	69	1.3%	0.00
Antidepressant Use					
>30 - 90 DDD	237	4.5%	332	6.3%	0.17
>90 DDD	1,155	22.1%	1,487	28.4%	
Antipsychotic Use					
≤30 DDD	98	1.9%	175	3.3%	0.14
>30 DDD	116	2.2%	238	4.5%	
Charlson Comorbidity Index					
1	1,487	28.4%	1,406	26.9%	0.07
2	677	12.9%	747	14.3%	
>2	535	10.2%	612	11.7%	
Income quintile	3,210	61.4%	3,159	60.4%	0.03

Table S7: Baseline demographics and characteristics of stratum2 HDPS high-dose cohort. Use of 90 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 2: Born 1934-1944	>90 DDDs Matched to Never Users				
	Non-Exposed n= 3,061		Exposed n= 3,061		
	n	%	n	%	Std diff
Autoimmune disorder	122	4.0%	128	4.2%	0.01
Cardiovascular disease	417	13.6%	439	14.3%	0.02
COPD	214	7.0%	187	6.1%	-0.04
Depression	968	31.6%	1,041	34.0%	0.05
Diabetes mellitus	527	17.2%	469	15.3%	-0.05
Dyslipidemia	494	16.1%	453	14.8%	-0.04
Hypertension	1,393	45.5%	1,303	42.6%	-0.06
Hypothyroidism	161	5.3%	129	4.2%	-0.05
Peptic ulcer disease	35	1.1%	47	1.5%	0.03
Antidepressant Use					
>30 - 90 DDD	145	4.7%	202	6.6%	0.17
>90 DDD	791	25.8%	1,012	33.1%	
Antipsychotic Use		0.0%			
≤30 DDD	73	2.4%	131	4.3%	0.16
>30 DDD	76	2.5%	169	5.5%	
Charlson Comorbidity Index					
1	877	28.7%	830	27.1%	0.06
2	413	13.5%	452	14.8%	
>2	368	12.0%	390	12.7%	
Income quintile	1,822	59.5%	1,844	60.2%	0.02

Table S8: Baseline demographics and characteristics of stratum 3 HDPS medium-dose cohort.

Use of 30 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 3: Born 1924-1934	>30 DDDs Matched to Never Users				
	Non-Exposed n= 4,525		Exposed n= 4,525		
	n	%	n	%	Std diff
Autoimmune disorder	196	4.3%	171	3.8%	-0.03
Cardiovascular disease	954	21.1%	865	19.1%	-0.05
COPD	312	6.9%	321	7.1%	0.01
Depression	922	20.4%	1,077	23.8%	0.08
Diabetes mellitus	748	16.5%	737	16.3%	-0.01
Dyslipidemia	611	13.5%	596	13.2%	-0.01
Hypertension	2,450	54.1%	2,392	52.9%	-0.03
Hypothyroidism	247	5.5%	259	5.7%	0.01
Peptic ulcer disease	76	1.7%	82	1.8%	0.01
Antidepressant Use					
>30 - 90 DDD	190	4.2%	280	6.2%	0.19
>90 DDD	726	16.0%	1,000	22.1%	
Antipsychotic Use					
≤30 DDD	78	1.7%	163	3.6%	0.15
>30 DDD	83	1.8%	135	3.0%	
Charlson Comorbidity Index					
1	1,225	27.1%	1,231	27.2%	0.04
2	705	15.6%	687	15.2%	
>2	674	14.9%	710	15.7%	
Income quintile	2,524	55.8%	2,534	56.0%	0.02

Table S9: Baseline demographics and characteristics of stratum 3 HDPS high-dose cohort. Use of 90 DDDs or more was defined as a user, zero exposure was defined as a non-user.

Stratum 3: Born 1924-1934	>90 DDDs Matched to Never Users				
	Non-Exposed n= 2,763		Exposed n= 2,763		
	n	%	n	%	Std diff
Autoimmune disorder	137	5.0%	111	4.0%	-0.05
Cardiovascular disease	595	21.5%	545	19.7%	-0.04
COPD	200	7.2%	218	7.9%	0.02
Depression	679	24.6%	743	26.9%	0.05
Diabetes mellitus	496	18.0%	459	16.6%	-0.04
Dyslipidemia	352	12.7%	358	13.0%	0.01
Hypertension	1,499	54.3%	1,475	53.4%	-0.02
Hypothyroidism	173	6.3%	165	6.0%	-0.01
Peptic ulcer disease	43	1.6%	53	1.9%	0.03
Antidepressant Use					
>30 - 90 DDD	123	4.5%	177	6.4%	0.22
>90 DDD	530	19.2%	725	26.2%	
Antipsychotic Use					
≤30 DDD	57	2.1%	111	4.0%	0.15
>30 DDD	59	2.1%	93	3.4%	
Charlson Comorbidity Index					
1	772	27.9%	744	26.9%	0.03
2	445	16.1%	428	15.5%	
>2	436	15.8%	443	16.0%	
Income quintile	1,533	55.5%	1,535	55.6%	0.01

Chapter 7: Conclusion

There is a large and growing body of observational studies looking at the association between many classes of medications, such as PPIs and benzodiazepines, and the risk of dementia. These studies have come to widely varying conclusions, ranging from a significant and substantial increase in risk all the way to a protective effect. This situation is more problematic than just researchers not agreeing on what the correct conclusion is as these results, especially those that suggest these drug classes are dangerous are picked up by media sources and widely reported, lead persons who rely on these drugs to experience stress and possibly to discontinue needed therapy. The result is a general confusion among both patients and clinicians on how to respond to this literature. In an attempt to understand why these studies come to such divergent findings I conducted a methodological sensitivity analysis looking at both benzodiazepines and PPIs and their effect on dementia risk. Additionally, I conducted an analysis looking at individual characteristics that were associated with incident PPI use as well as those associated with an increased duration of use to see if they might explain more about the divergent findings.

In the examination of the relationship between PPIs and dementia (Chapter 4) the initial results showed that people who have a higher cumulative exposure to PPIs between the ages of 45 and 65 were at higher risk of dementia, whereas there was no increase in risk for those who started use between the ages of 65 and 75. PPI users also had significantly higher rates of baseline comorbid medical conditions, such as diabetes, cardiovascular disease, and depression, which are dementia risk factors. When these factors are accounted for in statistical models, the statistical association between PPI use and dementia disappears. There was also a relationship between increased duration of exposure to these classes of drugs (Chapter 5) as measured in DDDs, and increased rates of these conditions, all of which have been shown to independently increase the risk of dementia themselves. This relationship is one potential explanation for the many published findings linking PPIs to dementia.

When the relationship between benzodiazepines and dementia was examined (Chapter 6) a similar pattern was seen. Again, the youngest users, those who started use between the age of 45 and 55, had higher rates of dementia, 61% difference in relative terms. However, this was only a 0.8% absolute difference in risk. Again, users were more likely to have medical comorbidities associated with dementia risk, and including these in a multivariable analysis decreased the associate between benzodiazepine exposure and dementia but, unlike with PPIs, there remained a statistically significant association when compared to the general populations. However, the general population is not the best control group to use in this analysis as there is significant risk of indication bias. Benzodiazepines are most used in individuals with depression or anxiety, both of which have been described as independent risk factors for dementia. Using a control group of similarly depressed or anxious persons who do not use benzodiazepines revealed no difference in the adjusted risk of dementia among users regardless of their cumulative exposure.

One of the major strengths of this research project was the length of both our exposure assessment and follow-up periods. All individuals had between 5 and 10 years of baseline data in which to measure drug use and assess comorbid conditions, and from 10 to 20 years of follow-up time. We were also able to accurately quantify prescription dispensations and include cumulative exposure in our regression models. A majority of the previously published research on this topic had much shorter follow-up periods, and most did not examine whether there was a dose-response effect. Short follow-up periods are problematic when looking at a condition like neurodegenerative dementia (as opposed to vascular dementia), as the underlying disease process, although not well understood, is known to begin at least one to two decades prior to diagnosis. The lack of a dose-response relationship is important when one is assessing whether there is a causal link between drug exposure and an outcome. Instead, most analysis used a user/non-user design which groups together individuals who filled a single prescription (and may

have not even taken it) with people on drug therapy for multiple continuous years. An additional strength of this research was the use of detailed dosage information in the analysis.

One of the main weaknesses in my research is the number of cases of dementia in our data, which was a problem when looking at our youngest stratum where follow-up started at age 55. About half the cohort would still be less than 65 years of age at the end of the study, when the risk of dementia really starts to rise. This resulted in a lack of precision and wide confidence intervals around our point estimates. It would be worthwhile for others to replicate this study design in a larger population to determine whether our lack of significance in this youngest group was a null result or if we were simply underpowered. However, despite this limitation this work still had more comprehensive and longer-term data than most of the other studies in this area. In any case, for both classes of drugs, the absolute crude difference in dementia rates was small in the youngest strata, and non-existent in the oldest. This suggests that even if these drugs did increase the risk of dementia, this effect is small and our focus should be on other, more important risk factors such as diabetes, cardiovascular disease, and maintaining social, cognitive and physical activity as we age.

The pharmacoepidemiological research into dementia risk among medication users is messy. If one does not adequately control the noise in the data, then many signals of questionable validity can be found. Adding one more study to this body of evidence with inadequate controls does little to solve the issue and continues to leave patients, caregivers and clinicians confused. In this work, a more robust methodological sensitivity analysis was conducted to demonstrate that PPI and benzodiazepine users are at higher risk of dementia, but that this is not due to their drug exposures but rather related to confounding and study biases. It is hoped that this systematic approach will raise the bar for future research in this area. Perhaps future researchers, before rushing to publish alarm findings, assess whether they have truly controlled for confounding, reduced the risk of bias, and that their study design can answer the question they are trying to ask.

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Appendix A: Annotated Bibliography of PPI-Dementia Papers

In 2015, German researchers using data from the AgeCoDe longitudinal study on aging published a paper that reported a 44% increase in risk of Alzheimer's dementia and a 38% increase in any dementia among PPI users as compared to non-users.[22] In 2016, the same group of researchers replicated this work, this time using administrative data and reported a 44% increase in dementia among PPI users.[23] This second paper received significant media attention resulting in 146 news stories in outlets including CBC News, The New York Times, and NBC Nightly News.[1,2,175] These were the first in a series of over 20 research papers that have been published examining this topic.[22-25,103-119,176-183] New papers looking at PPIs and dementia continue to come out, with one of the most recent, a Danish study by Pourhadi *et al* that included almost 100,000 cases of dementia did find a significant increase.[183] Despite the significant amount of attention given to this problem, the accumulating evidence remains inconclusive. A number of systematic reviews have tackled this problem, with a plurality of the most recently published papers reviewed coming to the conclusion that there is either no association, or that the association seen may not be causal.[184-194]

This annotated bibliography is meant to serve as a summary of the different methods, sources of data, and results in the published record. These studies were identified by scanning through a number of systematic reviews and pulling all the mentioned studies, including some that were not included in the final meta-analysis.

2013 - Prevalence and associations of the use of proton-pump inhibitors in nursing homes: a cross-sectional study[177]

This paper is a cross-sectional study of French nursing home patients to assess correlates of PPI use and has been included in several meta-analyses despite not being designed nor presented as an examination

of potential outcomes of PPI use. Instead, it is a descriptive study that looked at the characteristics of PPI users in nursing homes, with dementia being just one of nine comorbidities examined. Users of PPI were defined as those with a prescription within one week of observation date. They found that persons with dementia were less likely to using PPIs than non-demented patients (36.4% vs 46.7%, p<0.001).

2015 - Risk of dementia in elderly patients with the use of proton pump inhibitors[22]

This was the first PPI study focused on risks of dementia among users. These researchers used data from AgeCoDe, a prospective longitudinal study on aging. Persons 75 years of age or older living in the community were followed over a six-year period. Clinical experts assessed dementia status every 18 months allowed for the robust classification of dementia and Alzheimer's disease status. PPI use was determined by examining the interview documentation on medication use. Outcomes were modelled using time dependent exposure status, which was allowed to change over time based on PPI use in the previous 18-month period. They found an association between regular PPI use and outcomes of all-cause dementia (HR 1.38, CI 1.04–1.83; p = 0.02) and for Alzheimer's disease HR 1.44, (95 % CI 1.01–2.06; p=0.04).

2016 - Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis[23]

This was a "prospective" claims based cohort study of older (>75 years of age) persons that compared regular PPI users (at least 1 prescription per quarter year) versus never-users. The study was designed to replicate the AgeCoDe study, and included researchers associated with the above publication, but using administrative data for exposure and outcome assessment. Persons who used PPIs intermittently were excluded from analysis. This study found an association of PPIs and all-cause dementia HR 1.44 [CI 1.36-1.52; P < .001] that mirrored the results from their earlier study. The confounders of depression, stroke, age, female sex, and polypharmacy all increased the risk of dementia, while those with ischemic heart

disease had a lower risk of dementia. They also found that increasing duration of PPI use was associated with higher risks. When stratified by age, the effect of PPIs on dementia risk decreased with age (age 75-79, HR = 1.69; 80-84, HR= 1.49; >85, HR = 1.32).

2016 [104] Risk factors for dementia diagnosis in German primary care practices[104]

Case control study conducted in Germany between 2010 and 2014 that matched users to non-users based upon age, sex, type of health insurance and physician. The use of statins, antihypertensive and PPI (ever-users vs never-users, OR 0.93 95%CI 0.9 - 0.97) were associated with a lower risk of dementia. This study was not specifically designed to examine PPIs, but rather looked at a large variety of drugs and medical conditions to look for potentially modifiable dementia risk factors.

2016 [105] Prolonged use of proton pump inhibitors and cognitive function in older adults.[105]

Prospective study conducted in Bucharest comparing age matched participants who used long term PPIs versus a non-users control group. Long term PPI was defined as >6 months of continuous use per year for 3 consecutive years, as reported by the patient. This study of 150 total persons reported the highest association between PPI use and dementia outcomes or any published study thus far, with an OR 3.67 (p= 0.002). There are several problems with the study, however. Study participants were required to not have a pre-existing dementia diagnosis and were then given a mini-mental state exam (MMSE), and those with a score of 25 or under when classified as demented, although persons with scores between 19 and 23 are usually considered mild cognitive impairment, and the MMSE is not diagnostic for tool for dementia.

2017 - Prolonged use of proton pump inhibitors and cognitive function in older adults.[106]

This was a retrospective administrative-data cohort study of Taiwanese individuals >40 years of age with no dementia at baseline. PPI users were matched to non-users on age, sex, propensity score, and index

year. Their definition of dementia required a diagnosis made by a psychiatrist or a neurologist. Cumulative PPI dose was time-varying. They reported an increased risk of dementia among PPI users (HR = 1.22, 95% CI 1.05-1.42. They also looked at the relationship between dose and dementia, dividing users into dose-based quintiles and found a significant trend of increased dose = increased risk. Those with hyperlipidemia and ischemic heart disease also had high rates of dementia.

2017 - Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia.[103]

This prospective study looked at PPI use and the risk of transition from normal cognition to mild-cognitive impairment (MCI), or from normal/mild impairment to dementia. Participants were age 75 and older, and were either normal cognitively, or had MCI, at baseline. They had annual study visits where PPI use and cognitive status was measured. PPI use was broken down into three use categories; use at every visit, intermittent use, and no use. Outcome was cognitive decline, whether from normal to MCI or AD, or from MCI to AD. Many confounders were included, including, H2RB and anticholinergic drug use. PPIs were significantly protective against decline. There was also a protective dose-response effect, with always users < sometimes users < never users. (HR = 0.82, 95% CI = 0.69-0.98)

2017 - No Association Between Proton Pump Inhibitor Use and Risk of Alzheimer's Disease.[107]

A Finnish, claims based, matched, case-control study. Outcomes were assessed using the Social Insurance Institute (SII) special reimbursement program, which requires certificates of diagnosis for Alzheimer's disease to receive benefits, potentially resulting in a higher accuracy of diagnosis in claims data than most simple billing data. This study used all diagnoses made between January 2005 and December 2011 (a seven-year span). Up to 4 sex, age, and region matched controls were used for each case. Controls were required to not have dementia when selected, but were allowed to later become cases, when they would then be matched to up to 4 controls of their own. Index date is date of diagnosis. PPI use was determined from the prescription database, and the PRE2DUP (a Finnish

algorithm used to determine use-periods from data without days supply information). Cumulative duration of use was determined from 1995 up to index date. Lag windows of 0 (no lag), 3, and 5 years were used – with all covariates and drug exposure in lag windows being discarded. Comorbidities were determined from the SII register or hospital records using any diagnosis in the pre-lag observation period going back as far as 1972. Long term use was defined as > 3 years. No significant association was observed (no lag period OR = 1.02; 3-year lag OR= 1.03; 5-year lag OR = 1.05).

2018 - Proton Pump Inhibitor Use and Dementia Risk: Prospective Population-Based Study.[108]

This paper reports results from the prospective Kaiser Permanente ACT (Adult Changes in Thought) study where participants were clinically assessed ever 2 years over a relatively long time period, with a mean follow-up of 7.5 years. PPI use was assessed using prescription records, with cumulative PPI dose being the primary exposure measure, and was expressed as SDDs (standardized daily doses) over the previous 10 years. Exposure was modelled as a time-varying measure, using the 10 years prior to each point in time as the exposure assessment window (excluding prescriptions in the immediately preceding years last year to minimize protopathic bias. stuff). Other exposure measures included total duration of use, and longest duration of use. Demographics, exercise, gait speed, and other comorbidities were assessed using standardized questionnaires and claims data. Cox regression was used to analyse the data, with patient age being used as the time scale. In the primary analysis, patients were censored if/when they had any non-AD dementia diagnosis (although all-cause dementia was also examined). Time-varying measures were also used for coronary heart disease, stroke, hypertension, diabetes, and medication use (using the moving 10 year assessment window). No significant effect was found, with all point estimates clustered around 1.

2018 - The Uncertainty of the Association Between Proton Pump Inhibitor Use and the Risk of Dementia: Prescription Sequence Symmetry Analysis Using a Korean Healthcare Database Between 2002 and 2013.[24]

This study used a prescription sequence symmetry analysis. They looked at users who started taking PPIs within 3 years of a dementia diagnoses, contrasting the number of users who initiated treatment before diagnosis with those initiating use after. H2RB users were used a as a negative control group. Persons with less than 6 months between diagnosis and first prescription were excluded to avoid protopathic bias. The sequence ratio (SR) is the number of persons who used a PPI before dementia divided by the number who used after dementia diagnosis. They used H2RBs, NSAIDs, and statins as negative controls, assuming that these drugs are not associated with dementia. Duration of exposure was also examined, grouping people into <30 days, 30-60 days, and > 60 days. They also did a sensitivity analysis looking at 1-, 2-, and 6-year exposure windows. NSAIDs and statins were also used as negative controls. They looked at Alzheimer's disease, vascular dementia, and "other dementias" separately. The adjusted sequence ratio (aSR) for PPIs was 1.21 [1.16-1.27]; H2RBs aSR= 1.91 [1.80-2.02]; NSAIDs aSR= 1.5 [1.36-1.65]; statins aSR= 1.44 [1.37-1.52]. The concluded that there was no association between PPI use and dementia.

2018 -Association Between Proton Pump Inhibitor Use and Alzheimer's Disease in Older Adults.[111]

This analysis was published as a letter to the editor in the Journal of the American Geriatrics Society. Using the Taiwanese NHID (National Health Insurance Database) they conducted a case-control analysis in persons age >65. Patients were matched on age, sex, and comorbidities. Four controls were assigned to each of the 428 patients with newly identified AD. The main analysis focused on ever/never use, and they also looked at cumulative duration of use. Neither analysis found a significant effect for ever use (OR= 0.79 [0.63-1.01], or for duration of use (OR= 0.99 [0.63-1.02]).

2018 - A Nationwide Population-Based Cohort Study of Dementia Risk among Acid Suppressant Users.[109]

A Korean administrative data study that looked at both PPI and H2RB use and the risk of dementia using data from 2002 to 2013. The cohort consisted of those who used the health care system (i.e., had at least one health examination prior to the start of the follow-up period which started in 2007). The study used a 1-year (2002) washout to remove prevalent users. Drug use, health behaviours, comorbidities, and demographics were determined during a 3-year period prior to index date (January 2007). Any cases that occurred in the first 3 years of follow-up were excluded to reduce protopathic/prodromal/latent effects. Follow-up continued until the end of 2013. The primary exposure was cumulative use of PPIs and H2RBs. They found that PPI use was not associated with dementia (HR= 0.99 (95% CI 0.7-1.39)), although H2RB use was (HR= 1.31 (95% CI 1.13-1.51). Concurrent use of both drugs was associated with a non-significant increase (HR= 1.25 (95% CI 0.76-2.05)). When examining the risks by individual H2RB molecules, cimetidine (HR=1.31 (95% CI 1.01-1.71)) but not ranitidine (HR=1.19 (95% CI 0.77-1.84)) showed significant harmful effects.

2018 - Proton Pump Inhibitor Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case–Control Analysis.[110]

A case-control study using CPRD (Clinical Practice Research Datalink) data from the UK looking a PPI use and the risk of AD or vascular dementia (VaD). Index date was date of first diagnosis or fill of a dementia medication. Excluded persons with Down's syndrome, HIV/AIDS, EtOH or substance abuse, or multiple sclerosis. Users were matched 1:1 on year of birth, age, sex, calendar time, and years of medical history in within the database. Users were compared to non-users, as well as categorizing users by number of prescriptions (1-4, 5-19, 20-49, 50-99, >100). Users of H2RB's were used as a negative control, and categorized as ever/never users, as well as by the number of prescriptions (1-5, 5-19, >20). The usual

comorbidities were used as covariates, as was use of blood thinners, NSAIDs, SSRI/SNRIs, as well as using the CCI, smoking, and BMI. To compensate for protopathic bias, a 1-year lag analysis was done by pushing the index date backwards by one year (for cases and controls). Neither PPIs nor H2RBs were associated with AD or VaD.

2019 - Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin.[25]

This is an actual randomized controlled study that was conducted to examine the effects of rivaroxaban vs aspirin vs both drugs together on cardiovascular outcomes. As an additional component a subgroup of non-PPI users was randomization to use PPI use to assess whether this reduced risk of bleeding. The safety analysis looked at dementia, pneumonia, clostridium difficile infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 month for a 3 years. Although described as a long-term study, in the context of dementia research this was actually a pretty limited period of follow-up. For dementia, they reported a non-significant increase in risk (OR= 1.25 [0.81-1.78]) after 3 years of regular use as compared to placebo treated patients.

2019 - Does Long-Term Proton Pump Inhibitor Use Increase Risk of Dementia? Not Really! Results of the Group-Based Trajectory Analysis.[112]

PPI use was assessed using a group-based trajectory model to assign users to one of three latent groups (short, intermittent, and long-term users). These categories were then used to assess the risk of dementia based on group membership. This was a user-only analysis, with short-term users being used as the reference group. The Taiwanese NHIRD database was used to identify persons who initiated treatment in 2005. Trajectories were assessed over the first 3 years of data (2005-2008), while outcomes were assessed in the last 5 years. Time-varying Cox models including changing ACB

(anticholinergic burden) and the use of "at-risk" medications during the follow-up period. Competing risk of death was examined using the sub-distribution hazard method. No significant difference was observed between the differing levels of use with estimates ranging from HR= 0.91 (95% CI 0.76-1.09] to HR= 1.16 (95% CI 0.93-1.17).

2019 - Beyond uncertainty: Negative findings for the association between the use of proton pump inhibitors and risk of dementia.[113]

A Taiwanese study comparing incident PPI users to incident H2RB users using data from 2003 to the end of 2013 (11 years). Date of first PPI prescription was defined as the index date. Lags of 0, 1, 2, and 3 years were used to reduce protopathic bias. Use of antidepressants, antipsychotics, benzodiazepines, anti-dementia drugs NSAIDs, anti-thrombotics, z-drugs, statins, anti-hypertensive drugs, diabetes drugs, Charlson comorbidity index scores, and other chronic conditions were assessed and used to calculate propensity score. In models with no lag period PPIs were associated with a slight but significant increase in dementia risk (IRR= 1.13, 95%CI 1.08, 1.18). This effect decreased with increasing lag period duration, and was seen to be protective, when compared to H2RBs, in the 3-year lag period analysis (IRR= 0.83, 95% CI 0.78-0.88), showing PPIs protective compared to H2RBs. The results from the unmatched cohort were like those in the matched cohort. No trend was seen with increased dose or duration of PPI use.

2020 - Proton pump inhibitors and dementia risk: Evidence from a cohort study using linked routinely collected national health data in Wales, UK.[115]

This is a large Welsh database study with a high number of cases of dementia (~37,000) as compared to many other studies, had a large cohort of users, and lengthy follow-up times (mean 9.8 years). Ever-users were compared to never-users, and up to 15 years of follow-up was possible. Index date was date of first PPI prescription, or a random date for non-users. Covariates, including diabetes, cardiovascular disease, depression, anxiety, head injury, hypertension, hyperlipidemia, anemia, vitamin B12 deficiency,

drug use (anxiolytics, antidepressants, blood thinners, statins, hormone replacement therapy, vitamin B12, and blood pressure drugs) were included if they were significant in univariate models. A sensitivity analysis looking at "who developed dementia within 2-4 years, 5-9, or >10 years post index was also done. A significant protective effect was seen in the main (HR= 0.67 [0.65-0.69], as well as in all sensitivity analysis (2-4 yrs HR=0.58, 5-9 HR= 0.46, >10 HR= 0.29, all significant).

November 2020 - Acid suppressants use and the risk of dementia: A population-based propensity score-matched cohort study.[117]

A propensity-score matched cohort study of incident histamine-2 receptor blockers (H2RB) users, PPI users, and non-users, comparing each group against the other (i.e. 3 "comparison cohorts"). Exposure was modeled as cumulative daily defined doses (DDDs) between first use and the end of follow-up. A user was defined as anyone with more than >60 cumulative DDDs of one drug class (i.e. H2RB or PPI), and non-use of the other, while a non-user was somebody with no prescriptions for either class. Propensity scores were calculated based on demographics, user index date, and comorbidities (based on claims in the year prior to start date). Index date was defined for users as the date they met the cumulative 60 DDD threshold. The index date for non-user was that of their matched user. Depression was assessed at baseline, while peptic ulcer disease and gastroesophageal reflux disease (GERD) was determined at baseline and during follow-up. Neither PPIs (HR= 0.72 [0.5-1.03]) nor H2RBs (HR= 0.95 [0.7-1.2]), when compared to non-users, showed any significant effect. The head-to-head comparison of PPI users to H2RB users also had a null finding (HR= 0.82 [0.58-1.17]).

2020 - Clinical Use of Acid Suppressants and Risk of Dementia in the Elderly: A Pharmaco-Epidemiological Cohort Study.[114]

Another Taiwanese administrative data study, this time comparing incident H2RB users to non-users, and incident PPI users to non-users. Initial prescription date was defined as index date. Patients were

matched on age, sex, index year, and CCI (Charlson comorbidity index) on a 1:1 basis. Comorbidities were assessed at baseline. Cumulative DDDs were determined from start date until dementia or censoring. A separate model looked at users vs non-users (no DDD measure), with user status allowed to revert from users to non-user status if PPI use was halted in the first 6 years of the study period (start of 2000 to the end 2005). Exposures were lagged 1 year to avoid protopathic bias. The number of physician visits was used to adjust for detection bias. This study found a dose-response effect for both PPIs (1-30 DDD HR= 1.09 (95% CI 0.91-1.37); 31-180 HR= 1.59 (95% CI 1.2-1.9); 181-365 DDDs HR= 1.8 (95% CI 1.2-2.1); >365 DDD HR= 2.0 (95% CI 1.4-2.3) and H2RBs (1-30 DDD HR= 1.7 (95% CI 1.2-1.9); 31-180 HR=1.9 (95% CI 1.5-2.2); 181-365 HR= 1.8 (95% CI 1.5-2.4); >365 DDD HR= 2.0 (95% CI 1.6-25)

2020 - Proton pump inhibitors and the risk of Alzheimer's disease and non-Alzheimer's dementias.[116]

Spanish administrative data study of persons >45 years of age (excluding persons using benzodiazepines or Z-drugs) using data from 2002 to the end of 2015 (14 years). They used a 5-year lag period (any outcomes in the 5 years after first use were ignored). Outcomes were a) Alzheimer's disease or b) non-AD dementia (primarily vascular dementia). Results were adjusted for age, sex, hypertension, diabetes, and dyslipidemia. An effect was seen for both dementia types in the crude analysis, but after adjustment only non-AD dementias were significant (OR= 1.2 (95% CI 1.05-1.37)). No dose response relationship was seen.

2022 - Emulating a target trial of proton pump inhibitors and dementia risk using claims data.[118]

A study using German administrative data was constructed to emulate a hypothetical randomized controlled study. A total of almost 2.7 million individuals aged 40 and older were included. PPI prescriptions were ascertained using claims data, with the outcome of dementia and other medical diagnoses were determined using medical claims and hospital abstracts. Individuals were assigned to the PPI user group on the date they filled their first prescription, provided they were dispensed at least

56 DDDs within the first year of use. Non-users were selected among those who did not initiate PPI use with randomly assigned index dates. Weighted Cox regression models were used to control for confounding at baseline. Time-varying analysis was also performed by recalculating the IPT weights in half year intervals. Comparing initiators to non-initiators, emulating an intention-to-treat analysis, PPI users had a significantly elevated risk of dementia (HR= 1.54 (95% CI 1.51, 1.63)). Time-varying analysis found similar results (HR= 1.56 (95% CI 1.50, 1.63)). While this was a large study, it's main weakness was its short median follow-up time 4.3 years.

2022 - Associations between proton pump inhibitors and Alzheimer's disease: a nested case–control study using a Korean nationwide health screening cohort.[119]

This study used Korean administrative data to conduct a nested case-control analysis to assess the effect of PPI use on Alzheimer's risk in individuals aged 60 years and over. PPI users were matched to controls (non-PPI-users) at a 1:4 ratio. The paper was unclear as to whether matching was done using exact matching based on age, sex, income quintile, region (urban vs rural) and index date (as stated in figure 1); or by using a propensity score based on those covariates as well as Charlson comorbidity index, BMI, tobacco smoking, and various lab measures. PPI use was assessed over a short period of 1 year prior to index date, not considering the prodromal dementia period, and was categorized as past use, current use, non-use, as well as being measured as total days of use. Using logistic regression, a small but statistically significant increase in Alzheimer's risk was found, with odds ratios ranging from 1.11 (95% CI 1.04, 1.18) to 1.36 (95%CI 1.26, 1.46).

2024 - Proton pump inhibitors and dementia: A nationwide population-based study[183]

One of the most recent studies looking at PPI and dementia, this Danish study using administrative data constructed a cohort of nearly 2 million individuals who they followed for up to 19 years, finding almost 100,000 dementia outcomes. The divided their cohort into age groups based on age at time of dementia

diagnosis. Like our PPI analysis, they considered the age at which PPI use began and included a 5-year lag period to reduce protopathic bias. They also did not find a significant difference between lag and non-lag models. They also examined duration of use and found a duration-response effect where increasing duration of use was associated with higher risk of dementia, most prominently in their youngest age group. However, the magnitude of the association decreased with increasing age at time of diagnosis, from an adjusted incidence rate ratio of 1.365 (1.29, 1.43) for those diagnosed between the ages of 60-69 years, down to 1.03 (0.91, 1.17) for those diagnosed at the age of 90 and above.

Appendix B – Approvals

This appendix contains submissions to, and approvals from the Manitoba Centre for Health Policy (MCHP), the University of Manitoba Human Research Ethic Board (HREB), and the Health Information Privacy Committee (HIPC) (now called the Provincial Health Research Privacy Committee (PHRPC)).

Submission to MCHP: Feasibility and data access quote request form

MCHP PROJECT FEASIBILITY AND DATA ACCESS QUOTE REQUEST FORM

University of Manitoba | Rady Faculty of Health Sciences

For assistance in completing this form please contact mchp_access@cpe.umanitoba.ca.
Please allow a minimum of 10 working days for processing of review. This timeline does not apply to incomplete submissions

A. Project Title and PI

1. Full Title of Project	Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer's Disease.
2. Principal Investigator	Kevin Friesen
a. E-mail Address	[redacted]
b.Institution & Department:	Rady Faculty of Health Sciences, College of Pharmacy
c.Telephone No.	[redacted]
d. Full Mailing Address:	College of Pharmacy, Apotex Centre, 750 McDermot Avenue, Winnipeg Manitoba, R3E 0T5
3. Project Coordinator or PI's Assistant Name & E-mail Address, to be included on all correspondence	Kevin Friesen, friese13@myumanitoba.ca
4. Project is a Thesis	◉ Yes ○ No (continue to A5)
a. Level or Type of Thesis	PhD
b. Name and Contact Information of Thesis Supervisor (May be external to MCHP):	Dr Shawn Bugden. [redacted] College of Pharmacy, Apotex Centre, 750 McDermot Avenue,
5. U of M Project Associated Investigator: **Required** for all projects with a non-U of M PI. A U of M or WRHA researcher is required for submission to REB.	Shawn Bugden

B. Project

1. Project Description - Please attach copy of proposal or letter of intent.

◉ a. This is a new proposal **OR** ○ b. This is a letter of intent ***(feasibility only - cost estimate will not be provided)***

OR This proposal is a resubmission: ○ c. with no significant changes **OR** ○ d. with significant changes.

2. Related Project — This project is associated with another MCHP project. ○ Yes ◉ No — Project Reference Number(s): *(This can be the MCHP, HIPC, or REB number)*

3. Data Requirements — All data sources being used for the study and requiring approvals (HIPC, REB, non-health data (e.g., Education)) - both MCHP and non-MCHP data - must be identified. *Completion of Appendix 2 is not required if you are only using MCHP data.*

☒ Appendix 1 - MCHP data. Please attach a list all data sources/years required from the MCHP Data Repository.

☐ Appendix 2 - non-MCHP data. Please provide information for data not available in the Data Repository.

4. Analytic Requirements — Analyses includes the following identifiable subgroups of the population for which special privacy considerations apply. If none apply, leave blank and continue to B5.

☐ First Nations, Metis, Inuit ☐ Mental Illness ☐ Children in Care ☐ Children

☐ Developmental or Intellectual Disabilities ☐ School or school division level analysis

☐ Other (please specify):

5. Project Location — a. Analyses will take place only within MCHP secure facilities located at:

☐ MCHP Office: 408 Brodie Centre (Analysis to be conducted by an MCHP Analyst) ☒ Remote Access Site: (Analysis to be conducted by an external analyst) Pharmacy

b. This is a multi-site collaborative project. ◉ No ○ Yes *Please specify sites.*

Approval from MCHP: feasibility and data access quote request response

UNIVERSITY OF MANITOBA | Rady Faculty of Health Sciences

Max Rady College of Medicine
Manitoba Centre for Health Policy
Community Health Sciences
408-727 McDermot Avenue
Winnipeg, Manitoba
Canada, R3E 3P5
Phone: 204-789-3819
Fax: 204-789-3910
info@cpe.umanitoba.ca

- REPOSITORY ACCESS AND USE QUOTE VALID FOR ONE YEAR -

October 17, 2017

Kevin Friesen
College of Pharmacy
Apotex Centre
750 McDermot Ave.
Winnipeg MB R3E 0T5

Dear Kevin:

Re: Project Entitled, Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer's Disease

The above proposal has been reviewed by the Manitoba Centre for Health Policy (MCHP), and an estimate prepared for the use of the Manitoba Population Research Data Repository (Repository) and the associated MCHP resources required to complete the research outlined. As an estimate, it is subject to change if the project specifications change. Should significant revisions to the research plan be required, please contact MCHP with a revised proposal and a new estimate will be generated.

Based on the description of the project outlined in your proposal, the estimate to configure and extract information from the Repository is $2100.00. GST will be applied to projects that are invoiced outside of the University of Manitoba. The overall expected time to complete this project is 4 years.

MCHP requires written documentation of updated approvals from all requested data providers as well as the University of Manitoba Health Research Ethics Board and Manitoba's Health Information Privacy Committee (HIPC) prior to commencement of any data access for this project.
MCHP is the sole proprietor of the Manitoba Population Research Data Repository. It ensures the physical security and confidentiality of the repository networks and files. Strict privacy compliance measures are in force. Maintenance and updating of Repository files and of all equipment and software are regularly scheduled.

Please contact the Repository Access Unit (RAU) at mchp_access@cpe.umanitoba.ca when you have been notified of funding for this project. RAU will guide you through the process required to access the data. We have enclosed a "Next Steps" guide to assist you in this process.

Continued: MCHP feasibility and data access quote request response

Sincerely,

[redacted]

Charles Burchill
Associate Director, Data Access and Use
Manitoba Centre for Health Policy

Enclosure

From MCHP: Research Agreement approval letter

UNIVERSITY OF MANITOBA | Rady Faculty of Health Sciences

Max Rady College of Medicine
Manitoba Centre for Health Policy
Community Health Sciences
408-727 McDermot Avenue
Winnipeg, Manitoba
Canada, R3E 3P5
Phone: 204-789-3819
Fax: 204-789-3910
info@cpe.umanitoba.ca

August 27, 2018

Kevin Friesen
Rady Faculty of Health Sciences, College of Pharmacy
Apotex Centre
750 McDermot Ave.
Winnipeg MB R3E 0T5

Dear Kevin:

Re: Signal and Noise: A Comprehensive Assessment of the Relationship between Medication use and Alzheimer's Disease

MCHP project number: 2018-033

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health, Seniors and Active Living data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Manitoba Population Research Data Repository for your project. To proceed, please contact Charles Burchill (Associate Director, Data Access and Use) at charles_burchill@cpe.umanitoba.ca. Sophie Buternowsky, Senior grants Accountant, at MCHP will be contacting you regarding invoicing for your project.

If any changes are made to the original approved study protocol, they must be submitted to the Health Research Ethics Board for approval and the data providers. A copy of the submissions and approvals must also be sent to MCHP. Please remember due to process changes with both the Health Research Ethics Board and MCHP in Janauary 2016, it is the PI's responsibility to provide MCHP an electronic copy of your Health Research Ethics Board Annual Approval Certificate. To prevent project access delays please send the approval to the MCHP Repository Access Unit via mchp_access@cpe.umanitoba.ca within the month of expiration.

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website: http://umanitoba.ca/medicine/units/mchp/resources/access_reporting.html. Should you have any questions, please do not hesitate to contact the Repository Access Unit at (204) 975-7770.

Sincerely,

[redacted]

Charles Burchill

Submission to HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

Manitoba
Health, Seniors and Active Living
Information Management and Analytics
4040-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-788-7139 F 204-944-1911
www.manitoba.ca

Health Information Privacy Committee

Request for Access to Personal Health Information Held by the Government of Manitoba

Complete ALL questions on the application form. Application forms that are not completed in full will not be reviewed by the HIPC. One (1) copy must be submitted by email to the HIPC Coordinator at HIPC@gov.mb.ca. Ten (10) hard copies must be delivered to the HIPC Coordinator at 4043 - 300 Carlton Street, Winnipeg, Manitoba, R3B 3M9. For more detailed information, please see the 'Guidelines for Completing a Request for Access to Personal Health Information Held by the Government of Manitoba' and 'Submission Requirements' on the HIPC website.

Date of Request (MM/DD/YYYY): 10/15/2017

Title of Research Project:

Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer's Disease

I. Researcher Information

Principal Investigator (PI): Kevin Friesen

Affiliation: College of Pharmacy, University of Manitoba **Phone:** [redacted]

Email: friese13@myumanitoba.ca **Fax:** [redacted]

Address: 750 McDermot Avenue, Winnipeg, Manitoba R3E 0T5

Academic Advisor (if PI is a student): Dr Shawn Budgen

Affiliation: College of Pharmacy, University of Manitoba **Phone:** [redacted]

Email: Shawn.Bugden@umanitoba.ca **Fax:** [redacted]

Address: 750 McDermot Ave, Winnipeg, Manitoba R3E 0T5

II. Co-investigators

List all co-investigators, their affiliation and *specific* role (e.g., data analyst, statistical or clinical consultant, data collection) in the proposed research project. If the PI is a student, please list all Advisory Committee Members. Attach a list of co-investigators if more space is needed.

Name	Affiliation	Primary role	Line-level data access? Yes/No
Dr Jamie Falk	College of Pharmacy, University of Manitoba	Advisory committee member	No
Dr Dan Chateau	Manitoba Centre for Health Policy	Advisory committee member	No

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

III. Conflict of Interest

(a) Do you or the co-investigators have multiple roles/access to information within the context of this research or relationships with other organizations which may present a possible conflict of interest?

Yes ☐ No ☒

If yes, please complete the Conflict of Interest Disclosure Form accessible through the HIPC website.

IV. Description of the Research Project

(a) What is the anticipated duration of this study (month/year)?

From: 01/2018 **To:** 06/2021

(b) Is this project part of a program of research? Yes ☐ No ☒

If yes, has the program of research already received HIPC approval-in-principle?

Yes ☐ No ☐

→ **HIPC File Number:**

→ **Briefly summarize the program of research:**

(c) Please describe the purpose of the research project and list the specific research questions, objectives, and/or hypotheses that will be tested.

This research project will look at the potential association between prescription drug use and the risk of developing Alzheimer's disease (AD). Several class of drugs will be examined, starting with proton pump inhibitors, then moving on to additional drug classes such as statins (used to control cholesterol levels), antidepressants, benzodiazepines and sedatives, antihypertensives, estrogens, drugs with anticholinergic properies, and non-steroidal anti-inflammatory drugs (NSAIDs). I hypothesize that many of the medications, including those listed above, which have been been associated with either increased or decreased risk of AD have been largely due to the chance findings arising from flawed research designs, and residual confounding. Our objective is to provide clarity to an area of research clouded by confusion by reassessing these claims using better methods which take their shortcomings into consideration in their design.

(d) Please provide a description of the research project, focusing on the proposed methodology.

Note: The description should include the context and/or background, design, methods and analysis plan, variables of interest, anticipated results and significance of the study. Limit the description to one page and do not refer to the protocol and/or attachments.

Alzheimer's disease (AD) is a well characterized disease of declining cognitive function, particularly memory loss, and is by far the most common cause of dementia. According to an Alzheimer's Society of Canada report, there are over 564,000 persons living with AD in Canada at an annual societal cost of $10.4 billion. Due to increasing life expectancy and the aging of the population overall, the number of persons with AD is expected to continue to rise over time.

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

A large body of work exists looking at whether the risk of AD is modified by prescription drug use, including work looking at statins, antidepressants, benzodiazepines and sedatives, antihypertensive drugs, estrogens, anticholinergic drugs, and non-steroidal anti-inflammatory drugs (NSAIDs). However, the results of these studies are confusing and often contradictory, even when focused on a single drug class. For example, studies looking at PPIs have found that their use both increases and decreases the risk of AD. I hypothesize that many of the medications that have been associated with AD are chance findings related to flawed research designs and residual confounding.

Several factors make AD a difficult disease to study. First, AD progresses very slowly at their start, with a period of time measured in years to decades, from the beginning of the disease process, to the appearance of prodromal symptoms, and eventually reaching an AD diagnosis. Secondly, the prodromal symptoms themselves are frequently treated, and often with drug classes of interest, such as antidepressants and sedatives. Lastly, many of the drug classes under study are also used to treat conditions that are themselves risk factors. For example, metabolic disorders, which are a risk factor for AD, is commonly treated with metformin, which has itself been suggested may increase the risk of AD. Failure to take these factors into consideration when designing a study can easily lead to spurious findings. Educational attainment is an important variable as is strongly associated with decreased AD risk. We will use the University of Manitoba student records database to identify those who attended or graduated from this University.

My proposed research will, by attempt to extract the actual safety signal from the noise that clouds this issue by taking re-examining this issue using study methods that take these factors into account. The first step in my doctoral research will involve replication of some of previously published studies that looked at PPIs and AD risk, using the original study design but with Manitoba data. Then I will redo this study using a new study protocol either based on the original, with the needed modifications, or if necessary using an entirely new study design. With the first step I hope to show that the original study would arrive at similar conclusions if done with our data, while the second step will show how, by addressing the studies shortcomings, we arrive at a significantly different, possibly opposite result, showing that the original design is biased.

After completing this first step, this methodology will be applied to several other drug classes, as time permits. Potential classes include statins, antidepressants, benzodiazepines and sedatives, antihypertensive drugs, estrogens, anticholinergic drugs, and NSAIDs. Some of these other drug classes' present additional methodological challenges which may require alternative study designs and more advanced methods such as mediation analysis, which can be used to statistically separate direct and indirect effects such as in the case where the drug of interest is used to treat disease state which, by itself, has an effect on the risk of AD. High-dimensional propensity scoring will be used to aid in creating matching controls, and which also helps decrease unmeasured confounding. Systematic sensitivity analyses will be used to examine the robustness of our results, and to determine the amount of residual confounding that would be necessary to account for our findings in the hypothetical cases that they are not real.

(e) Will the study involve direct access to potential study participants? Yes ☐ No ☒

If yes, provide one (1) emailed copy and ten (10) hard copies each of the introductory letter that will be sent to the potential participants, the Information and Consent Form, questionnaires and any other materials that potential participants will receive.

(f) Will the study involve correspondence with potential participants that is mailed out?
Yes ☐ No ☒

If yes, will Manitoba Health, Seniors and Active Living be asked to facilitate a blind* mail-out?
Yes ☐ No ☐

The researcher would not know the identity of those who are mailed letters.

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

V. Specific Data Required

(a) Please attach a Data Extraction Form (unless only one database is requested) to indicate ALL databases to be accessed, years of data required, the variables of interest, and the rationale for such requests. Please be as specific as possible. The Data Extraction Form template has been provided below.

Note: The Personal Health Information Act (PHIA) requires that only the minimum information necessary to accomplish the purpose of the research project be released to researchers.

Data Extraction Form Template			
Database Name of database requested **e.g.,** Hospital Discharge Abstract	**Years** Years of data requested **e.g.,** April, 2000– March, 2012	**Data Fields / Variables** Specific information or data fields required from a database **e.g.,** Admission date, Separation date, Diagnoses, Procedures	**Rationale** Describe in general terms how the information to be collected relates to the study purpose, hypotheses and study questions. If the information does not relate directly to these, provide explanation as to why the information is being collected. **e.g.,** To develop indicators of health status, health services use and health risk
See attachment			

* Manitoba Health, Seniors and Active Living administrative data is organized according to fiscal years beginning April 1st through March 31st.
* If data prior to 1985 is required, please consult the HIPC Coordinator.
* The HIPC will not prospectively approve access to data beyond that which is currently available. Updates must be submitted as a protocol amendment request to the HIPC when such data does become available.
* Please mention specific years for the in the data extraction form (asking for the "latest available" is not acceptable).

(b) Inclusion/exclusion criteria (e.g. age, gender, region of residence, diagnoses)

Inclusion and exclusion criteria will be dependent on the drug class being studied. There are no gender restrictions. We are restricting our cohort to those 18 years of age and over.

(c) Is a control group required to be extracted for this study? Yes ☒ No ☐

If yes, please describe the matching ratio and criteria for the control group and provide a rationale for the specific parameters requested:

We plan on matching cases and controls on year of birth, sex, and year of diagnosis, and propensity scores as matching criteria. As we will be using high-dimensionality propensity scores, the matching criteria involved will be largely driven by the data itself. Ideally, to maximize the power of our study, we would like to use between 1:4 and 1:10 as our matching ratio, but may have to use 1:1 matching if there are problems with finding a sufficient number of controls for some analyses.

(d) Will First Nations, Métis or Inuit populations be a focus of interest and/or is there intent to stratify analyses or outcomes by First Nations Metis or Inuit populations?

Yes ☐ No ☒

If yes, provide a copy of the letter of support from the Manitoba First Nations Health Information Research Governance Committee and/or other First Nations, Métis or Inuit partners as appropriate.

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

(e) Will data held by a department or agency of the Government of Manitoba be linked or merged with data from another department or external source(s)? Yes ☐ No ☒

If yes, please describe the nature of the linkage (e.g. the data/databases that will be linked), including the process for linking data from varied sources.

Note: If the external database(s) contains individual-level data, permission from the trustee is required and a copy of this permission must be submitted to the HIPC.

If the external database is a clinical patient registry, please provide a copy of the Information and Consent Form requesting the patient's permission to link data in the clinical registry to other data sources. If informed consent was not obtained, please explain.

VI. Level of Intrusion

Please indicate only the highest level of intrusion associated with the proposed research project.

☐ **1. Minimal or no Intrusion**: Aggregate statistical information or person specific information with no individual identifiers or record linkages, which could potentially identify individuals.

2. Potential Intrusion: Person specific information in anonymized form with data linkages that create the risk of identification of individuals. The degree of risk increases with the type of data linkage as follows:

☐ **2a.** Minimal linkage or specificity of use within Manitoba Health, Seniors and Active Living data, which create no potential for the identification of individuals (e.g. linking the Hospital Abstracts and the Medical Claims databases with aggregate level data for a certain geographic location within a Regional Health Authority);

☐ **2b.** Multiple linkage or specificity of use within Manitoba Health, Seniors and Active Living data which may create the potential for identification of individuals (e.g. linking the Hospital Abstracts, Medical Claims, and DPIN databases);

☒ **2c.** Linkage of Manitoba Health, Seniors and Active Living data files to other publicly available and aggregate level data sources where all individual identifiers have been removed or modified (e.g. linking the Hospital Abstracts, Medical Claims, and DPIN databases with outside neighborhood level data from the census);

☐ **2d.** Linkage of Manitoba Health, Seniors and Active Living data files to other person-specific data files where individual identifiers have been removed or modified, or in the case of surveys, no direct contact with the individual will be made (e.g. linking the Hospital Abstracts, Medical Claims, and DPIN databases with data from Statistic Canada's Canadian Community Health Survey). *This does not include cases where the population group or information concerned falls within category 5.*

☐ **3. Moderate Intrusion**: Person-specific information such as patient charts, surveys or personal interviews will be used but the individuals affected will be asked for their consent prior to the disclosure of any personal health information to the researcher. *This does not include cases where the population group or information concerned falls within category 5.*

☐ **4. High Intrusion**: Person-specific information involving linkage of Manitoba Health, Seniors and Active Living data files to other person-specific files for which the researcher has access to individual identifiers without consent, for example, patient information collected in clinical settings, specialized programs, and disease registry files with identifying information. *This does not include cases where the population group or information concerned falls within category 5.*

☐ **5. Highly Sensitive**: Requests for information which would otherwise fall into categories 2b or higher where the population involved is vulnerable or dependent (e.g. minors), where the nature of the information is highly personal and sensitive (e.g. persons with mental disabilities, sexually

transmitted diseases), or where there will be a focus of interest and/or an intent to stratify outcomes by First Nations, Métis or Inuit populations.

Please provide a rationale for your choice and discuss the importance of this research in relation to the level of intrusion.

Note: PHIA, 24(3) requires that the HIPC must determine that the research is of sufficient importance to outweigh the necessary intrusion into privacy from the disclosure of personal health information.

This project will involve secondary analysis of de-identified data files only, with linkages to other files where identifiers have been removed or scrambled. The research will provide valuable results to clinicians and patients regarding possible long term, adverse effects of prescription drug use in regards to the risk of developing Alzhemiers disease. The data we extract from all data sources will have identifiers removed before the data are transferred to MCHP for linkage. The linkage will be made using PHINs which will be scrambled by Manitoba Health.

VII. Data Security

(a) Please indicate specifically where the data will reside:

All data will be stored on on Manitoba Centre for Health Policy computer servers

Complete address (including room/office number):

408 - 727 McDermot Avenue, Winnipeg, Manitoba R3E 3P5

(b) How will the confidentiality of the data be protected by the researcher(s)? Please include a discussion of the security measures, how and when the data will be destroyed, and other relevant data protection issues (e.g., physical, technical and administrative controls and safeguards).

MCHP operates according to rigorous standards regarding security, privacy, and confidentiality of data files contained in the Population Health Research Data Repository. Physical measures include restricted, alarm-protected, access to the facility. Electronic measures include multiple levels of passwords, electronic firewalls, encryption of transmitted information, and other security measures.

Repository data is in the form of de-identified computer files, securely stored at the University of Manitoba, and accessed via the MCHP Unix system at the Bannatyne Campus. Privacy of information is protected through a number of measures, most notably that no files at MCHP contain names or addresses, and that identifiers (e.g., Personal Health Information Number (PHIN) and Registration Number) are changed by MH to be not recognizable.

Access to, and use of, the data are carefully controlled and monitored on an ongoing basis. All MCHP staff sign a Confidential Information Agreement and comply with terms related to the use and dissemination of information derived from the data repository. Analyses involving 5 or fewer events or persons are suppressed. Publications generated from database analyses are reviewed by Manitoba Health prior to release.

Security measures to protect the privacy and confidentiality of individuals are described in MCHP policies and procedures documents (available upon request), and are based on the Data Sharing Agreement in place between Manitoba Health and other data owners and the University of Manitoba and are compliant with legislative requirements.

All study-associated data and programming code will be archived at the time of study completion and removed from MCHP's analysis system. Study completion is identified by the principal investigator or by the submission of a final REB notification of study completion. Consistent with University of Manitoba protocols, archives will be maintained at MCHP for a period of at

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

least seven (7) years and no more than ten (10) years after completion to allow time for questions and clarifications of publications and then all study-associated data will be destroyed. The programming code may be retained indefinitely.

(c) Will the data be accessed remotely? Yes ☒ No ☐

If yes, by whom? Kevin Friesen

Where is the remote terminal located? Room 25B/C, Apotex Centre, 750 McDermot Ave, Winnipeg, Mb, R3E 0T5

What level of data (i.e. aggregate vs. line-level) will be accessed? Line level

Describe the specific security measures in place to ensure that data security is not compromised by remote access.

The remote access sites are located in locked room, located with the College of Pharmacy building. This building is regularly patrolled by security and is equiped with surveillenc cameras. Keys to these doors are restricted to individuals authorized by the MCHP to use this site. The access node is password protected, requiring a MCHP username, and a continously varying password via an RSA SecurID token. All data remain on the MCHP main server, with zero stored on the RAS terminals. Files can be neither downloaded or removed from the remote terminal.

VIII. Publication of Study Results

(a) Who will be receiving the study results?

The study results will be kept within the research group. No results will be released to anybody outside the research group without prior vetting by HIPC. The results of this research will eventually be published both as a thesis and submitted for publication in appropriate medical journals. .

(b) Will there be any publication of the study results? Yes ☒ No ☐

If yes, a copy must be sent to Manitoba Health, Seniors and Active Living for review prior to publication.

Note: At least thirty (30) calendar days prior notice is required for every intended publication in learned journals or thesis presentation; at least ten (10) calendar days prior notice is required for every poster or oral presentation where such presentation material will be released.

IX. Other Information

Please describe any other information relevant to this application.

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

X. Attachments

The following documentation is attached:

☐ **Proof of research funding**

**** Required for every HIPC submission.*

Please specify funding source: Internal departmental funds.

**** All funding sources must be specified. Please submit a copy of a letter of support from the granting agency. If grant funding has not been awarded at the time of submission, a letter of support for alternative funding must be attached. For example, if internal departmental funds will be used in lieu of grant funding, a letter of support from the department head is required.*

Is the research being funded by Private Industry? **Yes** ☐ **No** ☒

**** If the study is funded by Private Industry, please review the guidelines on Private Industry-Sponsored Research by Manitoba Health, Seniors and Active Living. These Guidelines are available upon request from the HIPC Coordinator.*

☐ **Research Ethics Board approval**

Pending ☒

**** Required for every HIPC submission.*

☐ **Letter of Support from the Manitoba First Nations Health Information Research Governance Committee and/or other First Nations, Métis or Inuit partners as appropriate**

Pending ☐

☐ **Organization or Institutional Research Review Committee approval (please specify):**

Manitoba Centre for Health Policy quotation for study cost

Pending ☒

☐ **Organization or Institutional Research Review Committee approval (please specify):**

WRHA approval to use the Long Term Care MDS Assessment database

Pending ☒

☐ **Organization or Institutional Research Review Committee approval (please specify):**

University of Manitoba approval to use student data

Pending ☒

☐ **Organization or Institutional Research Review Committee approval (please specify):**

Pending ☐

Note: Projects will not receive full approval until all the appropriate documentation is received by the HIPC Coordinator.

Continued: HIPC: Request for Access to Personal Health Information Heald by the Government of Manitoba

XI. Declaration

I declare that:

a) This research project complies with *The Personal Health Information Act* of Manitoba.

b) The information being requested will only be used for the purpose of the research project outlined in this application.

c) The information being requested is the minimum amount necessary to accomplish the objectives of the research project outlined in this application.

d) The security safeguards outlined in this application reasonably ensure the security and confidentiality of the personal health information and its destruction when the research project is finished.

e) All reports, publications, and presentations resulting from this project will be submitted to the Information Management and Analytics Branch of Manitoba Health, Seniors and Active Living for review prior to distribution or publication (in accordance with the timelines described in the Guidelines), to assure that the anonymity of the study cohort is preserved and that any references to Manitoba Health, Seniors and Active Living or other trustees, are factually correct.

f) A copy of all published reports and articles will be provided to the Information Management and Analytics Branch of Manitoba Health, Seniors and Active Living for its records.

October 16, 2017
Date

Signature of Principal Investigator

***Please print name*:** Kevin Friesen

October 16, 2017
Date

Signature of Academic Advisor
(if PI is a student)

***Please print name*:** Dr Shawn Bugden

XII. Declaration for Use of Identifiable Personal Health Information

To be signed only when identifiable personal health information is being requested.

I declare that this research cannot be done without using identifiable personal health information, and that it is impossible or impractical to obtain consent from the people the personal health information is about.

Date

Signature of Principal Investigator

Please print name:

From HIPC: Final project approval

Manitoba
Health, Seniors and Active Living
Health Information Privacy Committee
4040-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-786-7204 F 204-944-1911
www.manitoba.ca

August 3, 2018

Kevin Friesen
College of Pharmacy, University of Manitoba
750 McDermot Avenue, Winnipeg, Manitoba R3E 0T5
friese13@myumanitoba.ca

HIPC No. 2017/2018 – 46
File number to be quoted on correspondence

Dear Kevin,

Re: Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer's disease

The Health Information Privacy Committee has considered and *approved* your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Seniors and Active Living for review. Specifically, manuscripts must be submitted *at least 30 calendar days* prior to the intended publication and presentation materials must be submitted *at least 10 calendar days* prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by **MCHP**. If you have any questions or concerns, please do not hesitate to contact Saila Parveen, Committee Coordinator at (204)786-7204.

Yours truly,

[redacted]

Teresa Cavett, B.Sc., M.D., C.C.F.P., F.C.F.P., M.Ed.
Chair, Health Information Privacy Committee

c.c. D. Malazdrewicz

To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

UNIVERSITY OF MANITOBA

Bannatyne Campus Research Ethics Boards
P126-770 Bannatyne Avenue
Winnipeg, Mb R3E 0W3
Phone: (204) 789-3255

For Administrative use only		
REB File Number:	Date Received:	Initials:

BANNATYNE CAMPUS RESEARCH ETHICS BOARD SUBMISSION FORM for RETROSPECTIVE CHART OR RECORDS REVIEW

(Including Application Instructions and Application Review and Notification)

This form must only be used to submit a request for ethical approval to conduct a retrospective chart/record(s) or retrospective database review where there is no intent of contacting individuals. Please complete the full Bannatyne Campus Research Ethics Board Submission Form for all other studies

Application Instructions:

- Members of the Colleges of Medicine, Dentistry, Pharmacy, Rehabilitation Sciences and the affiliated teaching hospitals, their associated research foundations, and Winniepg Regional Health Authority Researchers (WRHA) may submit their protocols to the applicable Bannatyne Campus Research Ethics Board (REB).
  - To qualify as a WRHA Researcher you must be a researcher who is (i) employed by the WRHA or have a written contract for services with the WRHA; or (ii) have privileges under the WRHA's Medical Staff By–Law. If you are requesting review as a WRHA Researcher, your study must be carried out at facilities owned by or operated by the WRHA or under the direction of the WRHA.
- Submit **one copy:**
  - of this submission form.
  - a data capture sheet.
  - Master List
  - supporting documentation (e.g. a protocol if applicable). **NOTE:** A protocol is not required if this submission form is completed in full.
  - CV template required with first ethics submission by the Principal Investigator for the calendar year
- Submit **one electronic copy** of each document listed above on a CD or Flash drive
- COMPLETE ALL SECTIONS OF THE FORM AS REQUIRED. **DO NOT REFERENCE PAGES in ATTACHED DOCUMENTS (e.g. do not indicate - See protocol).** INCOMPLETE SUBMISSIONS WILL BE RETURNED to the applicant for completion.
- Use no smaller than 10 point font; handwritten submissions are not acceptable.
- Deliver completed submission to the *Health Research Ethics Board* by the monthly full board **submission deadline date for new studies** (DO NOT FAX or EMAIL). The submission deadline for all new studies, including those that qualify for expedited/delegated review, and those that require full Board review is the same date. (Please see web site for specific deadline dates.)
- The form is locked which will allow you to tab to each question. To conduct a spell check you must first unprotect the document. Go to "***Tools***" on the Tool Bar and in the drop down menu select "***Unprotect Document"***, no password is required. If working with Word 2007, go to "***Review***" tab, then click the "**Protect Document**" pane, click on ***"Restrict Formatting and Editing"*** and then click on "**Stop Protection**". No password is required.
- DO NOT DELETE QUESTIONS OR THE SUBMISSION WILL BE RETURNED to the applicant.

Application Review and Notification:

- Forms are date stamped upon receipt in the Research Ethics Board Office (REB).
- Forms submitted after the submission deadline date for the full Board meeting may be deferred to the next month.
- Applications requesting and qualifying for delegated/expedited review typically reviewed by the Health Research Ethics Board (HREB) Chair.
- The HREB Chair may refer the application to the full Board or to another University of Manitoba Research Ethics Board (REB) member or REB. In this case you will be contacted to provide additional or revised copies of the application.
- Certificates of approval or letters of conditional approval will be sent to the local Principal Investigator (or designate) within approximately 5-7 business days following the full Board meeting date (provided the submission deadline is met). **If you have not received a response within the period stated above please contact our office at 789-3255.**

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

PART A:

TYPE OF STUDY:

1.0 Indicate which of the following best describes the type of investigation proposed:

☐ Retrospective Chart Review ☒ Retrospective Database Review

This form must only be used to submit a request for ethical approval to conduct a retrospective chart/record(s) or retrospective database review where there is no intent of contacting individuals. Please complete the full Bannatyne Campus Research Ethics Board Submission Form for all other studies or your submission will not be processed and will be returned to the submitter.

PART B:

PROJECT REGISTRATION:

2.0 Title of Research Study:

Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer 's disease

3.0 Is this proposal closely linked to any other proposal previously/simultaneously submitted to either the Biomedical Research Ethics Board (BREB) or Health Research Ethics Board (HREB)?

☐ Yes ☒ No

If yes, describe the relationship of this proposal to the primary study and provide the REB file #:

4.0 Principal Investigator:

The Principal Investigator must be:

- an employee or student of the University of Manitoba; or
- have an academic appointment or affiliation with the University of Manitoba; or
- a researcher affiliated with the WRHA (see definition below).

University of Manitoba Employee or student ID number: [redacted]

Name and Title(s): Mr Kevin Friesen

Department/Program:

☐ College of Medicine ☐ College of Dentistry ☒ College of Pharmacy

☐ College of Rehabilitation Sciences

OR,

☐ WRHA Researcher *(To qualify as a WRHA Researcher you must be a researcher who is (i) employed by the WRHA or have a written contract for services with the WRHA; or (ii) have privileges under the WRHA's Medical Staff By–Law. If you are requesting review as a WRHA Researcher, your study must be carried out at facilities owned by or operated by the WRHA or under the direction of the WRHA.)*

[redacted]

5.0 Is this the Principal Investigator's first time submitting to the Research Ethics Board during the present calendar year? ☒ Yes ☐ No

If yes, please summarize your credentials/experience relevant to this project in the University of Manitoba Bannatyne Campus CV template (maximum two page document) provided on the website and include one copy with this submission. Do not submit your full CV unless requested by the Board.

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

6.0 **Is the Principal Investigator a student?** ☒ Yes ☐ No
If yes, name of supervisor: Dr Shawn Bugden
Department/Program:
☐ College of Medicine ☐ College of Dentistry ☒ College of Pharmacy
☐ College of Rehabilitation Sciences OR, ☐ WRHA Researcher (defined in question # 8.0)

[redacted]

shawn.bugden@umanitoba.ca
Purpose of Study: ☐ Course Work ☐ Thesis ☒ Dissertation

7.0 **Co-Investigators**
Name: Jamie Falk Institution: University of Manitoba
Name: Dan Chateau Institution: Manitoba Centre for Health Policy
Name: I fan Kuo Institution: University of Manitoba
Name: Institution:

8.0. **Name of Study Coordinator (if applicable):**
Name: **Institution:**
Mailing Address:

Phone: **Fax:** **E-Mail Address:**

9.0 REB correspondence to be directed to (*Note: correspondence will be forwarded to one contact only*):

☒ **Principal Investigator** or ☐ **Study Coordinator**

INSTITUTIONAL APPROVAL:

Prior to commencing any research related activity, approval of the custodian of records and/or institutional approval are required. It is the Principal Investigator's responsibility to contact the site to inquire as to the procedures required to obtain approval at the institutional level. Please provide evidence of this approval for our file. This approval can be submitted following final Research Ethics Board approval.

10.0 **Indicate locations(s) where the study will be conducted and the custodian(s) of any records accessed:**

☒ University of Manitoba — Specify: College of Pharmacy, 750 McDermot Ave
☐ Winnipeg Regional Health Authority — ☐ HSC ☐ SBGH ☐ Concordia ☐ Victoria ☐ SOGH ☐ Miscercordia ☐ GGH ☐ Deer Lodge Centre
Other –specify: _____
☐ Cancer Care Manitoba (CCMB)
☐ Community — Specify: _____
☐ Manitoba Health
☒ Manitoba Centre for Health Policy
☐ School Division/School — Specify: _____
☐ Diagnostic Services Manitoba
☐ Other Specify: _____

11.0 **Has your research proposal/protocol been submitted for approval to the custodian of records and/or the Research Department of the institution where you intend to conduct the research?**
☒ **Yes** **Date submitted or anticipated date:**
☐ **No**
If no, indicate the rationale for not requesting institutional approval.

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

FUNDING SOURCE/SPONSOR AND BUDGET:

12.1 **Funding Source(Name of sponsor/funding agency/industry partner – state full name and address):**

Internal funding

12.2 **Classify the type of funding:**

☐ For-profit sponsor ☐ Grant ☒ U of M Internal Funds ☐ No Funding ☐ Other

If other please specify: _____

12.3 **For studies that receive funding from a "for profit sponsor", please provide either a University of Manitoba Account # or the billing contact and address of the sponsor:**

The office of the Dean of Medicine will assess a fee of $2500.00 for protocols that are funded by the private sector. *Protocols that are not funded by a private sector organization and protocols with small external grants will not be billed.* ***The $2500.00 fee is NOT dependent upon approval and is applied whether the study is submitted to the full Board or expedited review.*** *The review fee will also apply if the submission is withdrawn after it has been reviewed.*

12.4 **Is a budget attached or outlined below?** ☐ **Yes** ☐ **No**

If no, please explain why: (*A budget of predicted expenditures must be submitted for all studies regardless of whether they are funded or not, prior to the REB granting final approval for the study.*)

Data Access Fees $5000 (Uof M Internal funds)
Graduate Student Stipend $54 000 ($18 000 x 3 years, funded through my University of Manitoba graduate fellowship)

12.5 **If the study is funded, where and by whom will the budget be administered?**

☐ No funding
☒ University of Manitoba (Please provide Project # if applicable: _____)
☐ Winnipeg Regional Health Authority ☐ HSC ☐ SBGH ☐ Concordia ☐ Victoria ☐ SOGH ☐ Miscercordia ☐GGH ☐ Deer Lodge Centre
Other –specify: _____
☐ Cancer Care Manitoba (CCMB)
☐ Community Specify: _____
☐ Manitoba Health
☐ Manitoba Centre for Health Policy
☐ School Division/School Specify: _____
☐ Diagnostic Services Manitoba
☐ Other - Specify: _____

PART C:

PROJECT DESCRIPTION:

13.0 **Provide a clear statement of the purpose, objectives and the question(s) to be examined in the review.**

Numerous conflicting studies have been published suggesting that use of some classes of commonly used drugs can increase (or decrease) an individual's risk of developing AD. Our hypothesis is that many of these studies that have serious design problems, particularly failing to consider the slow degenerative nature of AD, and instead examining use immediately prior to diagnosis. Using the administrative healthcare databases at the Manitoba Centre for Health Policy, I will evaluate previously reported associations between drug use and AD, but with study designs that take into account the prolonged course of the disease. Classes of drugs I will look at include proton pump inhibitors (PPIs), antidepressants, benzodiazepines and other sedatives, statins, antidiabetic agents, drugs with anticholinergic properties, and NSAIDs.

14.0 **Outline the anticipated public and scientific benefits expected from the research.**

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

There are currently no effective treatments for Alzheimer's disease, with the few currently marketed agents providing, at most, minor and temporary benefit to patients. This magnifies the importance of prevention, and the identification of potential modifiable risk factors. This research will investigate several widely used drug classes to determine if there use increases the risk of Alzheimer's disease. It is important not only to identify those that do increase risk, but also that don't, as incorrectly labelling a drug class as a risk can cause patients and prescribers to avoid, or discontinue necessary treatment for diabetes, depression, or cardiovascular disease. This research aims to clear some of the confusion created by previously published reports, giving patients and prescribers the tools they need to make informed decisions about the potential long term benefits and consequences of the treatment decisions they make.

15.0 **Provide background information and/or literature supporting the potential benefits to follow from the proposed review.**

Estimates of the proportion of Alzheimer's disease due to modifiable risk factors, sometimes referred to as the population attributable risk, range from 28% (Norton, Matthews, et al 2014) to 66% (Xu, Tan, et al 2015). If we assume the lower estimate to be correct, this means that reducing exposure to these modifiable risk factors by 10% would reduce the overall prevalence of Alzheimer's by over 8%. The risk factors examined in these studies include smoking, diabetes, physical activity, depression, diabetes, and cardiovascular disease. The identification of additional risk factors that can be modified, such as exposure to certain drugs, would increase the proportion of cases that could potentially be avoided. However, accurate data on the magnitude and direction of the effect of drug use on Alzheimer's is necessary in order for preventative strategies to be effective. The research findings from this research project will contribute to the formation of such strategies, hopefully increasing the proportion of cases which can, potentially, be prevented.

PARTICIPANT POPULATION:

16.0 **Specify the population being studied, including the ages and conditions of the subjects, etc.**

This study will be examining individuals with Alzheimer's disease (AD), and comparing them to a comparable control group from without. Both cases and controls will be selected from those who were 18 years or older between April 1995 and March 2016.

16.1 **Will the research hypothesis be concerned with whether or not a participant is Aboriginal (Inuit, Métis and members of First Nations)?** ☐ Yes ☒ No

16.2 **Will the analysis of the research results use Aboriginal community membership as a variable?** ☐ Yes ☒ No

16.3 **Will the interpretation of the research results refer to Aboriginal people, language, history or culture?** ☐ Yes ☒ No

If yes to any of the above (16.1-16.3), please outline any process to be followed respecting the consultation with the appropriate community in the design and conduct of the study.

SAMPLE SIZE:

17.0 **Provide an approximation of the number of charts/records that you expect to review:** Population based cohort study drawn from Manitoba population over 18 years of age and older (est 1 million person).

RECRUITMENT:

18.0 **Indicate how the charts/records to be reviewed are to be obtained?**

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

This study involves an analysis of already collected administrative data from the Population Health Data Repository held by MCHP; therefore, no recruitment or direct contact with individuals is necessary.

INFORMED CONSENT PROCESS AND DOCUMENTATION:

19.0 Will consent be obtained from potential participants prior to reviewing the chart(s)/record(s) or database(s)? ☐ Yes ☒ No

19.1 If no, please explain why participant approval to review their charts/records is impractical, impossible, and /or would adversely affect the research and proceed to question 20.0?

All records contained in the MCHP database are de-identified, making contacting individuals impossible. It is also not necessary, as use of this information is permitted under section 24(3)c of the Personal Health Information Act.

19.2 If yes, describe the procedures/processes used to obtain informed consent including where, by whom and under what circumstances.

DATA TO BE COLLECTED:

20.0 Identifiability of data to be reviewed in the study:

☒ De-identified or anonymized data (e.g. larger datasets that have scrambled PHINs or other anonymized identifiers)

☐ Identifiable data (e.g., chart records with names included)

21.0 Provide a copy of the data capture sheet or list the fields that details precisely what specific information/variables will be extracted and collected and from the specific source (s):

☐ Data capture sheet (attached) is mandatory for chart review studies (The submission will be returned to PI and not reviewed if this is not included)

☒ List of data fields (attached) for large database studies is acceptable

22.0 If person/identifiable level data is to be used, are you collecting any of the following personal identifiers? Investigators should plan to collect personal data at the lowest level of identifiably necessary to achieve the study objectives. Even a dataset without direct identifiers may present a risk of indirectly identifying data subjects if the database contains extensive information about the individuals concerned. For guidance, consult the "*CIHR Best Practice Guidelines for Protecting Privacy and Confidentiality*":

DIRECT IDENTIFIERS	YES	NO	INDIRECT IDENTIFIERS	YES	NO
Full Name (recommend only initials)	☐	☒	Initials	☐	☒
Address	☐	☒	Date of Birth (day/month/year)	☒	☐
Telephone number	☐	☒	Age at time of data collection or year of birth	☒	☐
PHIN#	☐	☒	Full postal code (recommend using first 3 digits only)	☒	☐
e-mail address	☐	☒	First 3 digits of Postal Code	☒	☐
Medical Records Number	☐	☒	Health Care Provider (recommend type of provider, {e.g. family physician, VON} only)	☒	☐

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

Full Face Photograph	☐	☒	Fax number	☐	☒
OTHER *(Specify below:)	☐	☐	Scrambled PHINs or other anonymized identifier (Specify:	☒	☐
	☐	☐	OTHER (Specify below:)	☐	☐
	☐	☐		☐	☐
	☐	☐		☐	☐
	☐	☐		☐	☐
	☐	☐		☐	☐

22.1 **If you are collecting any of the above personal identifiers, justify why each item is required:**

The scrambled PHIN will be used to link records across databases within the MCHP's data repository at MCHP. Date of birth will be used to calculate age. The full postal code is required to link neighborhood level census data to individuals to determine socio-economic status. Physician specialty and scrambled ID number are used to determine type of care, and continuity of care (i.e. whether they are seeing their usual physician, or multiple).

23.0 **Describe in general terms how the information to be collected relates to the study's purpose, hypotheses, and study questions. If the information does not relate directly to these, provide explanation why the information is being collected.**

Prescriptions (i.e. DPIN), medical claims, and hospital abstracts are all necessary to determine AD status, comorbid conditions, drug exposure, and time in hospital – core components of our analysis. Long term care data will be used to complement these data sources. Higher levels of educational attainment have been shown to be associated with decrease risk of AD, and we hope to use the University of Manitoba student records database to identify some individuals who attended or graduated from the U of M. The Manitoba Health registry will be used to determine the number of people registered, determine start and end dates of coverage (due to either moving out of province or death, and to provides demographic information such as date of birth, sex, and postal code. Canada Census data can be used to determine the socio-economic status for the neighborhood in which a person lives by using their postal code.

24.0 **Describe the methodology and data analysis to be used in the chart/record review process.**

We will be using both case-control and longitudinal cohort based study design to answer our research questions. Where possible we will use matching methods (matching on age, sex, calendar year, and high dimensional propensity scores) to decrease confounding. A variety of statistic methods, including multi-variable linear, logistic, conditional logistic, and Cox regression models, as well as mediator analysis, to determine the effect of drug exposure on AD risk.

25.0 **Specify the approximate time period during which information from the charts/records will be extracted (e.g. April-May, 2008). From: December 2017 to May 2021**

26.0 **Specify the approximate time range over which the information in the charts/records was collected (e.g. all patients seen between 2000 - 2008).**

All Manitoba residents who reached age 18 or over between 1995 and 2016

DATA PRESENTATION/PUBLICATION OF RESULTS OF REVIEW:

27.0 **Outline your intentions with respect to how the data will be used with respect to reports, presentations, and/or publication:**

- ☒ **Only aggregate data will be presented**
- ☐ **Individual de-identified/anonymized data will be presented**
- ☐ **Other – Please specify:**

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

PRIVACY AND CONFIDENTIALITY:

28.0 Specify where the charts/records are maintained and where the abstracting of the information from them will occur, paying particular attention to the privacy and security of the work environment in which the information extraction is to occur.

All of the analyses will be conducted within the secure computer environment of the Manitoba Centre for Health Policy (MCHP) located at 408 - 727 McDermot Avenue, Winnipeg, Manitoba R3E 3P5.

29.0 Provide a detailed description of the methods that will be used to protect the privacy and confidentiality of individuals whose information is being reviewed. *(Note: Data capture should be done only on paper or electronic forms that are coded and do not contain personal identifying information. All direct identifiers should be segregated/stripped from clinical data; a unique study identifier (i.e. a randomly generated or meaningless ID number) should be assigned to each patient/participant record; the Master list linking the ID with identifiable material should be stored in a separate compute file and /or physical location; and the Master list should be locked and password protected).*

MCHP operates according to rigorous standards regarding security, privacy, and confidentiality of data files contained in the Population Health Research Data Repository. Physical measures include restricted, alarm-protected, access to the facility. Electronic measures include multiple levels of passwords, electronic firewalls, encryption of transmitted information, and other security measures.

Repository data is in the form of de-identified computer files, securely stored at the University of Manitoba, and accessed via a remote access site in the College of Pharmacy. Privacy of information is protected through a number of measures, most notably that no files at MCHP contain names or addresses, and that identifiers (e.g., Personal Health Information Number (PHIN) and Registration Number) are changed by Manitoba Health to be not recognizable.

Access to, and use of, the data are carefully controlled and monitored on an ongoing basis. All MCHP staff sign a Confidential Information Agreement and comply with terms related to the use and dissemination of information derived from the data repository. Analyses involving 5 or fewer events or persons are suppressed. Publications generated from database analyses are reviewed by Manitoba Health prior to release and are compliant with legislative requirements.

Security measures to protect the privacy and confidentiality of individuals are described in MCHP policies and procedures documents (available upon request), and are based on the Data Sharing Agreement in place between Manitoba Health and the University of Manitoba.

30.0 Indicate the steps to be taken to ensure security of data with direct or indirect personal identifiers. Please check all that apply.

NOTE: *If direct identifiers must be retained they should be isolated on a separate dedicated server/network without external access (i.e. research databases with participant information should not be housed on portable devices such as laptops or flashcards).*

PROCEDURAL MEASURES	Yes	No
• Data access to the segregated /identified data will be limited to a " need to know" basis	☒	☐
• There will be an audit trail (i.e. who accessed the data and when) of access to electronic records (*An audit trail is required if direct identifiers are maintained*	☒	☐

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

in electronic form– NOTE: Word, Excel and Access programs do not have audit trail capability)		
PHYSICAL	☐	☐
• Completed data abstraction forms will be stored in locked filing cabinets in secure location – Specify: No abstraction will occur	☐	☒
• Computer will be housed in a locked secure location – Specify: All analyses will be conducted within MCHP or remote access site on a secure server. Linkages of files by scrambled PHIN are conducted for the specific analyses only; no permanent datasets are retained beyond the study period, or transmitted outside MCHP offices.	☒	☐
• Data file backup will be stored in a separate, locked location – Specify: as above	☒	☐
• Other – Specify:	☐	☐
TECHNICAL	☐	☐
• Data will be stored on a computer which is password protected	☒	☐
• Data will be stored in a computer file which is password protected	☒	☐
• Frequent backups of data will occur	☒	☐
• Data will be stored on a computer systems with virus protection	☒	☐
• Data will be stored on computer systems with uninterrupted power source	☒	☐

31.0 **Will individual level data be sent outside of the institution where it was collected and/or will you be receiving individual level data from other sites (for example, in the case of a multi-site study where you are the coordinating site receiving data)?** ☐ **Yes** ☒ **No**
(If no, go to question 32.0)
If yes, explain why is it necessary to send/receive data outside of the institution where it was collected.

31.1 **How will data be transmitted?**

Transmission of data via:	Sent?	Rec'd*?
Fax – Security of the receptor site MUST be described:	☐	☐
E-mail (Encryption protocol MUST be attached)	☐	☐
Private Courier (Must be able to trace delivery)	☐	☐
Canada Post Expresspost or Priority Courier (Regular mail may NOT be used)	☐	☐
Other – Specify: No individual level data will be transmitted	☐	☐

31.2 **Where will data be sent?**

No individual level data will be transmitted

31.3 **Specify the names and affiliations of persons or commercial companies outside your study team (e.g. technical service providers, other researchers) who will have access to the data. Also specify the level of identifiably or the data they will have access to (e.g. personal, identifiable, anonymized, etc.)** *Data sent or received by the institution may require that the parties enter into an information/data transfer agreement before the data transfer takes place.*

n/a

32.0 **Specify how long study data including personal data will be retained and the procedures for securing/storing records.**

All study associated data and programming code will be archived at the time of study completion and removed from MCHP's analysis system. Study completion is identified by the principal investigator or by the submission of a final REB notification of study completion. Consistent with University of Manitoba protocols, archives will be maintained at MCHP for a period of at least seven (7) years and no more than ten (10) years after completion to allow time for questions and clarifications of publications and then all study associated data will be destroyed. The programming code may be retained indefinitely.

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

33.0 **Specify whether and when the data will be destroyed or irreversibly anoymized (i.e. the key identifying the link between data and the individual identity is deleted). Describe the procedures used to destroy or anonymize study data.**

Data used at MCHP are de-identified at the source. Manitoba Health datasets created for the purposes of this study will be deleted after completion of the project. Source data are maintained in the Population Health Research Data Repository.

34.0 **Identify all individuals by name, staff affiliation and their precise role in the project who will have access to the master list (with personal identifying information), data capture information and how access to this information is secured and monitored.**

None of the team members will have access to the 'master list'; only de-identified data are sent to MCHP. Only Manitoba Health has access to a list of the scrambled PHINs found in MCHP data along with identifying information. For this project it is not necessary to identify individuals within our study.

The Personal Health Information Act(PHIA)requires that all employees, students, or agents who handle or are exposed to personal health information take the University of Manitoba PHIA Orientation and sign a pledge of confidentiality that acknowledges that they are bound by written policy and procedures.

35.0 **Has PHIA Orientation and pledge-signing been completed by all employees, students and agents who will handle or be exposed to personal health information?**

☒ **Yes** ☐ **No**

If "No," the Principal Investigator must contact the University Access & Coordinator's Office to make arrangements for completing this requirement. fippa@umanitoba.ca

Where individuals have not completed PHIA Orientation and signed a pledge, and for the purpose of ensuring that they do, Principal Investigators' contact information will be provided to the University Access & Privacy Coordinator's Office.

36.0 **Will an electronic database be created in the process of the review?** ☐ **Yes** ☒ **No**

If yes, indicate whether the database will be used only for the purpose of data analysis and outline any intention to maintain the data for a period of time beyond the data analysis phase of the review.

36.1 **If yes to question 35.0, explain how this database is complaint with the Personal Health Information Act of Manitoba (PHIA).** Information with respect to compliancy can be found on the Bannatyne Campus Research Ethics Board website - "Requirement of PHIA compliancy for Databases".

POTENTIAL CONFLICT OF INTEREST:

Continued: To HREB: Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review

SIGNATURES:

Signature of Principal Investigator attesting that:

a) all investigators/co-investigators have reviewed the research as outlined in this application and are in agreement with the application submitted;
b) all investigator/co-investigators have read the Tri-Council Policy Statement and the University of Manitoba Policy 1406 and agree to abide by the guidelines therein;
c) I and all study personnel will adhere to the **application** as approved by a Bannatyne Campus Research Ethics Boards (REB);
d) I and all study personnel have signed a pledge of confidentiality with the institution(s) from which we are collecting data
e) information will not be used for any purpose other than for the project for which it was provided. The information will be shared only with those individuals listed on this form except for authorized oversight of the study;
f) information will be kept in a location that is physically secure and to which access is given only to the individuals(s) listed on this form
g) all direct identifiers will be segregated/stripped from clinical data; a unique study identifier (i.e. a randomly generated or meaningless ID number) will be assigned to each patient/participant record; the Master list linking the ID with identifiable material will be stored in a separate compute file and /or physical location; and the Master list will be locked and password protected:
h) as the principal investigator I will be responsible for notifying the REB of any changes made to the application as per Bannatyne Campus REB guidelines;
i) the study will not commence until I have received the final certificate of approval from the REB;
j) the study will not commence until the appropriate institutional approval (i.e. local hospital approval or local ethics approval) has been obtained;
k) I will submit a request for annual approval to the REB prior to the expiry date indicated on the approval certificate;
l) I will submit a final study status report to the REB when all study activity is completed at the local site;
m) if I am a University researcher, I hereby consent that the REB may provide written notice of their approval of this protocol to the institution in which the research will be conducted;
n) if I am a WRHA Researcher, I hereby consent that the REB may provide written notice of their review of this protocol to the WRHA and any WRHA facility in which the study will be conducted. The written notice may include my name, whether the protocol was approved or rejected, the reasons for any rejection and any conditions placed on approval.
o) I understand that the **$2,500 fee assessed for REB review on applicable protocols (for profit private funder) is NOT dependent on approval and must be paid in a timely manner**. The review fee applies even if the submission is withdrawn or not approved by the Research Ethics Board. **I have made the sponsor aware of this policy.**

Printed Name of Principal Investigator [redacted]

Signature of Principal Investigator: [redacted] **Date:** Nov 3 2017

Required Signature for Student Projects:

Printed Name of Supervi [redacted]

Signature of Supervisor: _____ **Date:** Nov 3 2017

Required Department Head or Delegate Signature for all Projects:

If you are having difficulties obtaining the department head signature prior to the submission deadline, please provide explanation in a cover letter to the board indicating when these signatures will be obtained. The department head signature/delegate is required prior to releasing the certificate of final approval.

Signature of Department Head or Delegate attesting that:

I have reviewed this research protocol and confirm that there is sufficient scientific merit to warrant this submission.

Printed Name of Department Head or Delegate:

(The department head or delegate signature cannot be involved in the trial as the Principal, Co-Principal Investigator or study coordinator.)

Signature of Department Head or Delegate: [redacted] **Date:** Nov 3 2017

W[redacted]

The form is locked which enables you to tab to each question and check box with ease. To conduct a spell check you must first unprotect the document. After you have completed answering all questions, go to *"Tools"* on the tool bar and in the drop down menu select *"Unprotect Document"*. No password is required. *If working with Word 2007, go to "Review" tab, click on "Protect Document", click on "Restrict Formatting and Editing" and then click on "Stop Protection".* No password is required.

DO NOT DELETE QUESTIONS on this form or THE SUBMISSION WILL BE RETURNED to the applicant.

From HREB: Full project approval

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Kevin Friesen	U of M /Pharmacy	HS21343 (H2017:404)
APPROVAL DATE: December 5, 2017	**EXPIRY DATE:** December 5, 2018	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. Shawn Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
NA	Signal and Noise: A Comprehensive Assessment of the Relationship between Medication Use and Alzheimer 's disease
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
November 1 and December 1, 2017	November 1 and December 4, 2017

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:
Proposal submitted November 1, 2017 including Clarifications as per Letter dated December 1, 2017
Consent and Assent Form(s):

Other:
Data Capture Sheet

October 16, 2016

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

Continued: From HREB: Full project approval

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus