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RESEARCH ARTICLE

Benzodiazepine use and the risk of dementia

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Abstract

Introduction: Benzodiazepines (BZDs) are commonly prescribed for anxiety and agitations, which are early symptoms of Alzheimer's disease and related dementias (ADRD). It is unclear whether BZDs causally affect ADRD risk or are prescribed in response to early symptoms of dementia.

Methods: We replicate prior case-control studies using longitudinal Medicare claims. To mitigate bias from prodromal use, we compare rates of ADRD diagnosis for beneficiaries exposed and unexposed to BZDs for cervical/lumbar pain, stenosis, and sciatica, none of which are associated with dementia.

Results: Approximately 8% of Medicare beneficiaries used a BZD in 2007, increasing to nearly 13% by 2013. Estimates from case-control designs are sensitive to duration of look-back period, health histories, medication use, and exclusion of decedents. Incident BZD use is not associated with an increased risk of dementia in an "uncontaminated" sample of beneficiaries prescribed a BZD for pain (odds ratios (ORs) of 1.007 [95% confidence interval [CI] = 0.885, 1.146] and 0.986 [95% CI = 0.877, 1.108], respectively, in the 2013 and 2013 to 2015 pooled samples). Higher levels of BZD exposure (>365 days over a 2-year period) are associated with increased odds of a dementia diagnosis, but the results are not statistically significant at the 5% or 10% levels (1.190 [95% CI = 0.925, 1.531] and 1.167 [95% CI = 0.919, 1.483]).

Discussion: We find little evidence of a causal relation between BZD use and dementia risk. Nonetheless, providers should limit the extended use in elderly populations.

KEYWORDS
Benzodiazepines, case-control designs, causal estimates, dementia risk, Medicare beneficiaries

1 | BACKGROUND

Dementia researchers are increasingly optimistic that new treatments in development can stop or significantly delay the progression of Alzheimer's disease (AD) and related dementias (ADRD). This optimism reflects a growing understanding of the disease process, which can begin years or even decades before any signs of cognitive decline.[1] Developing new therapies for a complex disease is a slow and painstaking process; however, leading National Institutes of Health (NIH) and advocacy groups support of research that can have a more proximate impact on the risk of developing dementia.

One example is the growing body of research linking ADRD risk to medications prescribed for other chronic conditions.[2] For example, statins and antihypertensives have been associated with a lower risk of dementia apart from their impact on cardiovascular health.[3–6] The underlying mechanisms behind these so-called "pleiotropic effects" are

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not fully understood, but generally consistent findings across a number of recent studies suggest a link between these drugs and dementia risk. In the case of statins, a new large trial (PREVENTABLE) will assess the impact on dementia and cognitive impairment in real-world clinical settings.[7]

Conversely, a growing number of drug classes have been associated with increased dementia risk. The most widely cited are medications with anticholinergic properties used to treat an array of conditions, including allergies, incontinence, and depression.[8–10] Another class of medications linked to ADRD risk is benzodiazepines (BZDs), central nervous system depressant drugs used to treat anxiety, agitations, insomnia, and other conditions. Although BZDs can be an effective treatment, they have been shown to increase the risk in older adults (adults age 65 and older) of falls, hip fractures, cognitive impairment, and drug-associated hospital admissions.[11–14] Because of these risks, BZDs are on the Beer's list of potentially inappropriate medications for older adults[15] and were initially excluded from coverage in Medicare Part D. Nonetheless, BZDs are widely used. Data from the National Ambulatory Medical Care Survey (NAMCS) estimated the number of ambulatory visits with one or more prescriptions for a BZD increased from 27.6 million in 2003 to 62.6 million in 2015, with the highest use among the elderly.[16]

A growing number of studies relating BZD use to dementia risk find mixed results.[17–26] No studies have used a randomized control trial study design due to ethical considerations, and estimating a causal effect with observational data is uniquely challenging because the conditions for which BZDs are prescribed (e.g., anxiety, agitations, insomnia) are also symptoms of ADRD. Thus it is unclear whether BZDs causally affect ADRD risk or are sometimes prescribed in response to early symptoms of ADRD.

To mitigate potential bias from prodromal use, most studies use a case-control design that matches individuals with and without an incident ADRD diagnosis at time (*t*) and their exposure to BZDs years earlier. A longer "look-back" period reduces the likelihood of prodromal use, but increases the risk of omitted variable bias given that model covariates are measured at the time of exposure. Thus the onset of ADRD risk factors (e.g., cardiovascular events) and medication use—including BZDs—occurring between exposure and outcome measurement are not captured. For example, a highly cited case-control study of Canadian seniors compared the use of BZDs 6 to 10 years before an incident dementia diagnosis (*t*).[21] They found that prior use of BZDs increased AD risk by 43% to 51% and that the risk increased with exposure (84% higher risk for those taking >180 daily doses). Although controls were matched on age group, gender, and duration of follow-up at time (*t*), cases and controls differed markedly at the time of BZD exposure (*t-6* to *t-10*) in the prevalence of hypertension, stroke, hypercholesterolemia, diabetes, anxiety, insomnia and depressive symptoms, all of which are associated with ADRD risk.

In this study, we replicate prior case-control designs to assess the robustness of the estimates to several factors: (1) length of the look-back period; (2) inclusion of a broad set of physical and mental health diagnoses and related medications; and (3) exclusion of decedents. Given the inherent challenges in obtaining casual estimates using a case-control design with look-back, we abandon the case-control design and identify a subgroup of patients whose incident BZD exposure is likely unrelated to their ADRD risk. We identify a sample of older beneficiaries without a history of depression, anxiety, agitation, or insomnia (or related medications), but with a diagnosis of chronic pain. Although BZDs are most often used to treat behavioral conditions, they are also prescribed for the treatment of musculoskeletal diseases and spinal disorders, none of which are known prodromal symptoms of dementia.[15] We compare rates of ADRD diagnosis over 5 years for beneficiaries exposed and unexposed to a BZD for chronic pain to obtain plausibly causal estimates. Given the persistent and widespread use of BZDs in older persons, it is important to understand their effect on dementia risk.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the growing body of evidence linking risk of Alzheimer's disease and related dementias (ADRD) to medications prescribed for other chronic conditions. For example, statins and antihypertensives have been associated with lower risk of dementia apart from their impact on cardiovascular health, whereas benzodiazepines (BZDs) have been associated with increased dementia risk.
2. **Interpretation**: Estimating a causal effect of BZDs with observational data is uniquely challenging because the conditions for which BZDs are prescribed (anxiety, agitations, insomnia) are also symptoms of ADRD. We find no statistically significant relationship between BZD use and dementia risk in an "uncontaminated" sample of beneficiaries prescribed a BZD for pain.
3. **Future directions**: We measure BZD use over a 2-year period to mitigate prodromal use, but do not account for medication dosage or strength or use after the initial 2-year period. A more detailed, longer follow-up period is needed to confirm or refute our findings.

2 | METHODS

2.1 | Data and study sample

Through the Centers for Medicare & Medicaid Services (CMS), we linked a 100% sample of fee-for-service Medicare beneficiaries from 2006 to 2020 to data on enrollment; demographics; vital status; and Parts A, B, and D claims. In addition to large sample sizes, the data included information on all diagnosed conditions, health care use, and prescribed medicines. Enrollment and claims data were supplemented with claims histories from the Chronic Conditions Data Warehouse (CCW).

The study sample includes a number of restrictions. First, we include only beneficiaries continuously enrolled in traditional Medicare (TM) and Part D from the start of their observation period to 2016 or later depending on the analysis. We exclude those enrolled in a Medicare Advantage plan because they do not have complete medical claims or claim histories in the CCW. We exclude beneficiaries with a history of BZD use prior to their observation window, as well as those with a prior diagnosis or drug claim for ADRD, a history of motor neuron disease, HIV/AIDS, multiple sclerosis (MS), Down syndrome, or alcohol abuse before 2016.

BZDs were excluded from coverage in Medicare Part D due to safety concerns from 2006 to 2012. However, employer-sponsored Part D plans (EGWPs) were exempt from this exclusion. Thus the study sample is restricted to EGWP enrollees from 2006 to 2012 and all beneficiaries enrolled in standalone prescription drug plans (PDP) from 2013 to 2020.

2.2 | Use of benzodiazepines

We measure use of Class 1 benzodiazepines (or BZDs), including flurazepam, triazolam, temazepam, diazepam, alprazolam, and lorazepam. We also control for use of non-BZD hypnotics or sleep aids. Although these so-called "Z-drugs" also affect the chemical γ-aminobutyric acid (GABA), they are more targeted and affect only specific parts of the neurotransmitter GABA receptor (see Supplementary Appendix). We defined Class 1 BZD use based on one or more prescription drug claims for a minimum of 30 days. We categorize BZD exposure into five groups based on cumulative use over a 2-year period (0–29, 30–89, 90–179, 180–365, and >365 days) recorded in the Part D claims.

2.3 | Case-control design

Cases consist of Medicare beneficiaries 67 years of age and older with an incident ADRD diagnosis in 2015 or 2016, matched 3:1 to controls without an ADRD diagnosis through 2016 on sex, race, and 5-year age bands. A distinguishing characteristic of this type of design is that selection into the sample is based on the outcome rather than exposure, and exposure is measured 5, 10, or even 20 years earlier to mitigate bias from prodromal use. This approach raises a number of concerns. First, even with detailed matching in 2015 to 2016, cases and controls can differ markedly at the time of their exposure to a BZD, which is evident in Table 1. Furthermore, the onset of ADRD risk factors (e.g., stroke, diabetes) and medication use in the period between exposure and outcome measurement are not controlled for, given that the independent variables are measured at the time of exposure. This can introduce omitted variable bias that is difficult to quantify or mediate. Furthermore, an extended look-back period reduces external validity by excluding from the sample those who die before outcome measurement at time (t).

Despite these potential shortcomings, we replicate prior case-control studies to assess the sensitivity of the estimates to the duration of the look-back period, physical and mental health histories, medication use, and mortality selection. We create separate cohorts to vary the time between BZD exposure and ADRD measurement as illustrated in the Supplementary Appendix Figure S1. For each beneficiary-year starting in 2007, we create a cohort of beneficiaries without a history of BZD use or cognitive decline. We compare rates of ADRD diagnosis in 2015 to 2016 for beneficiaries initiating use of a BZD in 2007 (cases) to matched controls without a history of BZD use through 2007. We measure a binary (0,1) measure of incident BZD use in in 2007, as well cumulative use over 2 years (2007–20088) based on the total days' supply recorded in the Part D claims. The second cohort consists of beneficiaries without a history of BZD use or cognitive decline through 2007, some of whom initiated a BZD in 2008 (cases). The process continues through the 2013 cohort, which includes beneficiaries without a history of BZD use or cognitive decline through 2012, some of whom initiated a BZD in 2013. We measure incident use in 2013 and cumulative days' supply in 2013 and 2014. The association between incident BZD use and ADRD should be stronger in later cohorts if some fraction of BZD use is in response to prodromal symptoms of dementia, that is, closer to an ADRD diagnosis in 2015 to 2016.

We measure diagnosed dementia in 2015 to 2016 using codes from inpatient, outpatient, home health care, skilled nursing facility, carrier and drug claims, and the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9-CM, ICD-10-M) diagnoses codes for dementia as defined by the CCW. (Lists of specific codes are available in the Supplementary Appendix.) We require a second dementia diagnosis code to reduce measurement error from rule-out diagnoses, heretofore "verified" ADRD.

2.4 | Pain sample

Given the inherent limitations of using a case-control design in this context, we take a different approach. We identify a sample of beneficiaries without a history of depression, anxiety, insomnia, cognitive decline, or BZD use, but with a diagnosis of chronic pain in 2013. BZDs are prescribed for pain management, although less frequently than for anxiety, agitation and insomnia. We compare rates of ADRD diagnosis over 5 years for beneficiaries exposed (treatments) and unexposed (controls) to a BZD in 2013 for the treatment of cervical and lumbar pain, stenosis, and sciatica, none of which are associated with dementia (relevant ICD-10 diagnoses in the Supplementary Appendix). The key advantage of this approach is that incident exposure to a BZD is unlikely to be correlated with an individual's ADRD risk.

Because pharmacy claims do not report a medical diagnosis associated with a prescription, we define BZD use for the treatment of pain based on an incident prescription within 3 months of a pain diagnosis and the absence of any other diagnosis code for which BZDs are commonly prescribed. The treatment group consists of 12,964 beneficiaries prescribed an incident BZD for pain matched 5:1 on age, race, and gender to those diagnosed for the same conditions but unexposed to a BZD (N = 64,820). To increase the sample size, we also estimate

TABLE 1 Sample statistics of cases and controls in 2007 and 2013, measured at the start of exposure period

Cohort	2007 Control	2007 Case	2013 Control	2013 Case
Female	69,585 (64.54%)	23,195 (64.54%)	893,624 (68.07%)	297,963 (68.08%)
Non-Hispanic White	99,636 (92.41%)	33,212 (92.41%)	1,119,621 (85.29%)	373,207 (85.27%)
Black	3,012 (2.79%)	1,004 (2.79%)	91,289 (6.95%)	30,518 (6.97%)
Asian	3,258 (3.02%)	1,086 (3.02%)	33,888 (2.58%)	11,296 (2.58%)
Hispanic	1,635 (1.52%)	545 (1.52%)	62,058 (4.73%)	20,686 (4.73%)
American Indian/Alaska Native	275 (0.26%)	92 (0.26%)	5,865 (0.45%)	1,955 (0.45%)
70–74			181,677 (13.84%)	60,559 (13.84%)
75–79	19,191 (17.80%)	6,397 (17.80%)	255,651 (19.47%)	85,217 (19.47%)
80–84	30,447 (28.24%)	10,149 (28.24%)	294,267 (22.42%)	98,089 (22.41%)
85–89	32,046 (29.72%)	10,682 (29.72%)	308,142 (23.47%)	102,714 (23.47%)
90+	26,132 (24.24%)	8,711 (24.24%)	272,984 (20.80%)	91,083 (20.81%)
BZD users	7,578 (7.03%)	3,293 (9.16%)	145,652 (11.10%)	66,829 (15.27%)
Average days' supply per Year conditional on use (SD)	156.79 (113.77)	168.50 (114.01)	172.16 (115.38)	189.31 (116.32)
Hypertension	88,857 (82.42%)	30,915 (86.02%)	1,163,603 (88.64%)	404,073 (92.33%)
Hyperlipidemia	89,190 (82.72%)	30,213 (84.07%)	1,131,869 (86.22%)	385,102 (87.99%)
Acute myocardial infarction	3,863 (3.58%)	1,550 (4.31%)	78,842 (6.01%)	34,590 (7.90%)
Atrial fibrillation	13,348 (12.38%)	5,714 (15.90%)	254,056 (19.35%)	109,680 (25.06%)
Diabetes	30,515 (28.30%)	12,251 (34.09%)	495,653 (37.76%)	201,033 (45.93%)
Stroke	11,055 (10.25%)	5,106 (14.21%)	209,587 (15.97%)	106,752 (24.39%)
Antidepressant/antipsychotic use	18,934 (17.56%)	8,833 (24.58%)	403,936 (30.77%)	195,915 (44.76%)
Depression	17,251 (16.00%)	8,177 (22.75%)	274,065 (20.88%)	147,360 (33.67%)
Insomnia	11,210 (10.40%)	5,585 (15.54%)	238,275 (18.15%)	132,697 (30.32%)
Anxiety	12,843 (11.91%)	5,223 (14.53%)	269,775 (20.55%)	113,145 (25.85%)
N	107,816	35,939	1,312,721	437,662

Abbreviated model covariates include benzodiazepine (BZD) use and prior hsitory of an acute myocardial infarction (AMI) and atrial fibrilation (ATF).

models on a pooled sample of beneficiaries diagnosed with chronic pain in 2013, 2014, or 2015, comparing rates of ADRD diagnoses through 2018 for BZD users and non-users, as well as the level of exposure conditional on use.

2.5 | Statistical analysis

We use multivariate regression models to control for observed differences between exposure groups. The models control for a detailed set of demographic characteristics (age, gender, and race/ethnicity), physical health conditions (hypertension, hyperlipidemia, acute myocardial infarction, atrial fibrillation, and stroke) as measured by the (CCW), mental health conditions (depression, anxiety, and insomnia), and use of related medications (antidepressants, antipsychotics) prior to the exposure period. Given high rates of co-prescribing of BZDs and opioids, the models also control for the use of opioids and sleep aids (Z-drugs), all measured at the start of the exposure period. The primary outcome is ADRD status, either in 2015 to 2016 (case-control) or 2018 for the pain samples. The key independent variables are incident BZD use (0,1) and cumulative days' supply over a 2-year period.

3 | RESULTS

Table 1 presents summary statistics of the case-control samples for the 2007 and 2013 cohorts. Note that the 2007 sample includes EGWP plans only, consisting of 35,939 cases and 107,816 controls. BZDs are

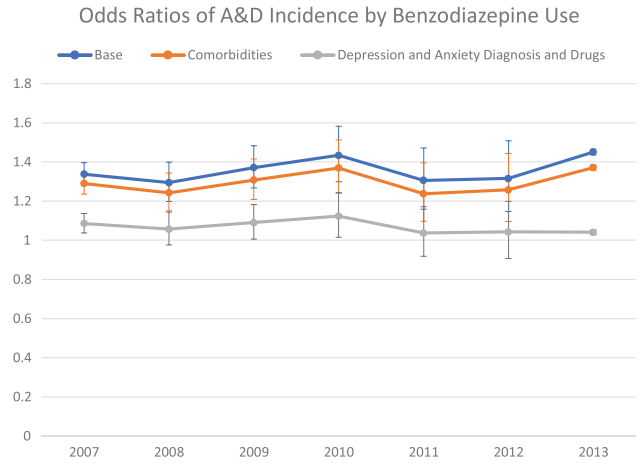

FIGURE 1 Odds ratios of an Alzheimer's disease and related dementias (ADRD) diagnosis in 2015 to 2016 associated with incident benzodiazepine use in each year. The base model controls for demographic characteristics of cases and controls, with additional adjustment for physical (hypertension, hyperlipidemia, acute myocardial infarction, atrial fibrillation, stroke) and mental health conditions (depression, anxiety, and insomnia, as well as use of antidepressants and antipsychotics), all measured at the start of the exposure period.

almost universally covered in all Part D plans starting in 2013, and thus sample sizes increase to 437,662 cases and 1,312,721 matched controls in that year. Approximately 7.0% of controls and 9.2% of cases used a BZD in 2007, increasing to 11.1% and 15.3% by 2013.

Although cases and controls are matched on sex, race, and 5-year age bands in 2015 to 2016, they differ at the time of their exposure window. Cases have markedly higher rates of depression, anxiety, and insomnia prior to BZD exposure periods in both the 2007 and 2013 cohorts, as well as higher prevalence of hypertension, hyperlipidemia, diabetes, and stroke. Differences across exposure groups underscore the primary limitation of a case-control design with an extended look-back period. Cases and controls can differ substantially on observed characteristics at the time of exposure and may not follow similar trajectories in the time between exposure and outcome measurement.

Figure 1 shows the adjusted odds of an ADRD diagnosis in 2015 to 2016 associated with incident BZD use in each of the seven cohorts, where a cohort is defined by the incident year of the BZD exposure period and cumulative use is measured over 2 years. The blue line (base model) controls only for demographic characteristics and shows odds ratios associated with BZD exposure just above and below 1.4 over the different cohorts. However, the odds ratios decline with adjustment for physical health (hypertension, hyperlipidemia, acute myocardial infarction, atrial fibrillation, stroke; orange line) and mental health (depression, anxiety, insomnia, and/or use of related medications; gray line). The association between incident BZD use and dementia is modestly higher in later cohorts, suggesting some degree of prodromal use. However, the differences across cohorts are mitigated after adjusting for physical and mental health histories and related medications.

To assess the importance of excluding decedents, we redefine the annual cohorts starting in 2007 to include any beneficiary without a history of an ADRD diagnosis or BZD claim prior to 2007, irrespective of their survival until 2015 to 2016. Supplementary Appendix Figure S2 shows the relative odds of an ADRD diagnosis associated with BZD use, separately for decedents and survivors. After adjustment, the relative odds of an incident ADRD diagnosis range from 1.5 to 1.7 for long-term survivors exposed to a BZD compared to 1.0 to 1.2 for decedents. This suggests that restricting case-control studies to longer-term survivors may overestimate the population-level association between BZD use and dementia risk.

Given the potential interrelationship between behavioral symptoms, BZD use, and ADRD risk, we abandon the retrospective case-control design. Rather, we estimate the association between incident BZD exposure and ADRD diagnosis among beneficiaries with a diagnosis of chronic pain, some of whom are prescribed a BZD. Table 2 shows the sample characteristics of the pain sample in 2013. Beneficiaries ini-

TABLE 2 Sample consists of 12,964 beneficiaries with an incident benzodiazepine (BZD) claim associated with a pain diagnosis, matched 5:1 on age, race/ethnicity, gender, and chronic pain diagnosis

Sample statistics of pain sample, 2013		
	Non-Users	BZD Users
Total	**64,820**	**12,964**
Age at diagnosis		
65–69	18,000 (27.77%)	3600 (27.77%)
70–74	23,205 (35.80%)	4641 (35.80%)
75–79	13,345 (20.59%)	2669 (20.59%)
80–84	6965 (10.75%)	1393 (10.75%)
85–89	2735 (4.22%)	547 (4.22%)
90+	570 (0.88%)	114 (0.88%)
Sex		
Female (%)	39,560 (61.03%)	7,912 (61.03%)
Race		
White (%)	59,115 (91.20%)	11,823 (91.20%)
Black (%)	1870 (2.88%)	374 (2.88%)
Asian (%)	1220 (1.88%)	244 (1.88%)
Hispanic (%)	1890 (2.92%)	378 (2.92%)
American Indian/Alaska Native (%)	100 (0.15%)	20 (0.15%)
Missing/Other (%)	625 (0.96%)	125 (0.96%)
Comorbidities at diagnosis		
Hypertension	0.8064	0.8662
Hyperlipidemia	0.8406	0.8859
Acute myocardial infarction	0.0345	0.0366
Atrial fibrillation	0.1213	0.151
Diabetes	0.3142	0.3625
Stroke	0.0865	0.1081
Opioid use	0.1702	0.3829
Z-drug use	0.024	0.0865

TABLE 3 Odds ratios of an ADRD diagnosis by use of a Class 1 benzodiazepine

	(1)	(2)	(3)	(4)
	2013 sample		2013–2015 pooled sample	
	ADRD 2018	ADRD 2020	ADRD 2018	ADRD 2020
BZD use (0,1)	1.007 [0.885–1.146]	1.073 [0.968–1.190]	0.986 [0.877–1.108]	0.999 [0.908–1.098]
Female	1.019 [0.921–1.127]	0.917* [0.846–0.995]	0.975 [0.890–1.068]	0.975 [0.906–1.050]
Black	1.333* [1.049–1.694]	1.430*** [1.170–1.748]	1.457*** [1.186–1.791]	1.308** [1.094–1.564]
Missing/other	0.793 [0.435–1.445]	0.905 [0.576–1.421]	1.117 [0.706–1.768]	1.261 [0.890–1.787]
Asian	1.037 [0.740–1.455]	0.999 [0.743–1.343]	1.210 [0.913–1.605]	1.297* [1.029–1.636]
Hispanic	1.098 [0.852–1.416]	1.198 [0.976–1.470]	1.190 [0.952–1.488]	1.040 [0.856–1.264]
American Indian/Alaska Native	0.902 [0.222–3.669]	1.099 [0.344–3.507]	0.684 [0.169–2.769]	0.662 [0.210–2.092]
70–74	1.627*** [1.373–1.929]	1.683*** [1.471–1.924]	1.849*** [1.555–2.198]	1.706*** [1.495–1.946]
75–79	3.109*** [2.626–3.680]	3.228*** [2.820–3.695]	3.438*** [2.900–4.076]	3.145*** [2.760–3.585]
80–84	4.465*** [3.735–5.338]	5.886*** [5.116–6.770]	5.366*** [4.502–6.396]	5.552*** [4.853–6.351]
85–89	8.072*** [6.643–9.808]	8.833*** [7.494–10.410]	8.966*** [7.446–10.795]	9.209*** [7.954–10.662]
90+	11.491*** [8.640–15.283]	13.176*** [10.072–17.235]	10.950*** [8.595–13.951]	14.713*** [12.083–17.914]
Hypertension	1.166 [0.996–1.367]	1.176* [1.036–1.334]	1.305** [1.111–1.534]	1.245*** [1.101–1.408]
Hyperlipidemia	1.024 [0.877–1.197]	1.010 [0.890–1.145]	1.130 [0.969–1.316]	0.935 [0.833–1.049]
AMI	1.114 [0.897–1.384]	1.190 [0.999–1.418]	1.100 [0.914–1.322]	1.091 [0.934–1.275]
ATF	1.038 [0.912–1.182]	1.172** [1.057–1.300]	1.197** [1.075–1.334]	1.224*** [1.120–1.338]
Diabetes	1.266*** [1.144–1.401]	1.150** [1.058–1.249]	1.172*** [1.069–1.284]	1.233*** [1.144–1.328]
Stroke	1.345*** [1.176–1.538]	1.203** [1.072–1.351]	1.466*** [1.310–1.640]	1.502*** [1.365–1.651]
Opioid	1.074 [0.956–1.208]	1.347*** [1.228–1.477]	1.260*** [1.141–1.391]	1.233*** [1.136–1.338]
Z-drug use	0.981 [0.747–1.287]	0.831 [0.659–1.046]	0.757 [0.569–1.009]	1.042 [0.850–1.278]
Displacement	1.037 [0.940–1.144]	0.982 [0.906–1.064]	1.051 [0.961–1.149]	0.910* [0.847–0.979]
Stenosis	0.976 [0.885–1.077]	0.944 [0.871–1.023]	0.989 [0.903–1.082]	1.021 [0.948–1.099]
Backpain	1.054 [0.939–1.183]	0.980 [0.893–1.077]	1.026 [0.926–1.136]	0.984 [0.906–1.069]

tiating use of a BZD for chronic pain have a slightly higher prevalence of cardiovascular conditions, but the differences are considerably smaller than observed in the case-control samples. Those who take a BZD for pain are more likely to have used an opioid or a sleep aid (Z-drug), which we control for in multivariate models.

Table 3 shows the odds ratios of an ADRD diagnosis by BZD use in the two pain samples. The first column presents regression results for the 2013 sample, and the second column for the pooled sample (2013-2015), where any ADRD diagnosis through 2018 is "verified" with a second diagnosis. Not surprisingly, age is the primary risk factor for dementia. Chronic pain sufferers 85 to 89 years of age in 2013 are eight times more likely to be diagnosed with ADRD within 5 years compared to similar beneficiaries 65 to 69 years of age. Minorities have higher risk, as do individuals with a history of hypertension, atrial fibrillation, diabetes, and stroke. By contrast, incident BZD use is not a statistically significant risk factor for dementia, with odds ratios of 1.007 (95% confidence interval [CI] = 0.885, 1.146) and 0.986 (95% CI = 0.877, 1.108), respectively in the 2013 and 2013 to 2015 samples. Although rarely controlled for in prior analyses, opioids may be co-prescribed with BZDs for the treatment of musculoskeletal conditions and are independently associated with a higher ADRD risk.

Table 4 presents results from the two pain samples, where BZD exposure is categorized by cumulative use over a 2-year period. BZD use of less than 180 days is not associated with higher ADRD risk over 5 years for the 2013 sample or 3 to 5 years for the pooled sample. Higher levels of BZD exposure (>180 days in the pooled sample or >365 days in the 2013 sample) are associated with an increased odds of a dementia diagnosis, but the results are not statistically significant at the 5% or 10% levels. The odds ratios associated with >365 days of BZD use are 1.190 (95% CI = 0.925, 1.531) and 1.167 (95% CI = 0.919, 1.483) in the 2013 and pooled samples, respectively.

4 | DISCUSSION

Although the deleterious cognitive effects of single-dose BZDs are well known, it remains unclear whether extended use affects Alzheimer's disease (AD), dementia, or cognitive decline. Several early studies from the UK and Canada found a strong, positive association between BZD use and ADRD risk,[17–22] with large dose-response effects. However, more recent analyses have raised concerns about the ability of case-control studies to yield causal estimates if some degree of BZD use is

TABLE 4 Odds ratios of an ADRD diagnosis by level of exposure to a Class 1 benzodiazepine

	(1) 2013 sample ADRD 2018 (verified)	(2) Pooled sample (2013–2015) ADRD 2018 (verified)
BZD use (30–89 days)	0.944 [0.789–1.130]	0.939 [0.802–1.099]
BZD use (90–179 days)	1.031 [0.783–1.357]	0.787 [0.592–1.045]
BZD use (180–365 days)	0.962 [0.714–1.297]	1.174 [0.913–1.510]
BZD use (>365 days)	1.190 [0.925–1.531]	1.167 [0.919–1.483]
Female	1.021 [0.923–1.129]	0.976 [0.891–1.070]
Black	1.335* [1.051–1.697]	1.458*** [1.186–1.792]
Missing/other	0.795 [0.436–1.448]	1.119 [0.707–1.772]
Asian	1.042 [0.743–1.461]	1.215 [0.916–1.611]
Hispanic	1.101 [0.854–1.419]	1.190 [0.952–1.488]
American Indian/Alaska Native	0.905 [0.222–3.680]	0.683 [0.169–2.766]
70–74	1.628*** [1.373–1.930]	1.851*** [1.557–2.201]
75–79	3.106*** [2.624–3.677]	3.436*** [2.898–4.073]
80–84	4.459*** [3.730–5.330]	5.364*** [4.501–6.394]
85–89	8.057*** [6.631–9.789]	8.941*** [7.426–10.766]
90+	11.484*** [8.635–15.274]	10.939*** [8.586–13.937]
Hypertension	1.166 [0.995–1.365]	1.304** [1.110–1.533]
Hyperlipidemia	1.024 [0.877–1.197]	1.130 [0.969–1.316]
AMI	1.115 [0.897–1.385]	1.100 [0.914–1.322]
ATF	1.039 [0.913–1.183]	1.199*** [1.076–1.335]
Diabetes	1.268*** [1.145–1.403]	1.172*** [1.070–1.285]
Stroke	1.345*** [1.176–1.538]	1.465*** [1.309–1.640]
Opioid	1.071 [0.953–1.205]	1.256*** [1.138–1.388]
Z-drug use	0.983 [0.749–1.290]	0.756 [0.568–1.007]
Displacement	1.038 [0.941–1.145]	1.053 [0.963–1.151]
Stenosis	0.977 [0.886–1.078]	0.990 [0.905–1.084]
Backpain	1.054 [0.939–1.183]	1.026 [0.926–1.136]

Note: Reference category is 0–29 days use. Abbreviated model covariates include benzodiazepine (BZD) use and prior hsitory of an acute myocardial infarction (AMI) and atrial fibrilation (ATF).

a response to early symptoms of dementia such as agitation, insomnia, and depression.[23–28]

In this study, we replicate prior case-control designs and find that those exposed to a BZD have markedly higher rates than matched controls of depression, anxiety, and insomnia *prior* to exposure and are more likely to have a history of hypertension, hyperlipidemia, diabetes, and stroke. Controlling for these differences and related medication use substantially reduces the association between BZD use and dementia risk and raises concern that prodromal use and unobserved or unmeasured differences across the two groups may be driving the association in prior studies. We find that estimates from case-control designs are sensitive to the duration of the look-back period, physical and mental health histories, prior medication use, and the exclusion of decedents. Although extending the look-back period reduces the likelihood of prodromal use, it is likely to exacerbate omitted variable bias given that model covariates are measured years or even decades earlier at the time of exposure.

To mitigate bias from prodromal use, we abandon the case-control design and simply compare adjusted rates of ADRD diagnosis for beneficiaries exposed and unexposed to BZDs for a series of pain diagnoses (cervical and lumbar pain, stenosis, sciatica), none of which are associated with dementia. Older age, minorities, patients with cardiovascular risk factors, and those co-prescribed an opioid are more likely to be diagnosed with ADRD within 5 years. Yet, we find no statistically significant association between BZD use and dementia diagnosis in this "uncontaminated" sample. Although beneficiaries with the highest exposure to BZDs over a 2-year period (>180 or >365 days) have higher point estimates in some specifications, the odds ratios are not statistically different from 1.0 at standard levels of significance.

Our study has several limitations. Measuring ADRD risk in claims data is imperfect. Yet, a handful of studies on sensitivity and specificity of dementia diagnoses suggest that dementia diagnoses may be both under- or over-estimated in claims data.[29–31] When comparing claims to clinical assessment in research settings, these studies have found that claims data correctly identify the majority of dementia and non-dementia cases, but that estimates vary. Incident BZD exposure and cumulative BZD use over a 2-year period is based on the total days' supply recorded in the Part D data. Pharmacy claims have been used widely to estimate medication use and adherence; however, they do not measure actual pill-taking behavior. We measure BZD use over a 2-year period to mitigate prodromal use, but do not account for the dosage or strength of each claim, or use after the initial 2-year period. Because pharmacy claims do not report a medical diagnosis associated with a prescription, we identify incident BZD use for the treatment of chronic pain based on a filled prescription within 3 months of a pain diagnosis and the absence of any other diagnosis code for which a BZD is commonly prescribed. Finally, we lack information on individual-level biomarkers for ADRD. Prior work suggests that individuals who are at genetic risk of AD who took anticholinergic drugs were more likely to develop mild cognitive impairment than those taking the medication without the risk factors.[32] In other words, there may be an interaction effect that we do not capture in our analyses.

Although benzodiazepines are widely recognized as being effective, the US Food and Drug Administration (FDA) recently updated the boxed warning on all benzodiazepines to underscore the risks of abuse, addiction, physical dependence, and withdrawal reactions.[33] The FDA advised physicians to screen for risk factors before initiating BZDs, including substance use disorders, cognitive impairment, concomitant use of opioids, and older age.[34] Although older individuals are more sensitive to the psychotropic adverse effects of BZDs, we do not find sufficient evidence that short- to intermediate-term use of BZDs increases the risk of dementia in older populations. Nonetheless, physicians should consider alternate pharmacological and behavioral strategies before using BZDs and engage older patients in a discussion regarding the risks and benefits of their use.

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CONFLICTS OF INTEREST

The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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