History of Benzodiazepine Prescriptions and Risk of Dementia: Possible Bias Due to Prevalent Users and Covariate Measurement Timing in a Nested Case-Control Study

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Abbreviations

ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
DEP	Drug exposure period
DDD	Defined daily dose
OR	Odds ratio
UK	United Kingdom

Abstract

Previous estimates of whether long-term exposure to benzodiazepines increases dementia risk are conflicting and are compromised by the difficulty of controlling for confounders and by reverse causation. We investigated how estimates for the association between benzodiazepine use and later dementia incidence varied based on study design choices using a case-control study nested within the United Kingdom's Clinical Practice Research Datalink. N=40,770 dementia cases diagnosed between April 2006 and July 2015 were matched to 283,933 controls on age, sex, available data history and deprivation. Benzodiazepines and Z-drug prescriptions were ascertained in a drug exposure period 4-20 years prior to dementia diagnosis. Estimates varied with the inclusion of new or prevalent users, with the timing of covariate ascertainment, and with varying time between exposure and outcome. There was no association between any new prescription of benzodiazepines and dementia (adjusted odds ratio 1.03; 95% confidence interval 1.00, 1.07), while among prevalent users and inverse association was observed (adjusted odds ratio 0.91; 95% confidence interval 0.87, 0.95), although this was likely induced by unintentional adjustment for colliders. By considering the choice of confounders and timing of exposure and covariate measurement, overall our findings are consistent with no causal effect of benzodiazepines or Z-drugs on dementia incidence.

Keywords: benzodiazepines, bias (epidemiology), case-control studies, dementia, risk

Dementia prevention is a public health priority. More than 152 million people are expected to be living with dementia by 2050, which is recognised as a leading cause of disability, and is the fifth most important cause of death with a global economic cost of US$1trillion (1, 2). There is no curative or disease modifying treatment for dementia, increasing the importance of identifying its risk factors (3). Several studies have suggested that long-term benzodiazepines use could increase dementia risk (4). If true this is an important opportunity to prevent dementia, as 9% of older US adults currently use benzodiazepines, with 31% of these being long-term users (5, 6).

Benzodiazepines including diazepam (Valium), alprazolam (Xanax) and others are the most commonly prescribed sedatives, and are typically used for insomnia or anxiety. Despite years of guidance advising against long-term benzodiazepine use owing to side effects, addiction and tolerance (7), there has been no decline in their use in the past decade in the US (8-10), while a small decline in the UK has been accompanied by greater use of benzodiazepine-related drugs including zopiclone, eszopiclone (e.g. Lunesta [Sunovion Pharmaceuticals Inc. Marlborough, MA]), zolpidem (e.g. Ambien [Sanofi-Aventis U.S. LLC, Bridgewater, NJ]), and zaleplon (e.g. Sonata [Wyeth Pharmaceuticals Inc., Philadelphia, PA]), collectively known as Z-drugs (11).

Benzodiazepines and Z-drugs have dose-related effects on memory and other aspects of cognitive function (12, 13). However, no biological mechanism has been demonstrated to underlie any link to dementia incidence. While studies using insurance records and epidemiologic cohort studies have suggested increased risks of dementia with long-term benzodiazepine use (14-16), other recent studies have suggested no association (17, 18).

These conflicting results may reflect genuine differences across populations, or different study designs, availability and use of covariate data, or analysis parameters such as minimum time-lag between exposure and outcomes (19, 20).

As it is not practical or ethical to randomize patients to benzodiazepine treatment to estimate harms, observational studies are central to addressing this important question. Individual patient level datasets now exist that include detailed histories of benzodiazepine use going back years or decades, details of diagnoses and treatment for cognitive disorders and records of many possible confounding variables for this relationship. However, several factors complicate any analysis. Benzodiazepines are often initiated before records for a patient begin, precluding the use of the 'new-user' design (21). This is particularly true for those with very long-term use, who may be most at risk (22). Second, the main indications for benzodiazepines, anxiety and sleep disturbance, are both risk factors for and prodromal symptoms of neurodegenerative disease that may occur many years before dementia diagnosis, necessitating a lag period to avoid protopathic bias (4). Furthermore, dates associated with diagnoses in electronic health records may reflect the time of the underlying event. Together these make the theoretical identification of confounding from mediating or colliding variables, as is often suggested (23, 24), difficult. This is important as valid causal inference relies on the correct identification and control for confounders (variables that are common causes of both the exposure and the outcome), but conditioning on mediators (variables on the causal pathway from exposure to outcome) or on colliders (common consequences of the exposure and the outcome) will introduce bias rather than reduce it (25).

Case-control studies, where exposures within an 'exposure period' are compared between cases of a disease and matched controls, are often used for estimating the associations between multiple complex exposures and a single outcome. Case-control studies are

particularly used when tackling rare adverse events, or those that may only become apparent after long-term exposures. However, selection based on outcome rather than exposure status further complicates the ascertainment of confounders. Clearly it is optimal to measure potential confounders at treatment initiation (20), but because cases and controls are not matched on exposure, the presence of treatment or time of treatment initiation will vary within a matched set. Hence it is difficult to know when to optimally ascertain and encode covariates. Measuring covariates recorded only up to the start of an exposure window (possibly years before exposure) risks missing confounders and omitted variable bias, while including covariates recorded during or after the exposure window (hence after the exposure) risks under-estimation through unintended adjustment for mediators or colliders (26).

We conducted a case-control study nested within an electronic health record dataset as part of a wider project estimating the associations of drug use on dementia incidence (27), and have explored several of these issues. We present estimates for the association between benzodiazepine and Z-drug prescription and dementia incidence, and explore how these depend on (a) the inclusion or exclusion of prevalent users, (b) the timing of covariate ascertainment, and (c) the minimum lag between treatment and dementia incidence. Finally, we explore the role of specific covariates, and implications for the conduct and interpretation of future similar studies.

METHODS

The study has been approved by the Independent Scientific Advisory Committee for the Clinical Practice Research Datalink (CPRD) research (protocol number 15_056R) and was

registered on the ENCePP e-register of studies (register number EUPAS8705). This manuscript has been prepared according to the REporting of studies Conducted using Observational Routinely-collected Data guidelines (28). Code lists for the outcome and covariates are available on request.

Study population and data

CPRD consists of anonymised electronic health records of 17 million patients from 719 general practices, and is representative of age, sex and ethnicity of the UK population (29). Available data include basic demographics and coded details of consultations, diagnoses, reported symptoms, drug prescriptions, referrals to specialist services, and laboratory test results.

Selection of cases and controls

All cases of dementia recorded in CPRD were indexed at the first mention of dementia as a diagnosis or symptom (see Web Table 1 for complete Read code list) or the first prescription of a dementia drug (memantine, donepezil, rivastigmine, galantamine, or tacrine) if it was followed by a dementia diagnosis code within twelve months.

Cases were included in the current study if their index date occurred between April 2006 and July 2015 and the patient was aged between 65 and 99 years on that date. Cases were excluded if the date of diagnosis was unknown, they had less than 6 years of 'Up-To-Standard' data history before the index date, or had any record of motor neuron disease, human immunodeficiency virus infection, acquired immune deficiency syndrome, multiple sclerosis, Down syndrome, or alcohol abuse.

For each case up to seven controls without dementia at the index date were randomly selected and matched on sex, year of birth (within 3 years), years of available Up-To-Standard data history, and index of multiple deprivation quintile. The index of multiple deprivation is a weighted sum of indicators of housing, employment, income, education, living environment and crime for each neighbourhood (30). We used incidence density sampling to select controls, hence cases could also be selected as controls up to the date of meeting case criteria.

Exposure assessment

We defined a drug exposure period (DEP) for each case/control group as the period starting after 1 year of Up-To-Standard data recorded, and at most 20 years before the index date, and ending four years before the index date (Web Figure 1) (31). This four year lag serves to reduce the risk of protopathic bias, as the use of benzodiazepines in this period may be a marker of undiagnosed dementia (32).

For all patients, we obtained details of all drugs prescribed before the index date. Our primary exposures were the number of defined daily doses (DDDs) prescribed for benzodiazepines (World Health Organisation Anatomical Therapeutic Chemical [ATC] category N05BA, N05CD, or N03AE) and benzodiazepine related drugs (Z-drugs; ATC N05CF) during the DEP. The DDD is the assumed average maintenance dose per day for a drug based on its main indication in adults; we used the DDD values assigned by the World Health Organisation's Collaborating Centre for Drug Statistics Methodology.

We defined 'new users' of benzodiazepines as those prescribed benzodiazepines during the DEP but with no benzodiazepine prescriptions in the 12 months before the DEP, and 'prevalent' benzodiazepine users as those prescribed benzodiazepines within both the DEP

and the 12 months prior (Web Figure 1). New and prevalent users of Z-drugs were defined similarly.

Covariates

Potential confounders were identified as any known or suspected risk factors for dementia (3, 33) or predictors of benzodiazepine initiation (34, 35). Each covariate was ascertained first using only the patient record up to the start of the DEP and second using the patient record up the end of the DEP.

The following covariates were measured as binary variables reflecting any history of a diagnosis: diabetes, diabetes complications, hyperlipidemia/dyslipidaemia, hypertension, stroke/transient ischaemic attack, congestive heart disease, heart failure, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, coronary artery operations, deep vein thrombosis, depression, urinary incontinence, Parkinson's disease, severe mental illness, drug abuse, epilepsy, anxiety, anxiety symptoms, insomnia, fatigue, other sleep problems, migraine, headache, back/neck pain, and neuropathic pain. Depression severity was measured as the maximum record in their history (mild, moderate, or severe), and depression duration defined as the years since first record of a depression diagnosis or symptom.

The following covariates were measured as recorded in the GP records in both the 12 months before the start and the end of the DEP: any fall, any fracture, number of consultations, any prescription for a selective serotonin reuptake inhibitor (ATC N06AB), tricyclic antidepressant (ATC N06AA), or an antipsychotic (ATC N05A). Smoking status (none, former, current), body mass index (<20, 20-24.9, 25-29.9, 30+ kg/m^2), and harmful alcohol

use (>49 units per week for men and >35 units per week for women) were measured according to latest record.

Statistical analyses

We used conditional logistic regression to estimate the association between categorised DDDs (0, >0-29, 30-364, 365-1459, or 1460+ DDDs) of benzodiazepines and Z-drugs and dementia incidence. Odds ratios (OR) and 95% confidence intervals were estimated unadjusted and then separately adjusted for birth year, practice region (Scotland, Northern Ireland, Wales and ten health regions of England), and the covariates listed above.

To test the impact of covariate ascertainment timing we estimated two sets of models, first including covariates measured at the start of the DEP, and second including covariates measured at the end of the DEP. We then estimated associations among new users and prevalent users compared to non-users in each case.

The impact of each covariate was measured by the change in log-odds ratio induced by adding that covariate to a model only including the exposure stratified into new and prevalent use (36). The impact of each covariate was compared when it was measured at the start or end of the DEP. Confidence intervals were calculated by non-parametric bootstrapping.

Finally, to test whether associations between new use and dementia incidence varied with the time between medication initiation and dementia incidence, we stratified ORs for any new prescription and total DDDs during the DEP by time of initiation in three periods: 15-20, 10-15, or 5-10 years prior to dementia (among those with at least 16, 11 and 6 years of Up-To-Standard data history respectively). For these analyses we adjusted for covariates at the later of the interval start date and the DEP start date.

Throughout, multiple imputation via chained equations was used to impute missing values of body mass index, harmful alcohol use and smoking (37) (see Web Appendix for details of imputation models). We used Stata version 14.2 for all statistical analysis. Statistical significance was determined using two-tailed tests, with a pre-specified threshold of $P<0.01$.

RESULTS

Of 66,136 cases of dementia recorded in CPRD between 2006 and 2015, 40,770 met inclusion criteria and were matched to 283,933 controls (Web Figure 2). The median (interquartile range) drug exposure period was 7.1 (4.0-11.3) years in duration; median age at index date was 83 (78-87) years and 63% were female (Table 1).

By definition, the proportion of patients with a history of each clinical condition increased over the DEP (Web Table 2). For example, up to the start of their DEP, 25,870 patients (8%) had a diagnosis of anxiety and 21,347 (7%) had insomnia. By the end of the DEP this had increased to 41,788 (13%) and 52,578 (16%) respectively. Cases were more likely than controls to have a history of cardiovascular disease and depression, and to visit their GP more frequently.

Among the cases, 8,010 (20%) were ever prescribed benzodiazepines and 3,130 (8%) were prescribed Z-drugs during their DEP, compared to 52,017 (18%) and 19,163 (7%) of the controls respectively. The five most common prescriptions were for Temazepam (32% of all benzodiazepine or Z-drug prescriptions), Zopiclone (19%), Diazepam (18%), Nitrazepam (14%), and Lorazepam (5%). See Web Table 3 for details of prescribing patterns.

Association between benzodiazepine prescriptions and dementia incidence

The unadjusted OR for dementia and any prescription of a benzodiazepine was 1.09 (95% confidence interval [CI]: 1.06, 1.12), but there was little suggestion of a dose-response relationship with the number of DDDs (Table 2). Adjusting for covariates measured at the start of the DEP, led to an inverse association between benzodiazepines and dementia (OR for ≥4 years of DDDs = 0.88, 95% CI: 0.82, 0.95). When adjusting for covariates measured at the end of the DEP the inverse association appeared stronger (OR=0.81 for any use, 95% CI: 0.75, 0.87).

New vs prevalent users of benzodiazepines

Of those prescribed benzodiazepines, 37,303 (62%) patients were new users during the DEP, while 22,724 (38%) were prevalent users (Table 2). New users had shorter average exposures to benzodiazepines during the DEP than prevalent users who represented most cases of 'chronic' use. Among new users there was little evidence for an association between benzodiazepines and dementia incidence when adjusted for covariates measured at the start of the DEP (hence adjusted for factors recorded before medication initiation; OR=1.03, 95% CI: 1.00, 1.07), but the negative association was still apparent among prevalent users (OR=0.91, 95% CI: 0.87-0.95), for whom the start of the DEP is after medication initiation. When adjusted for covariates measured at the end of the DEP, a negative association was seen for both new use (OR=0.91, 95% CI: 0.88-0.95) and prevalent use (OR=0.85, 95% CI: 0.81-0.89) of benzodiazepines.

Impact of each covariate

The number of physician consultations, anxiety, insomnia, depression, and antidepressant prescriptions each substantially modified the estimated association between benzodiazepine

use and dementia incidence when added to the conditional logistic regression models, while other factors did not (Web Figure 3 and Web Table 4). Covariates modified the association more when measured at the end of the DEP; patterns were similar for prevalent and incident use.

Proximity between exposure and outcome

New use of benzodiazepines was not significantly associated with an increased risk of dementia regardless of whether the first prescription was 5-10, 10-15 or 15-20 years prior to dementia (Table 3). Although estimates are imprecise, associations did appear to increase with closer proximity between exposure initiation and outcome.

Z-drug prescriptions and dementia

Of those prescribed Z-drugs, 18,704 (84%) patients were new users during the DEP, while 3,589 (16%) patients had received prescriptions during the DEP and additionally in the previous 12 months. There was a positive association between Z-drugs and dementia incidence without adjusting for covariates. No association was observed when adjusting for covariates measured at the start of the DEP, and evidence of a negative association was observed when adjusting for covariates measured after the DEP (Web Tables 5 and 6). The pattern of the impact of individual covariates was almost identical for Z-drugs and benzodiazepines, with depression, antidepressant use, physician consultations, anxiety and insomnia having the greatest impact on estimated associations (Web Figure 4 and Web Table 7). As with benzodiazepines, this impact was up to three or four times greater when covariates were measured at the end of the DEP compared to the start of the DEP, and was consistent for both prevalent and new users of Z-drugs.

DISCUSSION

Associations between benzodiazepine and Z-drug prescriptions and dementia incidence depend on the timing of covariate ascertainment and whether prevalent or only new use is considered. When covariates were only measured before exposure, associations were typically null or slightly positive. When covariates were included in the models that may have occurred before or after initiation of drug exposure, associations were typically negative. Taken together, our results suggest no causal link between benzodiazepines or Z-drug use and later dementia incidence, that any positive association is an artefact of either inadequate control of confounding factors or protopathic bias, and any negative association is the result of adjusting for colliders in regression models.

In every case, adjustment for depression, anxiety, antidepressant use, insomnia, fatigue, and number of recent physician visits had the most impact on our estimates. No other covariate substantially affected the relationships in any analysis. As well as being possible indications for benzodiazepines, depression, anxiety and sleep disturbance are known symptoms of dementia, and are suspected risk factors (3). Therefore, there are several equally plausible explanations for the observed relationships between these variables in our study. Figure 1 illustrates confounding, reverse causation, colliding and mediating relationships. Panels A and B show the importance of controlling for neuropsychiatric symptoms while panels C and D illustrate the danger in doing this, since the record of neuropsychiatric symptoms may act as a collider or a mediator. Note that in each case, neuropsychiatric symptoms might equally be recorded before or after the measured exposure and so these scenarios cannot be definitively distinguished theoretically or empirically.

Nevertheless, by varying the timing of covariate ascertainment compared to the timing to treatment initiation we can place reasonable bounds on causal associations by considering whether each analysis is more likely to under- or over-estimate it. For new users, the start of the DEP might be some time before treatment initiation, and so controlling for covariates measured up to this time risks residual confounding and over-estimating associations. Covariates measured at the end of the DEP may have occurred post-treatment and so including these risks under-estimation. For prevalent users, any measured covariate may have occurred post-treatment initiation hence under-estimation is more likely, while univariable analyses and those with short lag times are likely to lead to over-estimation.

The key strengths of our study include the detailed evaluation of the impact of varying study design parameters and use of an exposure period up to 20 years prior to diagnosis of dementia for a significant number of cases. Diagnosis of dementia in CPRD has been validated with a positive predictive value of 95% (2). The available data allowed us to carefully consider the roles of a wide range of potential covariates measured at different points. Measurement of exposure was based on prescription rather than use, but these are likely to be similar, particular for chronic users.

Substantively, our study updates and builds on the findings of Imfeld et al who reported no significant association with benzodiazepine or Z-drug use and risk of dementia (18), also based on a case-control study nested within CPRD although using a time period for case-ascertainment that began prior to financial incentives for the accurate recording of dementia diagnoses in UK primary care. Gray et al report a small association among low users that was not observed when the lag period was extended beyond two years, again suggesting no causal

link (17). A Swiss study also reported no association between benzodiazepine prescriptions and new dementia medication prescriptions, despite only allowing a two year lag period (38).

Study design choices might explain previously reported positive associations between benzodiazepine use and dementia. Two studies that did not apply any lag between exposure and outcome likely over-estimated the causal effect (14, 16). A study based on a Canadian insurance claims database reported a significant association with a dose-response relationship (15). Although they controlled for anxiety and sleep disturbance, they did not have any record of these indications for most users, suggesting that control of confounding factors was inadequate.

Inclusion of prevalent users in pharmacoepidemiologic studies is challenging. However, previous studies examining benzodiazepine use and dementia incidence report only slightly smaller associations with prevalent use compared to new use (14, 39).

In summary we find no evidence that benzodiazepine or Z-drug use is associated with risk of dementia. However, as benzodiazepines have known side-effects including falls and sedation and lead to tolerance (6), prescribers should to follow guidelines on avoiding or limiting their use.

Our study reinforces the challenges in estimating associations between long-term cumulative exposures and adverse events with long latent or prodromal periods, particularly where indications for the exposure are also prodromal symptoms of the outcome. Nevertheless, these remain important questions that observational studies provide almost the only opportunity to answer, and so these challenges must be addressed. Investigators should

carefully consider the causal framework for potential covariates, when measured at different time points and among prevalent and new users, and should be mindful that prodromal periods for neurodegenerative diseases could be extremely long. Given the inherent difficulty of measuring confounders and of separating confounding from mediating or colliding effects in these cases, observational studies should not necessarily aim to provide single unbiased effect estimates, but can provide robust upper or lower bounds on effect sizes, depending on study design, that should be considered alongside other forms of evidence using for example, a triangulation framework to narrow the range of plausibly true causal effects (40).

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Tables

Table 1. Sociodemographics and Data history of Dementia Cases and Controls in the United Kingdom, April 2006-July 2015

	Dementia Cases (n=40,770)		Controls (n=283,933)	
Characteristic	**No.**	**%**	**No.**	**%**
Women[a]	25,745	63.1	179,152	63.1
Age at index date, years[ab]	82.6 (6.8)		82.6 (6.8)	
Practice level Index of Multiple Deprivation quintile[a]				
1 (least deprived)	7,867	19.3	54,766	19.3
2	7,928	19.4	55,220	19.4
3	8,756	21.5	61,032	21.5
4	8,389	20.6	58,407	20.6
5 (most deprived)	7,830	19.2	54,508	19.2
Country				
England	30,615	75.1	223,468	78.7
Northern Ireland	1,508	3.7	8,720	3.1
Scotland	5,024	12.3	25,793	9.1
Wales	3,623	8.9	25,952	9.1
Drug exposure period length[ac], years	7.1 (4.0-11.3)		7.1 (4.0-11.3)	

[a] Matching variables

[b] Values are expressed as mean (standard deviation)

[c] Values are expressed as median (interquartile range)

Table 2. Association Between Benzodiazepine Prescriptions and Dementia, by Defined Daily Doses, New or Prevalent use, and when Covariates are Measured, in a Nested Case-Control Study in the UK, December 1988-July 2015

Number of Benzodiazepine	No. of	No. of	Unadjusted		Measured at Start of DEP		Measured at End of DEP	
DDDs During DEP	Cases	Controls	OR	95% CI	aOR[a]	95% CI	aOR[a]	95% CI
All Users								
Any benzodiazepine prescription	8010	52017	1.09 [b]	1.06, 1.12	0.99	0.96, 1.02	0.89 [b]	0.86, 0.92
DDDs during DEP								
0	32760	231916	1.00	Referent	1.00	Referent	1.00	Referent
0.1-29	3949	25390	1.10 [b]	1.07, 1.14	1.02	0.99, 1.06	0.92 [b]	0.89, 0.96
30-364	1998	12516	1.13[b]	1.08, 1.19	1.01	0.96, 1.06	0.88 [b]	0.84, 0.93
365-1459	1143	7775	1.04	0.98, 1.11	0.92	0.86, 0.98	0.84 [b]	0.78, 0.89
≥1460	920	6336	1.03	0.96, 1.11	0.88[b]	0.82, 0.95	0.81 [b]	0.75, 0.87
Users Stratified by New and Prevalent Use								
Any benzodiazepine prescription during DEP								
0	32760	231916	1.00	Referent	1.00	Referent	1.00	Referent
Any prescription by new users	5058	32245	1.11 [b]	1.08, 1.15	1.03	1.00, 1.07	0.91 [b]	0.88, 0.95
Any prescription by prevalent users	2952	19772	1.06 [b]	1.02, 1.10	0.91 [b]	0.87, 0.95	0.85 [b]	0.81, 0.89
DDDs during DEP								
None	32760	231916	1.00	Referent	1.00	Referent	1.00	Referent
Within New Users								
0.1-29	3568	23103	1.10 [b]	1.06, 1.14	1.02	0.99, 1.07	0.92 [b]	0.89, 0.96
30-364	1135	6987	1.15 [b]	1.08, 1.23	1.05	0.98, 1.12	0.88 [b]	0.82, 0.94
365-1459	269	1567	1.22 [b]	1.07, 1.39	1.10	0.96, 1.25	0.94	0.82, 1.07
≥1460	86	588	1.04	0.83, 1.30	0.96	0.76, 1.20	0.84	0.67, 1.05
Within Prevalent Users								
0.1-29	381	2287	1.18*	1.06, 1.32	1.00	0.89, 1.12	0.93	0.83, 1.04
30-364	863	5529	1.10 [b]	1.03, 1.19	0.97	0.90, 1.04	0.89 [b]	0.83, 0.96
365-1459	874	6208	1.00	0.93, 1.07	0.87 [b]	0.81, 0.94	0.81 [b]	0.75, 0.87
≥1460	834	5748	1.03	0.96, 1.11	0.87 [b]	0.81, 0.94	0.81 [b]	0.75, 0.87

Abbreviations: DDD, defined daily doses; DEP, drug exposure period; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval

[a] Adjusted for: all variables in Table 1 and Web Table 2

[b] $p < 0.01$

Table 3. Association Between New Benzodiazepine Prescriptions and Dementia, According to When the New Prescription was Issued, in a Nested Case-Control Study in the UK, December 1988-July 2015

Number of	No. of	No. of	Unadjusted		Adjusted for Covariates Measured at Start of DEP	
DDDs	Cases	Controls	OR	95% CI	aOR[a]	95% CI
New Use Initiated 15-20 Years Prior[b]						
Benzodiazepine prescription						
No	7747	43261	1.00	Referent	1.00	Referent
Yes	560	2916	1.06	0.97, 1.17	0.98	0.89, 1.08
DDDs during DEP						
0	7747	43261	1.00	Referent	1.00	Referent
0.1-29	283	1646	0.96	0.84, 1.09	0.90	0.79, 1.02
30-364	201	863	1.27[c]	1.09, 1.49	1.16	0.99, 1.36
365-1459	43	232	1.02	0.74, 1.42	0.91	0.65, 1.27
≥1460	33	175	1.02	0.70, 1.48	0.97	0.66, 1.41
New Use Initiated 10-15 Years Prior[d]						
Benzodiazepine prescription						
No	18097	105328	1.00	Referent	1.00	Referent
Yes	1316	6741	1.12[c]	1.05, 1.19	1.01	0.95, 1.08
DDDs during DEP						
0	18097	105328	1.00	Referent	1.00	Referent
0.1-29	849	4304	1.14[c]	1.05, 1.22	1.03	0.95, 1.11
30-364	322	1756	1.05	0.93, 1.18	0.93	0.82, 1.05
365-1459	107	464	1.32	1.06, 1.63	1.17	0.95, 1.45
≥1460	38	217	0.99	0.70, 1.40	0.92	0.65, 1.30
New Use Initiated 5-10 Years Prior[e]						
Benzodiazepine prescription						
No	31471	191614	1.00	Referent	1.00	Referent
Yes	2564	13636	1.14[c]	1.09, 1.19	1.03	0.99, 1.08
DDDs during DEP						
0	31471	191614	1.00	Referent	1.00	Referent
0.1-29	1904	10289	1.12[c]	1.07, 1.18	1.03	0.98, 1.08
30-364	528	2707	1.18[c]	1.08, 1.30	1.04	0.94, 1.14
365-1459	117	568	1.23	1.01, 1.50	1.08	0.88, 1.32
≥1460	15	72	1.26	0.72, 2.20	1.16	0.66, 2.02

Abbreviations: DDD, defined daily doses; DEP, drug exposure period; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval

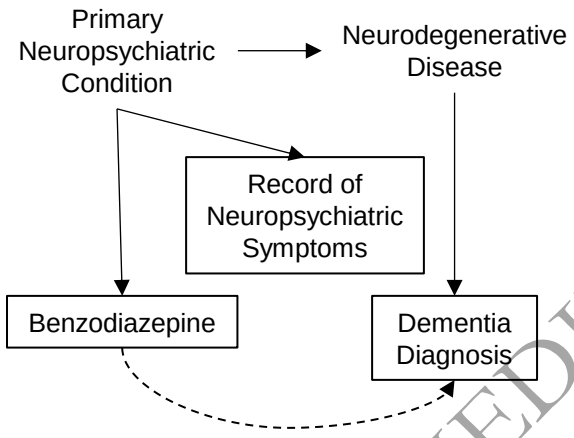
[a] Adjusted for all variables in Table 1 and Web Table 2
[b] Including patients with ≥16 years of Up-To-Standard data history before the index date
[c] $p < 0.01$

[d] Including patients with ≥11 years of Up-To-Standard data history before the index date. Start of period defined by the later of the start of the DEP and 15 years prior to the index date.
[e] Including patients with ≥6 years of Up-To-Standard data history before the index date. Start of period defined by the later of the start of the DEP and 10 years prior to the index date

Figure legend

Figure 1. Directed acyclic graphs in a nested case-control study in the UK, December 1988-July 2015, illustrating theoretically plausible relationships between psychiatric conditions, benzodiazepine prescription (exposure), neurodegenerative disease, and the record of psychiatric symptoms (measured covariate that might be caused by a primary neuropsychiatric condition or a latent neurodegenerative disease) and dementia diagnosis (outcome). Solid outlines indicate observed variables. Dashed lines indicate false associations induced by omitted variable bias (panel A representing confounding by indication and panel B representing reverse causation) or adjusting for a collider (panel C). Panel D shows that in the case of a genuine relationship between benzodiazepines and dementia, 'record of neuropsychiatric symptoms' following treatment initiation may reflect a mediator of the relationship.

A)



C)

D)