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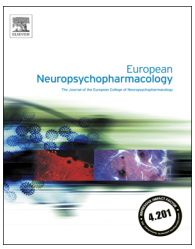

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Benzodiazepines and risk of death: Results from two large cohort studies in France and UK

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Abstract
Benzodiazepines are widely prescribed for the treatment of anxiety or insomnia, but their impact on mortality is still debated. This study investigated the impact of benzodiazepine use on short term mortality. Exposed-unexposed cohorts were constructed with the Clinical Practice Research Datalink (CPRD) in the UK and with the General Sample of Beneficiaries (EGB) in France. Benzodiazepine incident users were matched to incident users of antidepressants/non-benzodiazepine sedatives and to controls (non-users of antidepressants or anxiolytics/hypnotics) according to age and gender in both sources (and practice for the CPRD only). Survival at one year was studied using Cox regression model. In the CPRD, the final population comprised 94 123 patients per group (57 287 in the EGB). In the CPRD, adjusted HR was 3.73 in benzodiazepine users (95% CI, 3.43–4.06), and 1.61 (1.47–1.76) in antidepressant/non-benzodiazepine users compared to controls. When considering benzodiazepine use as a time-dependent covariate, adjusted HR for current use at 12 months was 1.70 (1.36–2.12). In the EGB, adjusted HR was 1.26 in benzodiazepine users (95% CI, 1.08–1.48), and 1.07 (95% CI, 0.91–1.27) in antidepressant/non-benzodiazepine users. When considering benzodiazepine use as a time-dependent covariate, adjusted HR for current use at 12 months was 1.03 (0.74–1.44). Using two nationally representative databases, we found a significant while moderate increase in all-cause mortality in relation to benzodiazepines, in a population of incident and mostly occasional users. This issue need to be monitored given the extensive use of these drugs.

1. Introduction

Several studies have investigated mortality related to benzodiazepine (BZD) use. Recently, two population-based cohort studies found a significant effect on all-cause mortality (Kripke

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et al., 2012; Weich et al., 2014), mainly in relation to chronic use. However, residual confounding cannot be ruled out in this area, because of the underlying motivations of benzodiazepine prescribing (intensity of psychiatric disorders, comorbidities). Psychiatric and clinical comorbidities are known confounders when studying this association (Kripke et al., 2012; Weich et al., 2014). As highlighted by Hausken et al., lifestyle and socioeconomic should also be taken into account (Hausken et al., 2007). Moreover, the underlying pharmacodynamic mechanisms explaining risk of death are likely to be related to respiratory and vigilance problems (falls, car crashes, accidents, respiratory depression), and would be in favour of a short-term effect. Literature reviews (Charlson et al., 2009; Amarasuriya et al., 2012) remained inconclusive. Several studies suggest an increased risk of death in specific populations (respiratory or renal disease (Winkelmayer et al., 2007; Obiora et al., 2013), schizophrenic patients (Tiihonen et al., 2012), patients with substance abuse disorders (McCowan et al., 2009) and the elderly (Huybrechts et al., 2011; Jaussent et al., 2013)). In healthcare settings, knowledge of these benzodiazepine-related risks led to specific measures of surveillance, as illustrated by a study on the effect of benzodiazepines use on respiratory outcomes (including death) in older adults with chronic obstructive pulmonary disease (Vozoris et al., 2014). All-cause mortality was found to be lower in users versus non users of benzodiazepines, although benzodiazepines were associated with all other adverse respiratory outcomes.

Thus, it is not clear how BZD impact the risk of death, most of the studies in the general population focusing on the long-term risk. Considering the pharmacodynamics properties of BZD on psychomotor performances, vigilance and respiratory system, we aimed to explore the impact of benzodiazepine on short-term (1 year) mortality. For this purpose, we conducted cohort studies using two nationally representative databases from 2 countries with high level of benzodiazepines use: the Clinical Practice Research Datalink (CPRD) in the UK and the *Echantillon Généraliste de Bénéficiaires* (General Sample of Beneficiaries, EGB) database (a representative sample of French beneficiaries of the national health insurance scheme).

2. Experimental procedures

2.1. Settings and population

The Clinical Practice Research Datalink (CPRD), previously the General Practice Research Database (GPRD) (Walley and Mantgani, 1997; Garcia Rodriguez and Perez Gutthann, 1998; Wood and Martinez, 2004), is a research database containing data of over 10 million patients from around 500 participating general practices in UK, corresponding to nearly 1500 general practitioners. It covers approximately 8% of the UK population. The information is recorded by General Practitioners (GP) as part of their usual medical practice. The source dataset (CPRD GOLD) comprises records of medical diagnoses, referrals to specialists and secondary care settings, prescriptions issued in primary care, diagnostic testing, lifestyle information, and other information as part of routine general practitioners practice. The CPRD has been widely used for research purposes (Charlton et al., 2008; Delaney et al., 2008; Devine et al., 2008).

The EGB is a permanent 1/97th representative sample of around 660,000 beneficiaries affiliated to the French health insurance system, selected from the SNIIRAM *(Systeme National Inter Régimes de l'Assurance Maladie*). The EGB has already been used for pharmacoepidemiologic research (Blin et al., 2012; Dupouy et al., 2013; Gallini et al., 2013). It includes salaried workers, agricultural workers and farmers, self-employed individuals, retired persons and patients with universal coverage (low income beneficiaries) (Tuppin et al., 2010).

The EGB includes longitudinal records of all reimbursed healthcare expenses, including consultations in primary and secondary care settings, dispensing data for all reimbursed medications (primary and secondary care) and diagnostic testing performed. The EGB does not contain medical data or laboratory results, but major chronic diseases can be identified using International Classification of Diseases (ICD), 10th Revision codes. The EGB contains basic demographic data (age, gender, area of residence) but does not record lifestyle data. This database has been linked with another large-scale information system containing data relating to hospital stays, including entry and discharge dates, procedures and diagnoses according to ICD-10 (Tuppin et al., 2010).

2.2. Patients

To ensure comparability between the UK and French cohorts while taking account of differences in the database contents and classification systems, the following eligibility criteria were used. Patients of either gender aged at least 18 years old were included. In the CPRD, patients were identified from 01/01/1999 to 10/01/2012 (study period), corresponding to the end of the Office of National Statistics (ONS) mortality data collection period at the time of extraction. Eligible patients were those whose practice participated in the linkage scheme, who were eligible for linkage to ONS mortality data and who had at least one year of up to standard follow-up during the study period. In the EGB, beneficiaries of main health insurance scheme (*Régime Général des Travailleurs Salariés*) were identified from 01/01/2006 to 31/12/2012. To be eligible, patients in both data sources had to have been registered in the database for at least one year.

Benzodiazepine incident users were those who had at least one prescribing (in the CPRD) or dispensing event (in the EGB) for the benzodiazepine anxiolytics/hypnotics of interest (Anatomical Therapeutic Chemical (ATC) codes N05BA, N05CD-CF). Similarly, a cohort of antidepressant/non-benzodiazepine incident users was made up of patients receiving at least one antidepressant (N06A) or one non-benzodiazepine anxiolytic or hypnotic drug (other N05B/C). This control cohort of antidepressant/non-benzodiazepine users was intended to reduce indication bias in further comparisons, as already suggested (Charlson et al., 2009). Although antidepressants have different therapeutic indications than BZD, the resulting cohort was expected to be closer in terms of baseline characteristics than a cohort of BZD never users.

The first prescribing or dispensing event of the substance of interest in each group was taken as the index date. As this study was based on a new-user design (Johnson et al., 2013),

subjects who had been exposed to any benzodiazepine or non-benzodiazepine anxiolytic/hypnotic drugs, clonazepam or tetrazepam (2 benzodiazepines available in France and /or UK, but not indicated for anxiolytic/hypnotic purposes), or antidepressants in the 12 months preceding the index date were excluded.

A control group was made up of subjects with a first outpatient GP consultation (index date) after a period of at least 12 months with no recorded GP consultation and no recorded prescription/dispensing for any benzodiazepine or non-benzodiazepine anxiolytic/hypnotic drugs, clonazepam or tetrazepam, or antidepressants. Each benzodiazepine user was matched to one participant in each cohort (1:1:1) on age ($\pm$ 5 years) and gender in both sources (and general practitioner practice for the CPRD only), using risk set sampling.

2.3. Exposure and outcome

The Anatomical Therapeutic Chemical (ATC) and defined daily dose (DDD) system was used to classify and quantify drug exposure (WHO, 2015). Duration of exposure to benzodiazepines was defined as the period between the first and the last prescribing (CPRD) or dispensing (EGB) event, plus the number of days of treatment based on the last dispensing event (derived from DDD, one Defined Daily Dose being considered as one day). Treatment discontinuation was defined as a minimum gap of 35 days between two prescribing or dispensing records. Sensitivity analyses were conducted for gaps of 60 days, 90 days and 120 days.

Other drugs of interest, identified through their ATC codes, were neuroleptic drugs (N05A), antidepressants (N06A) and non-benzodiazepine sedatives (excluding N05BA, N05CD-CF), antiepileptics (N03A excluding clonazepam), drugs used in alcohol dependence (N07BB), and drugs used in opioid dependence (N07BC).

The main outcome was death at one year, all causes included. In the CPRD, date of death and cause of death (ICD 9-10 coded) were available through linkage with the complete central mortality data of the ONS. In the EGB, date of death was provided by the National Institute of Statistics and Economic Research (INSEE), but cause is not recorded (Tuppin et al., 2010).

2.4. Confounders

Covariates referring to patient sociodemographics, lifestyle and the co-morbidities given below were also collected. Availability of covariates differed according to the data sources. Basic patient demographics, including age and gender were recorded in both datasets, with marital status being recorded in the CPRD only. In the CPRD, smoking and drinking status was ascertained from the closest record before the index date. Patients were categorised as current users, past users, and non-users. The body mass index (closest record to the index date) was categorised according to the World Health Organization Classification as underweight (body mass index $<$18.5), normal (18.5-24.9), overweight (25-29.9) or obese ($\geq$ 30).

Two measures of material deprivation were employed as a proxy of personal socioeconomic status: the Index of Multiple Deprivation (IMD 2007) in the CPRD (Payne and Abel, 2012) and the last available deprivation index (FDEp 2008 version (Rey et al., 2009; Rey et al., 2009; Ghosn et al., 2013) in the EGB. Both indices were computed as quintiles, ranging from the least deprived to the most deprived.

To build medical and psychiatric covariates at baseline, including the Charlson comorbidity index, we used information from hospital stays, as well as clinical and medical administrative information identified in the 12 months before the index date. In both data sources, diagnoses from hospital stays were available as ICD-9 or ICD-10 codes. Clinical medical administrative records used Read codes in the CPRD, and ICD-10 codes for long-term conditions in the EGB.

Medical conditions (cancer, epilepsy, cardiac, renal, or respiratory disorders) were derived from clinical or medical records or hospital diagnoses. They were mapped on the subcategories of the Charlson score, and were based on Read codes for the CPRD (Khan et al., 2010), and on a ICD-10 codes in the EGB (Quan et al., 2005). Similarly, psychiatric conditions (categorized as addiction, dementia, depression, neurosis, other mood disorders, personality disorders, schizophrenic disorders) were ascertained using the presence of at least one of the selected codes in either clinical or medical administrative records or hospital diagnoses in the 12 months before index date.

2.5. Statistical analysis

The baseline characteristics of the study population were analysed. In the CPRD, patients were censored at the earliest of (i) date of transfer out of the general practitioner practice, (ii) end of follow-up in a practice, (iii) last collection date for linkage data, (iv) end of ONS mortality data collection period (10/01/2012), defined as the end of the study period. In the EGB, patients were censored at the earliest of (i) date of transfer out of the EGB database, (ii) end of the study period (31/12/2012). Patients from the control and antidepressant/non-benzodiazepine groups receiving a benzodiazepine were censored at the date of first prescribing.

Survival was studied using the Cox proportional hazard regression model with time-dependent covariates, with stratification on matched pairs. Univariate analyses were first performed to select the variables with a P value $<$0.20, separately for each data source, followed by a multivariate approach (backward selection).

The following variables were considered as fixed covariates: number of general practitioner consultations (0, 1-2, 3-9, $>$10), number of different active substances (0, 1-4, 5-9, $>$10), Charlson score (0, 1-2, 3); medical conditions (cancer, epilepsy, or cardiac, renal, or respiratory disorders), presence of any hospital record (yes/no), psychiatric conditions (addiction, dementia, depression, neurosis, other mood disorders, personality disorders, schizophrenic disorders), use of other drugs of interest (antiepileptics, drugs used in alcohol dependence, antipsychotics, or drugs used in opioid

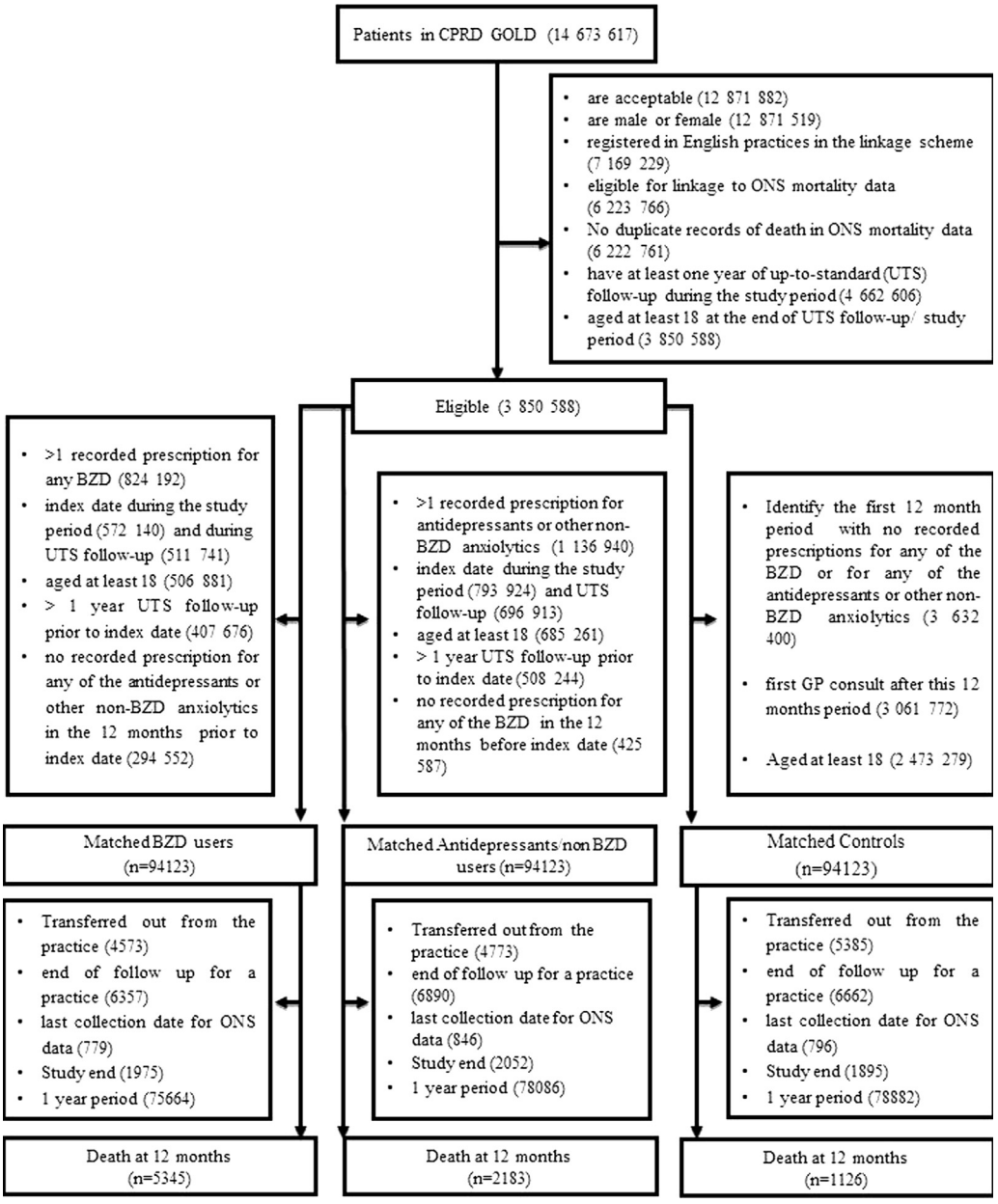

Fig. 1 Participant flow chart in the CPRD.

dependence). All these variables were derived from records in the year before index date. Covariates specifically available from the CPRD comprised marital status (single, married or remarried, widowed, not known) and lifestyle data (alcohol consumption or smoking: current and past user vs. non-user, and body mass index). Exposure to clonazepam or tetrazepam was entered as a time-dependent covariate. Missing data were included as a "missing" modality (i.e. without imputation).

The first analysis was based on a comparison between cohorts, with controls as the reference group. The effect of benzodiazepine use as a time-varying variable was examined separately.

Relevant interactions between covariates were checked. Proportional hazards assumption was tested for all covariates using interaction with time. The crude and adjusted hazard ratios and their 95% confidence intervals were estimated. Statistical analyses were performed using SAS 9.3® (SAS® Institute Inc, Cary NC, USA).

2.6. Ethical approval

This study received the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Study Seal on April 8, 2013.

2.6.1. Clinical practice research datalink data

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) Database Research.

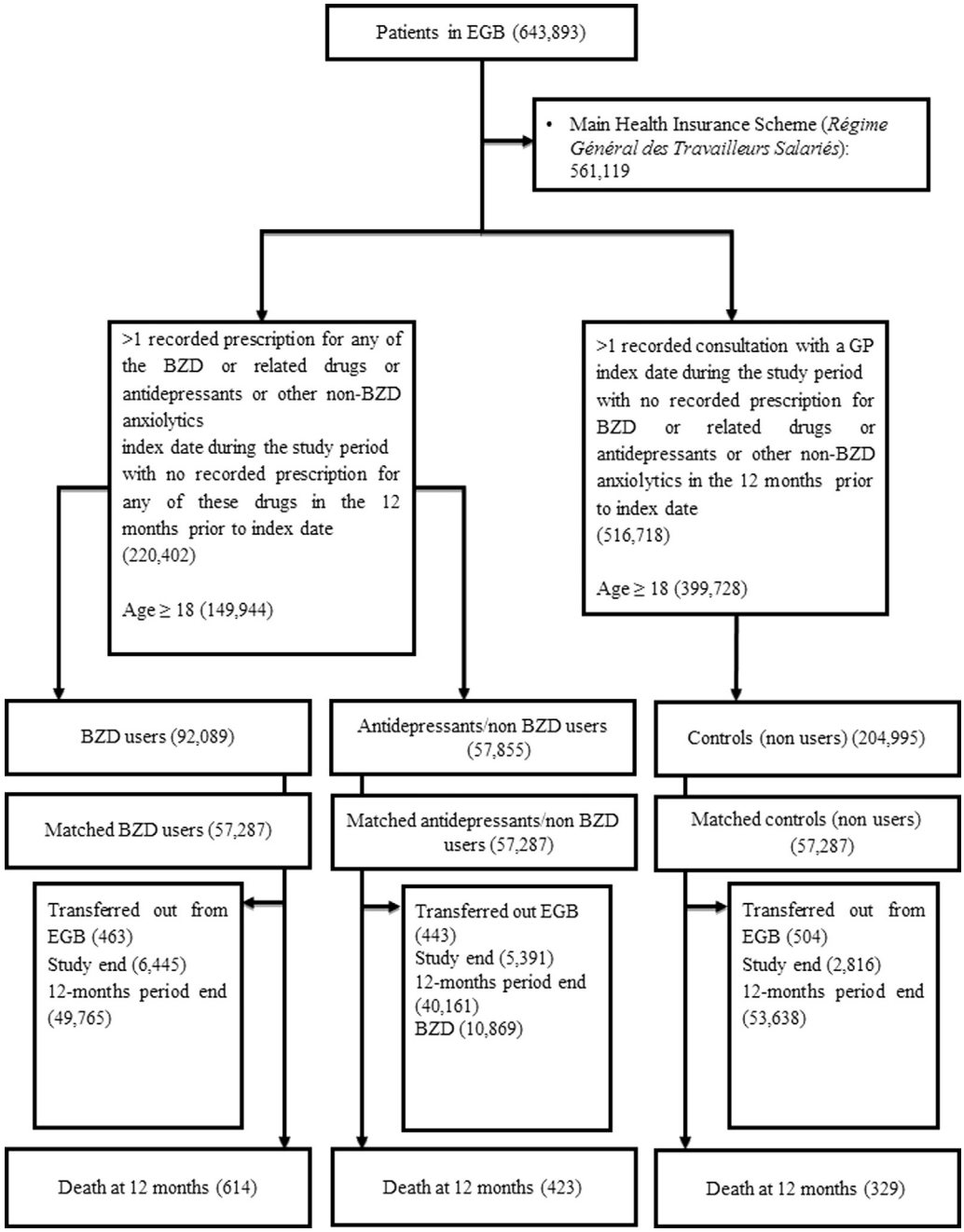

Fig. 2 Participant flow chart in the EGB.

2.6.2. General sample of beneficiaries data

We performed an observational study on anonymous data. Under French law, this does not require approval by a regulatory structure or an ethics committee. The use of the General Sample of Beneficiaries by research teams is therefore authorized by law and does not require the submission of a request to the national data protection commissions (the French Data Protection Authority (CNIL) and Advisory Committee for Data Processing in Health Research (CCTIRS)). The study synopsis including source of funding was submitted to the French Institute of Health and Medical Research (INSERM), which approved the project.

3. Results

3.1. Patient characteristics: demographics and socioeconomic status

In the CPRD, a random sample of 100,000 patients was extracted from the eligible patients for the benzodiazepine group; 94,123 benzodiazepine users were matched with 94,123 patients in the antidepressant/non-benzodiazepine users group, and with 94,123 in the control group (a total of 282,369 patients) (Fig. 1). Of the 643,893 patients recorded in the EGB database at the time of extraction, 354,928 met the inclusion criteria (Fig. 2). After matching for age and

Table 1 Study participants' characteristics at baseline.

	Antidepressant/non-BZD users	Controls	BZD users	Overall	*P* value
	EGB				
	***N*=57,287**	***N*=57,287**	***N*=57,287**	***N*=171,861**	
Female	35,859 (62.6)	35,859 (62.6)	35,859 (62.6)	107,577 (62.6)	-
Age					
Mean (SD)	47.5 (18.3)	47.5 (18.3)	47.5 (18.3)	47.5 (18.3)	-
Min-max	18-103	18-103	18-103	18-103	
FDep2008 [a] (41,192 missing)					<.001
Q1	8277 (18.9)	9119 (21.4)	8843 (19.9)	26,234 (20.1)	
Q2	8684 (19.3)	8623 (20.2)	8726 (19.7)	26,033 (19.9)	
Q3	8747 (19.9)	8439 (19.8)	8975 (20.2)	26,161 (20.0)	
Q4	8929 (20.4)	8268 (19.4)	8780 (19.8)	25,977 (19.9)	
Q5	9151 (20.9)	8142 (19.1)	8971 (20.0)	26,264 (20.1)	
	CPRD				
	***N*=94,123**	***N*=94,123**	***N*=94,123**	***N*=282,369**	
Female	53,336 (56.7)	53,336 (56.7)	53,336 (56.7)	160,008 (56.7)	-
Age					
Mean (SD)	57.8 (18.6)	57.8 (18.6)	57.9 (18.6)	57.9 (18.6)	-
Min-max	20-113	20-112	19-112	19-113	
Marital status					<.001
Data not entered	73,827 (78.4)	73,451 (78.0)	73,478 (78.1)	220,756 (78.2)	
Single	4384 (4.7)	4503 (4.8)	4418 (4.7)	13,305 (4.7)	
Married or remarried	13,988 (14.9)	14,068 (14.9)	14,380 (15.3)	42,436 (15.0)	
Separated or divorced	1924 (2.0)	2101 (2.2)	1847 (2.0)	5872 (2.1)	
IMD [a]					<.001
Q1	22,524 (23.9)	23,547 (25.0)	22,811 (24.2)	68,882 (24.4)	
Q2	22,210 (23.6)	22,918 (24.3)	22,382 (23.8)	67,510 (23.9)	
Q3	18,773 (19.9)	18,794 (20.0)	18,599 (19.8)	56,166 (19.9)	
Q4	17,830 (18.9)	16,932 (18.0)	17,857 (19.0)	52,619 (18.6)	
Q5	12,282 (13.0)	11,331 (12.0)	12,010 (12.8)	35,623 (12.6)	
Drinking [b, c]					<.001
Data not entered	70,994 (75.4)	72,816 (77.4)	71,041 (75.5)	21,4851 (76.1)	
Non-drinker	12,685 (13.5)	12,839 (13.6)	12166 (12.9)	37,690 (13.3)	
Past drinker	1488 (1.6)	963 (1.0)	1325 (1.4)	3776 (1.3)	
Current drinker	8956 (9.5)	7505 (8.0)	9591 (10.2)	26,052 (9.2)	
Smoking [b, c]					<.001
Data not entered	6486 (6.9)	12,874(13.7)	6571 (7.0)	25,931 (9.2)	
Non smoker	46,077 (49.0)	48,599 (51.6)	45,054 (47.9)	13,9730 (49.5)	
Past smoker	19521 (20.7)	15,701 (16.7)	19,364 (20.6)	54,586 (19.3)	
Current smoker	22,039 (23.4)	16,949 (18.0)	23,134 (24.6)	62,122 (22.0)	
Body mass index [b, c]					<.001
Mean (SD)	26.8 (5.7)	26.3 (5.2)	26.6 (5.5)	26.6 (5.5)	
Min-max	11.0-85.1	10.0-88.8	10.9-89.8	10.0-89.8	
Data not entered	11,759 (12.5)	15,340 (16.3)	11,907 (12.7)	39,006 (13.8)	
Underweight	2234 (2.4)	1747 (1.9)	2121 (2.3)	6102 (2.2)	
Normal	32,576 (34.6)	33,750 (35.9)	33,101 (35.2)	99,427 (35.2)	
Overweight	27,998 (29.7)	27,362 (29.1)	28,573 (30.4)	83,933 (29.7)	
Obese	19,556 (20.8)	15,924 (16.9)	18,421 (19.6)	53,901 (19.1)	

ADP, antidepressants; BZD, benzodiazepine; SD, Standard deviation; Fdep, French indice of deprivation; IMD, index of multiple deprivation.

[a]Quintiles for the FDep2008 or IMD 2007, ranging from the least (Q1) to the most deprived (Q5).

[b]Drinking, smoking status and body mass index: not available within General Sample of Beneficiaries.

[c]Drinking, smoking status : most recent record before index date retained/ Body mass index: closest record to index date retained.

Table 2 Medical and psychiatric comorbidities at baseline.

	ADP/non-BZD users (*N*=94,123)	CPRD Controls (*N*=94,123)	BZD users (*N*=94,123)	Overall (*N*=282,369)	*P* value	ADP/non-BZD users (*N*=57, 287)	Controls (*N*=57, 287)	EGB BZD users (*N*=57, 287)	Overall (*N*=171,861)	*P* value
Number of consultations, *n* [a]					<.001					<.001
0	2695 (2.9)	14,684 (15.6)	3139 (3.3)	20,518 (7.3)		3213 (5.6)	13,536 (23.6)	4028 (7.0)	20,777 (12.1)	
1-2	6272 (6.7)	16,406 (17.4)	7269 (7.7)	29,947 (10.6)		8676 (15.1)	14,282 (24.9)	9716 (17.0)	32,674 (19.0)	
3-9	20,901 (22.2)	24,873 (26.4)	21,860 (23.2)	67,634 (24.0)		29,224 (51.0)	22,472 (39.2)	29,052 (50.7)	80,748 (47.0)	
>10	64,255 (68.3)	38,160 (40.5)	61,855 (65.7)	164,270 (58.2)		16,174 (28.2)	6997 (12.2)	14,491 (25.3)	37,662 (21.9)	
Substances received, *n* [b]					<.001					<.001
0	14,293 (15.2)	40,098 (42.6)	14,383 (15.3)	68,774 (24.4)		3833 (6.7)	12,676 (22.1)	4590 (8.0)	21,099 (12.3)	
1-4	42,180 (44.8)	36,568 (38.9)	42,061 (44.7)	120,809 (42.8)		9348 (16.3)	16,197 (28.3)	10,211 (17.8)	35,756 (20.8)	
5-9	23,152 (24.6)	12,268 (13.0)	22,845 (24.3)	58,265 (20.6)		15,369 (26.8)	14,386 (25.1)	15,594 (27.2)	45,349 (26.4)	
>10	14,498 (15.4)	5189 (5.5)	14,834 (15.8)	34,521 (12.2)		28,737 (50.2)	14,028 (24.5)	26,892 (46.9)	69,657 (40.5)	
Charlson score					<.001					<.001
0	84,290 (89.6)	88,540 (94.1)	83,183 (88.4)	256,013 (90.7)		51,712 (90.3)	53,785 (93.9)	51,797 (90.4)	157,294 (91.5)	
1-2	8979 (9.5)	5208 (5.5)	95,06 (10.1)	23,693 (8.4)		2354 (4.1)	1497 (2.6)	1981 (3.5)	5832 (3.4)	
>3	854 (0.9)	375 (0.4)	1434 (1.5)	2663 (0.9)		3221 (5.6)	2005 (3.5)	3509 (6.1)	8735 (5.1)	
Medical conditions										
Cancer	1057 (1.1)	404 (0.4)	3243 (3.4)	4704 (1.7)	<.001	2688 (4.7)	1689 (2.9)	3042 (5.3)	7419 (4.3)	<.001
Cardiac	655 (0.7)	360 (0.4)	906 (1.0)	1921 (0.7)	<.001	457 (0.8)	327 (0.6)	494 (0.9)	1278 (0.7)	<.001
Epilepsy	120 (0.1)	132 (0.1)	368 (0.4)	620 (0.2)	<.001	76 (0.1)	55 (0.1)	115 (0.2)	246 (0.1)	<.001
Renal	1037 (1.1)	691 (0.7)	1038 (1.1)	2766 (1.0)	<.001	121 (0.2)	80 (0.1)	125 (0.2)	326 (0.2)	<.001
Respiratory	2018 (2.1)	1509 (1.6)	2139 (2.3)	5666 (2.0)	<.001	381 (0.7)	181 (0.3)	277 (0.5)	839 (0.5)	<.001
Any hospital record [c]	9700 (10.3)	10,456 (11.1)	6186 (6.6)	26,342 (9.3)	<.001	7412 (12.9)	4042 (7.1)	7784 (13.6)	19238 (11.2)	<.001
Psychiatric conditions										
Addiction	354 (0.4)	91 (0.1)	640 (0.7)	1085 (0.4)	<.001	43 (0.1)	20 (0.0)	62 (0.1)	125 (0.1)	<.001
Dementia	338 (0.4)	172 (0.2)	429 (0.5)	939 (0.3)	<.001	497 (0.9)	264 (0.5)	282 (0.5)	1043 (0.6)	<.001
Depression	2417 (2.6)	104 (0.1)	482 (0.5)	3003 (1.1)	<.001	186 (0.3)	56 (0.1)	197 (0.3)	439 (0.3)	<.001
Neurosis	2839 (3.0)	292 (0.3)	1680 (1.8)	4811 (1.7)	<.001	58 (0.1)	20 (0.0)	48 (0.1)	126 (0.1)	<.001
Other mood disorders	53 (0.1)	23 (0.0)	86 (0.1)	162 (0.1)	<.001	57 (0.1)	34 (0.1)	70 (0.1)	161 (0.1)	<.001
Personality disorders	43 (0.0)	9 (0.0)	42 (0.0)	94 (0.0)	<.001	153 (0.3)	45 (0.1)	200 (0.3)	398 (0.2)	<.001
	46 (0.0)	43 (0.0)	74 (0.1)	163 (0.1)	<.005	248 (0.4)	124 (0.2)	352 (0.6)	724 (0.4)	<.001

Schizophrenic disorders										
Drug use in previous year										
Antiepileptics [d]	1957 (2.1)	970 (1.0)	2419 (2.6)	5346 (1.9)	<.001	2036 (3.6)	737 (1.3)	1688 (2.9)	4461 (2.6)	<.001
Drugs for alcohol dependence	25 (0.0)	6 (0.0)	47 (0.0)	78 (0.0)	<.001	114 (0.2)	22 (0.0)	113 (0.2)	249 (0.1)	<.001
Antipsychotics	1031 (1.1)	645 (0.7)	1968 (2.1)	3644 (1.3)	<.001	1085 (1.9)	503 (0.9)	1124 (2.0)	2712 (1.6)	<.001
Opiate substitutes	66 (0.1)	19 (0.0)	110 (0.1)	195 (0.1)	<.001	243 (0.4)	45 (0.1)	265 (0.5)	553 (0.3)	<.001

EGB, General Sample of Beneficiaries; CPRD, Clinical Practice Research Datalink; ADP, antidepressants; BZD, benzodiazepine.
[a]Number of medical consultations in the year preceding index date.
[b]Number of different active substances prescribed in the year preceding index date.
[c]Any hospital record in the year preceding index date.
[d]Anatomical Therapeutic Chemical (ATC) class N03 excluding clonazepam.

gender, the final population comprised 57,287 patients in each group (a total of 171,861). Mean (SD) duration of follow-up in the CPRD was 1583 days (1 219 days) and 1240 days (708 days) in the EGB. The patients' baseline characteristics are presented Table 1. Women accounted for 57% of the CPRD and 63% of the EGB study population. The CPRD study population was about 10 years older (mean, 57.9) than the EGB population (mean, 47.5 years). Benzodiazepine incident users and antidepressant/non-benzodiazepine incident users had more similar profiles of morbid conditions than controls (Table 2).

3.2. Drug exposure

Exposure to benzodiazepines in the CPRD was mainly represented by diazepam (56% of benzodiazepine users with at least one prescribing record, n=53 046), zopiclone (33%, n=31 129) and temazepam (19%, n=17 953). In the EGB, benzodiazepines were more diversified at inclusion, but more than half of the subjects were ever exposed over the study period to alprazolam (55%, n=31 719), bromazepam (52%, n=29 866) and zolpidem (51%, n=29 412), and 32% were exposed to zopiclone (n=18 193). There was a large part of occasional users in both databases: 62% with only one benzodiazepine dispensing record in the CPRD, and 45% in the EGB. Daily doses expressed in mg and in DDD are provided in Additional file 1.

3.3. Survival analysis

Causes of death, available only in the CPRD, are described in Table 3. Cancer, cardiovascular and respiratory diseases were the main causes of death, with more deaths due to cancer among benzodiazepine users (65% of all cancer deaths). Table 4 presents the results of univariate and multivariate analyses using the Cox proportional hazard model stratified on matched pairs, for the CPRD and the EGB cohorts, using both approaches of benzodiazepine exposure assessment and for all cause-mortality at 12 months.

During the first 12 months, 8654 deaths were recorded in the CPRD. As shown in Table 4, all-cause mortality was significantly higher among those exposed to benzodiazepines (crude HR, 5.67 (95% CI 5.30–6.07), adjusted HR 3.73 (3.43–4.06)) and in antidepressant/non-benzodiazepine users (crude HR, 2.00 (1.86–2.16), adjusted HR 1.61 (1.47–1.76)) compared with controls. Crude HR among benzodiazepines users from CPRD at 3 months was 11.12 (95% CI, 9.91–12.47), and 8.02 (95% CI, 7.35–8.75) at 6 months. When considering benzodiazepine use as a time-dependent covariate, HR for current use at 12 months was 3.42 (2.86–4.09), and 1.70 (1.36–2.12) after adjustment.

In the EGB study population, 1366 deaths were identified during the 12-month period. All-cause mortality was significantly higher among those exposed to benzodiazepines (crude HR, 1.99; (1.74–2.29); adjusted HR 1.26 (1.08–1.48)) and in antidepressant/non-benzodiazepine users (crude HR, 1.53 (1.32–1.77); adjusted HR 1.07 (0.91–1.27)), compared with controls. Crude HR among benzodiazepines users from EGB at 3 months was 2.17 (95% CI, 1.66–2.70), and 2.27 (95% CI, 1.88–2.73) at 6 months. When considering

Table 3 Cause of death in the Clinical Practice Research Datalink (Office for National Statistics mortality data).

	Cause description	ADP/non-BZD users (*N*=2183)	Controls (*N*=1126)	BZD users (*N*=5345)	Overall (*N*=8654)
	International classification of diseases, 10th revision chapter				
A00-B99	Certain infectious and parasitic diseases	22 (1.0)	9 (0.8)	21 (0.4)	52 (0.6)
C00-D48	Neoplasms	824 (37.7)	251 (22.3)	3471 (64.9)	4546 (52.5)
D50-D89	Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism	3 (0.1)	1 (0.1)	1 (0.0)	5 (0.1)
E00-E90	Endocrine, nutritional and metabolic diseases	32 (1.5)	22 (2.0)	53 (1.0)	107 (1.2)
F00-F99	Mental and behavioural disorders	48 (2.2)	60 (5.3)	106 (2.0)	214 (2.5)
G00-G99	Diseases of the nervous system	51 (2.3)	37 (3.3)	137 (2.6)	225 (2.6)
I00-I99	Diseases of the circulatory system	672 (30.8)	420 (37.3)	863 (16.1)	1955 (22.6)
J00-J99	Diseases of the respiratory system	283 (13.0)	171 (15.2)	368 (6.9)	822 (9.5)
K00-K93	Diseases of the digestive system	92 (4.2)	65 (5.8)	117 (2.2)	274 (3.2)
L00-L99	Diseases of the skin and subcutaneous tissue	8 (0.4)	2 (0.2)	6 (0.1)	16 (0.2)
M00-M99	Diseases of the musculoskeletal system and connective tissue	18 (0.8)	8 (0.7)	6 (0.1)	32 (0.4)
N00-N99	Diseases of the genitourinary system	43 (2.0)	19 (1.7)	55 (1.0)	117 (1.4)
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities	0 (0.0)	3 (0.3)	10 (0.2)	13 (0.2)
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings	38 (1.7)	26 (2.3)	51 (1.0)	115 (1.3)
S00-T98	Injury, poisoning and certain other consequences of external causes	1 (0.0)	1 (0.1)	4 (0.1)	6 (0.1)
_	Other causes [a]	48 (2.2)	31 (2.8)	76 (1.4)	155 (1.8)

ADP, antidepressants; BZD, benzodiazepine.
All causes: A00-Z99 (excluding V, W, X and Y codes)/ 001-V82 (excluding E800-E999).
[a]Other causes are cause classified V, W, X and Y (ICD10) or E800-E999 (ICD9).

benzodiazepine use as a time-dependent covariate, crude HR for current use at 12 months was 1.37 (1.02–1.84), and 1.03 after adjustment 0.74–1.44.

4. Discussion

This study on two large healthcare databases in the UK and France confirmed the association between benzodiazepines and all-cause mortality at 12 months. Mortality risk was moderately increased among new users of benzodiazepines in both data sources.

Like all studies performed with healthcare databases, data collection suffers from the same common limitations (Schneeweiss and Avorn, 2005). Additionally, in the CPRD, only primary care prescriptions are recorded, unlike in the EGB in which prescription from specialists are also recorded. There is a possibility for differential measurement bias according to data source, as medical and psychiatric covariates were partly based on all diagnoses recorded in the CPRD general practitioner clinical records, whereas we used long-term conditions registered in the EGB. However, covariates of interest were essentially moderate or serious conditions. Clinical (CPRD) or long-term conditions (EGB) were used in combination with hospital data in both data sources, thus enhancing the identification of cases. Moreover, in both data sources, prescriptions during hospitalisations were not available, resulting in an "immeasurable time bias". Specific medical conditions such as baseline psychiatric disorders could lead to differential prescribing of benzodiazepines. Efforts were made in the present study to reduce this potential for indication bias observed in a previous study (Kripke et al., 2012). Groups were selected in order to ensure comparability at baseline. Antidepressant/non-benzodiazepine users comprised patients starting on medications with similar indications, and although antidepressants have different therapeutic indications, in practice both medications may be prescribed simultaneously. The moderate risk observed for the antidepressant/non-benzodiazepine cohort, while not exempt for residual confounding, is consistent with what could be expected regarding some studies(Smoller et al., 2009; Coupland et al., 2011). When considering the difference of risk between the benzodiazepine and antidepressant/non-benzodiazepine cohorts, a large part of the suspected residual confounding is then removed and the residual difference could be interpreted as an argument in favour of a proper effect of benzodiazepines on death.

We may suspect a differential indication bias between the French and UK cohorts. Although the same inclusion criteria were applied, new users had a 10-year difference in age, and initiation of benzodiazepine treatment may occur at a different stage of the disease or patient complaint depending on national prescribing practices.

Table 4 Univariate and multivariate Cox models for all-cause mortality at 1 year.

	Events	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	CPRD *P* value	Events	Crude hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	EGB *P* value	
Groups [a]										
Controls	1126	1		1		329	1		1	
Antidepressant/ non-BZD users	2183	2.00 (1.86-2.16)	<.001	1.61 (1.47-1.76)	<.001	423	1.53 (1.32-1.77)	<.001	1.07 (0.91-1.27)	.40
BZD users	5345	5.67 (5.30-6.07)	<.001	3.73 (3.43-4.06)	<.001	614	1.99 (1.74-2.29)	<.001	1.26 (1.08-1.48)	<.001
Benzodiazepine use (time dependent exposure)[b]										
		1		1			1		1 [Reference]	
Benzodiazepine current use	-	3.42 (2.86-4.09)	<.001	1.70 (1.36-2.12)	<.001	-	1.37 (1.02-1.84)	<.004	1.03 (0.74-1.44)	.87

CPRD: HR Adjusted for number of different active substances (0, 1-4, 5-9, >10), Charlson score (0, 1-2, <3); medical conditions (cancer, cardiac, respiratory disorders), presence of any hospital record, psychiatric conditions (addiction, personality disorders, schizophrenic disorders), use of antiepileptics, use of antipsychotics (yes/no), smoking (current and past user vs. non-user), and body mass index (underweight (body mass index <18.5), normal (18.5-24.9)=reference, overweight (25-29.9) and obese (≥30)).
EGB: HR Adjusted for number of different active substances (0, 1-4, 5-9, >10), Charlson score (0, 1-2, <3); medical conditions (cancer, cardiac, respiratory disorders), presence of any hospital record, psychiatric conditions (addiction, personality disorders, schizophrenic disorders), use of antiepileptics, use of antipsychotics.

[a]Variables in the final model after backward selection. All variables were derived from records in the year before index date.

[b]Controls, antidepressant/non-BZD users and BZD users outside current exposure are set as the reference.

In our study design, particular attention was made to collect for factors that are traditionally not available, namely medical and psychiatric conditions, but also lifestyle and socioeconomic factors. The availability of these factors differed according to data sources: lifestyle data and marital status were not available in the EGB. Despite these efforts, residual confounding due to other factors could not be excluded.

The mortality hazards observed in our study are consistent with previous findings in the literature, including those from a recently published cohort study using the same data source (CPRD) (Weich et al., 2014). Although an increased risk of death was observed in the 2 cohorts, the plausibility of a causal effect must be considered. In our study, mortality risk was significantly increased earlier after exposure in new users in both sources. These results are more in line with a short-term effect rather than with a cumulative effect, by contrast with results of 2 recent studies (Kripke et al., 2012; Weich et al., 2014). Choice of the outcome in our study is consistent with underlying pharmacological mechanism of a benzodiazepine-related acute or sub-acute mortality, and could even be shortened in further studies. Actually, high risks reported with longer use should be attributed to indication bias. Additionally, decrease of risk over time could be explained by tolerance to the sedative effect of benzodiazepines among survivors (Maguire et al., 2009; Horsfall et al., 2012; Weich et al., 2014).

Contrary to the Weich's study, (Weich et al., 2014) we did not exclude occasional users in order to avoid selection bias and to estimate the risk in a "real-life perspective". Then, our population comprised a large part of users that were exposed to 1 DDD per day and sequences of 28 days. Given the weight of these users, range of doses was narrow and a dose-response relationship could not be estimated.

Examination of causes of death revealed a high part of cancer, but cancer patients were also overrepresented among benzodiazepine users. This should not enable to exclude involvement of benzodiazepines, together with the hypothesized mechanism (respiratory, vigilance), even in cancer deaths. As explained by Vosoris et al. (Vozoris et al., 2014), measures implemented to monitor the most severe patients initiating benzodiazepines could enable to prevent fatal outcomes. However, the level of monitoring in the general population is far lower than in specialized settings, and the apparent conflicting results found are prone to be explained by the context of the study.

Underlying pharmacodynamic mechanisms, supported by results in selected populations or for cause-specific mortality (Winkelmayer et al., 2007; McCowan et al., 2009; Huybrechts et al., 2011; Tiihonen et al., 2012; Obiora et al., 2013), tend to be in favour of a proper effect of benzodiazepines on early mortality. This risk remains visible at the population level, although moderate and not exempt from residual confounding, after aggregating all causes of death and even in a population of incident and mostly occasional users. This is

potentially an issue in everyday practice given the widespread use of benzodiazepines, but also an important subject for policymakers. According to the Office for National Statistics General Household Survey in 2007 (Office for National Statistics, 2007), prevalence of anxiolytics use in the past year in UK was 0.5% of the population. In France, annual prevalence of anxiolytics and in particular benzodiazepine is far more important, around 20% (Agence française de sécurité sanitaire des produits de santé, 2012).

This new-user design study, conducted in 2 large French and UK populations, used a short-term outcome (one-year all-cause mortality), in accordance with pharmacological properties of benzodiazepines. We found a significant while moderate increase in all-cause mortality in relation to benzodiazepines, after considering time-varying exposure and adjustment for a large set of confounders. This issue need to be monitored given the extensive use of these drugs.

Contributors

MLM, AP and JD conceived the original idea of the paper and designed the study. AP and JD conducted the data analyses. AP produced the initial draft of the paper. All authors were involved in the interpretation of the analyses and writing of the paper. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None declared.

Role of the funding source

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Appendix A. Supplementary Information

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