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Supplementary Table S1: Specification of codes used for definition of variables		
Variable	ATC code / Information, from Danish Prescription registry	Short/medium or long acting
EXPOSURE		
Benzodiazepines		
Alprazolam	N05BA12	Short/medium acting
Bromazepam	N05BA08	Short/medium acting
Brotizolam	N05CD09	Short/medium acting
Chlordiazepoxid	N05BA02	Long acting
Clobazam	N05BA09	Long acting
Clonazepam	N03AE01	Long acting
Diazepam	N05BA01	Long acting
Estazolam	N05CD04	Short/medium acting
Flunitrazepam	N05CD03	Long acting
Lorazepam	N05BA06	Short/medium acting
Lormetazepam	N05CD06	Short/medium acting
Midazolam	N05CD08	Short/medium acting
Nitrazepam	N05CD02	Long acting
Oxazepam	N05BA04	Short/medium acting
Temazepam	N05CD07	Short/medium acting
Triazolam	N05CD05	Short/medium acting
Benzodiazepine derivates		
Zaleplon	N05CF03	Short/medium acting
Zolpidem	N05CF02	Short/medium acting
Zopiclone	N05CF01	Short/medium acting
Other anxiolytics/hypnotics		
Bupiron	N05BE01	
Hydrixizine	N05BB01	
Pregabalin	N03AX16	
OUTCOME		ICD code / Information, from Danish National Patient registry
Dementia	N06D	ICD8: 290 ICD10:F00-F03; G30
COVARIATES		:
Depression subtype		
Manic/bipolar		ICD10: F30, F31
Single or recurrent depression, mild		ICD10: F320, F330
Single or recurrent depression, moderate		ICD10: F321, F331
Single or recurrent depression, severe		ICD10: F322, F323, F332, F333
Single or recurrent depression, other		ICD10: F328,F329,F334, F339
Persistent or unspecified affective disorder		ICD10: F34, F39
Anxiety		ICD8: 300-09,300-19 ICD10: F41-F42
Alcohol and drug abuse		ICD8: 303 ICD10: F10, F19
Diabetes mellitus	A10	ICD8: 250 ICD10:E10-E14

Cardiovascular disease		ICD8:410-414; ICD10:I , I
Comedication		
Antipsychotics	N05AA-N05AX	
Antidepressants	N06A	

Supplementary Table S2: Mortality (%) in relation to ever use of BZD, age and follow-up time.

	All	Deaths		Never BZD	Deaths		Ever BZD	Deaths	
Total	235,465	68,048	(28.9)	56,216	9,447	(16.8)	179,249	58,601	(32.7)
Age									
20-49 years	122,665	7,377	(6.0)	39,109	801	(2.0)	83,556	6,576	(7.9)
50-69 years	56,745	17,831	(31.4)	8,282	1,886	(22.4)	48,463	15,945	(32.9)
70- years	56,055	42,840	(76.4)	8,825	6,760	(76.6)	47,230	36,080	(76.4)
Follow-up									
0-2 years	235,465	26,211	(11.3)	56,216	4,617	(8.2)	179,249	21,594	(12.5)
2-20.1 years	195,895	41,837	(21.4)	46,089	4,830	(10.5)	149,806	37,007	(24.7)

Supplementary Table S3: Distribution of the most frequently (2 or more percent of all prescriptions) prescribed types of antidepressants in patients with affective disorder, 1995-2016.		
Benzodiazepine (ATC-code)	Total number of prescription (% of all prescriptions)	Number of ever users (%)
Zopiclone (N05CF01)	1942056 (19.2)	100,314 (42.6)
Oxazepam (N05BA04)	1863330 (18.5)	93,267 (39.6)
Diazepam (N05BA01)	1252766 (12.4)	60,677 (25.7)
Zolpidem (N05CF02)	1185630 (11.7)	69,004 (29.3)
Alprazolam (N05BA12)	885174 (8.8)	39,623 (16.8)
Nitrazepam (N05CD02)	534027 (5.3)	24,866 (10.6)
Pregabalin (N03AX16)	448 358 (4.4)	21,732 (9.2)
Bromazepam (N05BA08)	433 857 (4.3)	12,072 (5.1)
Clonazepam (N03AE01)	420 448 (4.2)	12,963 (5.5)
Triazolam (N05CD05)	212 310 (2.1)	12,354 (5.2)
Chlordiazepoxid (N05BA02)	203 541 (2.0)	18,528 (7.9)
Lorazepam (N05BA06)	202 060 (2.0)	8,787 (3.7)

Supplementary Table S4: Distribution of covariates in relation to ever use of benzodiazepines (BZD) and related drugs in patients with affective disorder, 1995-2016.

	Total Number	Number (%) BZD users
Total	235,465	179,249 (75.9)
Gender		
Male	91,463	67,160 (79.4)
Female	144,002	112,089 (77.8)
Age at baseline (years)		
20-49	122,665	83,556 (68.1)
50-69	56,755	48,463 (85.4)
70-110	56,055	47,230 (84.3)
Marital status at baseline (%)		
Unmarried	75,449	48,674 (64.5)
Married	92,504	73,619 (79.6)
Divorced	33,687	28,192 (83.7)
Widowed	32,048	27,710 (86.5)
Unkown	1,777	723(40.6)
Educational level at baseline (%)		
Basic only	88,226	67,937 (77.0)
Middle	88,724	66,080 (64.5)
High	34,339	26,244 (76.4)
Unknown	24,176	18,988 (78.5)
Depression subtype (%)		
Manic/bipolar	13,548	10,460 (77.2)
Single or recurrent depression, mild	31,898	23,657 (74.2)
Single or recurrent depression, moderate	65,771	49,423 (75.1)
Single or recurrent depression, severe	25,995	20,792 (80.0)
Single or recurrent depression, other	87,828	67,208 (76.5)
Persistent or unspecified affective disorder	10,425	7,709 (74.0)
Psychotropic medication at baseline (%)		
Antipsychotic drugs	54,051	49,694 (87.9)
Antidepressant drugs	175,307	140,672 (80.2)
Comorbidity at baseline (%)		
Anxiety	37,697	29,599 (78.5)
Drug and alcohol abuse	25,221	21,669 (86.0)
Diabetes Mellitus	13,750	10,798 (78.5)
Cardiovascular disease	23,134	20,615 (82.9)

Supplementary Table S5: The number (%) of patients with overlap in use of different drug types.

	Cohort study	Nested Case-control study	
		Dementia cases	Controls
Never	56,216 (23.8)	1,834 (18.8)	7,422 (19.0)
BZD, only	50,566 (21.5)	2,772 (28.4)	10,298 (26.3)
Z drugs only	28,915 (12.2)	873 (8.9)	4,465 (11.4)
Both	99,768 (42.3)	4,297 (44.0)	16,919 (43.3)
Never	56,216 (23.8)	1,834 (18.8)	7,460 (49.1)
Long acting , only	13,487 (5.7)	798 (8.2)	3,205 (8.2)
Short/medium acting, only	85,977 (36.5)	3,319 (34.0)	14,224 (36.4)
Both	79,685 (33.8)	3,813 (39.0)	14,215 (36.4)
Never	52,893 (22.5)	1,793 (18.4)	7,193 (18.4)
Other anxiolytics, only	3,326 (1.4)	41 (0.4)	229 (0.6)
BZD, only	151,144 (64.1)	7,324 (74.5)	28,776 (7.4)
Both	28 105 (11.9)	659 (6.7)	2,906 (7.4)

Supplementary Table S6: Hazard and Odds Ratios and 95% Confidence Intervals (CI) for associations of concurrent use of Benzodiazepines and related drugs with subsequent dementia in patients with affective disorders

	Cohort study		Nested Case-control study
	Adjusted HR 0-2 years	Adjusted HR 2-20 years	Adjusted OR
Never	1	1	1
BZ, only	1.02 (0.94-1.11)	0.97 (0.89-1.05)	0.99 (0.93-1.05)
Z drugs only	0.93 (0.82-1.05)	0.92 (0.82-1.04)	0.87 (0.80-0.95)
Both	0.97 (0.90-1.03)	0.94 (0.87-1.03)	0.99(0.92-1.05)
Never	1	1	1
Long acting , only	1.00(0.90-1.11)	0.95 (0.86-1.06)	0.93 (0.85-1.00)
Short/medium acting, only	0.96 (0.86-1.04)	0.94 (0.86-1.02)	0.95 (0.89-1.01)
Both	1.00 (0.93-1.09)	0.98(0.89-1.06)	1.02 (0.96-1.09)
Never	1	1	1
Other anxiolytics, only	0.99 (0.92-1.07)	0.96 (0.89-1.03)	0.97 (0.92-1.03)
BZD	1.26 (0.75-2.09)	1.34 (0.80-2.23)	1.15 (0.81-1.629)
Both	0.92 (0.76-1.09)	0.94 (0.78-1.12)	0.87 (0.77-0.98)

Adjusted models include: gender age, marital status, education, depression subtype, year of diagnosis, psychotropic medication and comorbidity.

Supplementary Table S7: Hazard Ratios and 95% Confidence Intervals (CI) for associations of timing of use of Benzodiazepines and related drugs with subsequent dementia in patients with affective disorders

	Cohort study	
	Adjusted HR 0-2 years	Adjusted HR 2-20.1 years
Never use (n=56,216)	1	1
All types, continuing use (n=105,039)	0.30 (0.26-0.35)	0.70(0.62-0.80)
All types, former user (n=43,581)	1.14 (1.05-1.22)	1.02(0.96-1.14)
All types, new user (n=30,629)	0.31 (0.29-0.34)	0.76 (0.70-0.84)
Never use (n=85,131)	1	1
BZD , continuing use (n=74,889)	0.34 (0.29-0.39)	0.78 (0.70-0.88)
BZD, former use (n=46,321)	0.99 (0.92-1.06)	1.05 (0.96-1.16)
BZD , new use (n=29,124)	0.33 (0.30-0.36)	0.83 (0.76-0.89)
Never use (n=106,782)	1	1
Z-drug, continuing use (n=51,789)	0.25 (0.22-0.29)	0.90 (0.54-0.75)
Z-drug, former use (n=38,738)	1.07 (1.00-1.14)	1.01 (0.92-1.11)
Z-drug, new use (n=38,156)	0.35 (0.33-0.39)	0.77 (0.72-0.83)
Never use (n=142,314)	1	1
Long acting, continuing use(n=32,343)	0.20 (0.17-0.24)	0.78 (0.70-0.80)
Long acting, former use(n=40,262)	0.98 (0.92-1.04)	1.05 (0.98-1.14)
Z-drug, new use (n=20,546)	0.33 (0.30-0.36)	0.86 (0.70-0.93)
Never use (n=69,803)	1	1
Short acting, continuing use (n=85,776)	0.32 (0.29-0.36)	0.70 (0.63-0.78)
Short acting, former use(n=43,274)	1.05 (0.97-1.13)	1.08 (0.97-1.19)
Short acting, new use (n=36,612)	0.40 (0.34-0.43)	0.78 (0.72-0.84)
Never use (n=204,037)	1	1
Other anxiolytics, continuing use (n=4,040)	0.15 (0.12-0.21)	0.59 (0.53-0.67)
Other anxiolytics, former use only(n=7,016)	0.93 (0.80-1.09)	1.10 (0.91-1.32)
Other anxiolytics, new use (n=20,372)	0.43 (0.30-0.62)	0.68 (0.47-0.99)

Never use= no pre or postdiagnostic use; continuing use= both pre- and postdiagnostic use; former use= prediagnostic use only, new use= postdiagnostic use , only.

All models include: gender age, marital status, education, depression subtype, year of diagnosis, psychotropic medication and comorbidity.

Supplementary Table S8. Odds Ratios and 95% Confidence Intervals (CI) for associations of Benzodiazepines (BZD) and Z drugs with dementia diagnosed before study entry

	Excluded dementia cases diagnosed before study entry	Nested controls	Adjusted** Odd Ratio
Never	4,389 (45.4)	4,815 (48.8)	1
Ever BZD or Z drugs*	5,282 (54.6)	4,856 (50.2)	0.93 (0.78-1.00)

*from 1995 until 2 years before diagnosis (before study entry)

** adjusted for gender age, marital status, education, depression subtype, year of diagnosis, psychotropic medication and comorbidity.

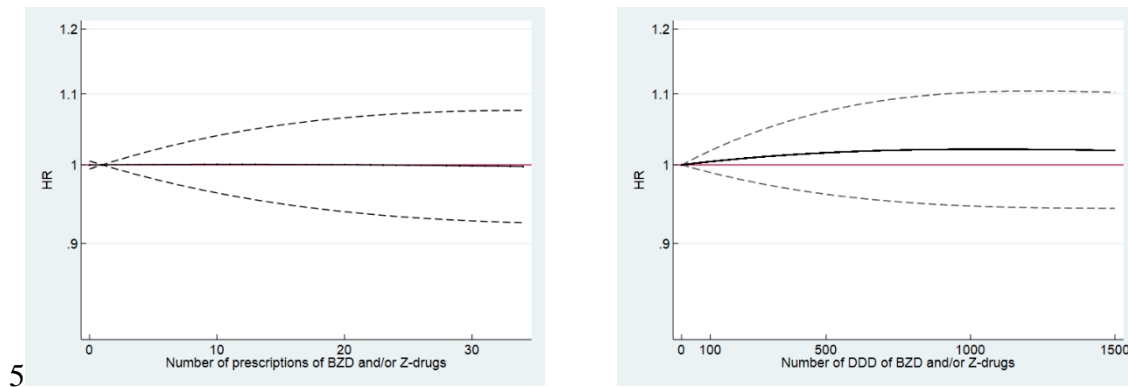
Supplementary Table S9: Subdistribution Hazard Ratios and 95% Confidence Intervals (CI) for associations of Benzodiazepines and related drugs at baseline with subsequent dementia in patients with affective accounting for competing mortality

	0-2 years follow-up	2+ years
<i>Ever use</i>	0.72 (0.68-0.77)	1.00 (0.93-1.08)
BZD	0.75 (0.72-0.79)	1.02 (0.96-1.09)
Z-drugs	0.77 (0.73-0.82)	0.96 (0.90-1.01)
Long acting	0.82 (0.77-0.87)	1.01 (0.95-1.06)
Short medium acting	0.75 (0.71-0.79)	1.00(0.94-1.07)
Other anxiolytics	0.77 (0.67-0.89)	0.90(0.76-1.06)

Models adjusted for gender and age.

Supplementary Figure S1: Adjusted Hazard and Odds Ratios (95% Confidence Intervals) of the association between number of prescriptions and cumulated dose (DDD) of treatment with BZD and Z-drugs as cubic splines with 4 knots and subsequent dementia in patients with affective disorders. A value of 1 prescription/DDD was reference value.

Cohort design (2-201 years follow-up)



Nested Case-control design

