

Appendix

eTable 1. List of Benzodiazepines Included in the Study

Benzodiazepines	Alprazolam, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Triazolam, Temazepam
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eTable 2. Complete list of baseline characteristics of study participants before and after high-dimensional propensity score matching

	Before PS-matching			After PS-matching		
Characteristic	BZD Initiators 1,686,410	BZD Non-initiators 1,930,159	ASD	BZD Initiators 1,252,988	BZD Non-initiators 1,252,988	ASD
	Mean (SD) or %			Mean (SD) or %		
Demographics						
Age	46.4 (13.8)	43.6 (14.6)	0.20	46.0 (13.8)	45.2 (14.6)	0.06
Male sex	31.7	39.9	0.17	35.1	34.6	0.01
Index year						
2004	6.8	6.8	0.00	7.1	7.1	0.00
2005	12.1	11.8	0.01	12.1	12.1	0.00
2006	11.1	11.0	0.00	11.1	11.1	0.00
2007	10.7	10.7	0.00	10.7	10.7	0.00
2008	11.0	11.1	0.00	11.1	11.1	0.00
2009	10.7	10.8	0.00	10.7	10.7	0.00
2010	9.7	9.6	0.00	9.7	9.7	0.00
2011	9.7	9.8	0.00	9.6	9.6	0.00
2012	9.3	9.3	0.00	9.2	9.2	0.00
2013	8.9	9.0	0.00	8.7	8.7	0.00
Comorbidities and life style factors						
Charlson comorbidity score	0.5 (1.2)	0.4 (0.9)	0.18	0.5 (1.1)	0.4 (1.0)	0.01
Smoking	5.6	3.7	0.09	4.5	4.5	0.00
Obesity or overweight	4.6	3.9	0.03	4.3	4.2	0.00
Hypertension	27.8	22.0	0.13	25.6	26.0	0.01
Congestive heart failure	1.7	1.1	0.05	1.4	1.4	0.00
Ischemic heart disease	5.6	3.9	0.08	4.9	5.0	0.00
Coronary revascularization	1.2	0.9	0.03	1.1	1.1	0.00
Atherosclerosis	0.5	0.3	0.03	0.4	0.4	0.00
Disrhythmia	4.4	3.0	0.07	3.7	3.7	0.00
Cerebrovascular disease	1.9	1.1	0.07	1.5	1.4	0.01
Venous thromboembolism	1.3	0.9	0.04	1.1	1.0	0.01
Peripheral vascular disease	1.2	0.8	0.04	1.1	1.1	0.00
Other cardiovascular diseases	6.1	4.1	0.09	5.1	5.1	0.00
Hyperlipidemia	26.2	22.1	0.10	24.8	25.2	0.01
Diabetes	9.7	8.9	0.03	9.6	9.7	0.00
COPD	3.3	1.9	0.09	2.6	2.5	0.01
Asthma	6.0	4.4	0.07	5.2	5.2	0.00
Pneumonia	1.9	1.3	0.05	1.6	1.6	0.00
Sepsis	0.4	0.3	0.02	0.4	0.3	0.02
Osteoarthritis	7.0	4.9	0.09	6.0	6.1	0.00
Rheumathoid arthritis	1.1	0.8	0.03	1.0	1.0	0.00
Other OA and MSK	29.0	22.8	0.14	25.9	25.9	0.00
Neuropathic pain	12.0	7.4	0.16	9.5	9.5	0.00
Back pain	22.7	14.8	0.20	18.6	18.6	0.00

	Before PS-matching			After PS-matching		
Characteristic	BZD Initiators 1,686,410	BZD Non-initiators 1,930,159	ASD	BZD Initiators 1,252,988	BZD Non-initiators 1,252,988	ASD
	Mean (SD) or %			Mean (SD) or %		
Fibromyalgia	5.2	3.1	0.11	4.0	3.9	0.01
Osteoporosis	2.0	1.3	0.05	1.7	1.7	0.00
Fractures	2.7	2.4	0.02	2.5	2.4	0.01
Falls	0.8	0.6	0.02	0.7	0.7	0.00
Kidney disease	3.4	2.4	0.06	2.9	2.9	0.00
Liver disease	3.3	2.1	0.07	2.6	2.6	0.00
Gastrointestinal disorders	3.3	2.5	0.05	2.9	2.9	0.00
Blood disorders	8.9	6.5	0.09	7.6	7.6	0.00
Headache	8.6	5.3	0.13	6.7	6.6	0.00
Migraine	4.6	2.5	0.11	3.4	3.3	0.01
Epilepsy or convulsions	1.5	0.8	0.07	1.1	1.0	0.01
Dementia	0.9	0.5	0.05	0.7	0.6	0.01
Parkinson's disease	0.2	0.1	0.03	0.2	0.2	0.00
Cancer	11.4	7.6	0.13	9.5	9.6	0.00
Frailty ¹	1.2	0.7	0.05	1.0	1.0	0.00
Anxiety	14.3	4.7	0.33	7.9	7.0	0.03
Insomnia	5.7	2.1	0.19	3.5	3.1	0.02
Other sleep disorders	5.3	3.4	0.09	4.4	4.2	0.01
Depression	16.3	8.0	0.26	11.5	11.1	0.01
Bipolar disorder	2.3	0.9	0.11	1.4	1.3	0.01
Psychosis	0.7	0.3	0.06	0.4	0.4	0.00
Delirium	0.7	0.3	0.06	0.5	0.4	0.01
Drug or alcohol abuse	2.2	1.2	0.08	1.6	1.5	0.01
Other psychiatric conditions	5.2	3.2	0.10	4.1	3.9	0.01
Medications						
ACE inhibitors	12.3	11.3	0.03	12.3	12.5	0.01
Angiotensin II receptor blockers	8.0	6.3	0.07	7.6	7.6	0.00
Beta-blockers	14.1	10.5	0.11	13.0	12.9	0.00
Calcium channel blockers	8.6	10.5	0.06	8.1	8.4	0.01
Thiazide diuretics	4.9	4.0	0.04	4.6	5.0	0.02
Loop diuretics	3.3	2.1	0.07	2.8	2.8	0.00
Nitrates	1.5	1.0	0.05	1.3	1.3	0.00
Other antihypertensives	3.3	2.4	0.05	3.0	3.0	0.00
Digoxin	0.7	0.5	0.03	0.6	0.6	0.00
Antiarrhythmics	0.6	0.4	0.03	0.5	0.5	0.00
Anticoagulants	2.3	1.8	0.04	2.1	2.1	0.00
Antiplatelets	2.3	1.7	0.04	2.1	2.2	0.01
Non-insulin glucose-lowering agents	7.1	6.9	0.01	7.1	7.8	0.03
Insulin	2.1	1.9	0.01	2.0	2.2	0.01
Lipid-lowering agents	20.9	18.2	0.07	20.2	20.9	0.02
COPD/Asthma therapy	9.9	7.7	0.08	8.8	9.1	0.01
Oral corticosteroids	13.5	9.6	0.12	11.4	11.7	0.01
DMARDs	2.2	1.6	0.04	1.9	2.0	0.01
NSAIDs	17.7	14.9	0.08	15.9	17.1	0.03

	Before PS-matching			After PS-matching		
Characteristic	BZD Initiators 1,686,410	BZD Non-initiators 1,930,159	ASD	BZD Initiators 1,252,988	BZD Non-initiators 1,252,988	ASD
	Mean (SD) or %			Mean (SD) or %		
COX-2 selective inhibitors	2.9	1.9	0.07	2.5	2.4	0.01
Opioids	35.0	24.0	0.24	30.1	28.8	0.03
Bisphosphonates	2.8	2.0	0.05	2.5	2.7	0.01
Anticonvulsants	8.8	4.2	0.19	6.1	5.9	0.01
Anti-migraine agents	4.2	2.3	0.11	3.3	3.0	0.02
Antiparkinson therapy	1.1	0.5	0.07	0.7	0.7	0.00
Dementia therapy	0.5	0.2	0.05	0.4	0.3	0.02
SSRIs	22.4	11.6	0.29	19.1	15.1	0.11
SNRIs	6.8	2.9	0.18	5.2	4.0	0.06
TCAs	3.4	1.7	0.11	2.6	2.3	0.02
Other antidepressants	9.7	4.4	0.21	7.6	6.0	0.06
Other hypnotics	11.6	4.3	0.27	8.0	6.1	0.07
Other anxiolytics	2.2	0.9	0.11	1.6	1.2	0.03
Lithium	0.5	0.2	0.05	0.3	0.3	0.00
Antipsychotics	2.7	1.1	0.12	1.7	1.6	0.01
Barbiturates	2.3	1.1	0.09	1.8	1.4	0.03
Indicators of health care utilization						
Any hospitalization	10.4	6.9	0.12	8.1	7.9	0.01
No. hospital days	0.8 (4.2)	0.5 (3.1)	0.09	0.6 (3.4)	0.6 (3.6)	0.00
No. physician visits	4.0 (3.6)	2.9 (2.9)	0.31	3.4 (3.2)	3.4 (3.1)	0.00
No. prescription drugs	5.9 (4.0)	4.3 (3.1)	0.43	5.1 (3.6)	5.1 (3.4)	0.01
Psychiatric visit	22.7	10.9	0.32	15.9	14.6	0.04
Psychiatric hospitalization	0.9	0.3	0.08	0.5	0.5	0.00
No. ICD9 diagnoses, 3rd digit level	9.3 (7.4)	7.0 (6.0)	0.35	8.0 (6.5)	8.0 (6.4)	0.00
No. cardiograms	0.3 (0.8)	0.2 (0.6)	0.15	0.2 (0.7)	0.2 (0.7)	0.00

PS: propensity score, BZD: Benzodiazepine, ASD: Absolute standardized difference, COPD: Chronic obstructive pulmonary disease, OA: Osteoarthritis, MSK: Musculoskeletal disorder, ACE: Angiotensin-converting-enzyme, DMARDs: disease-modifying anti-rheumatic drugs, NSAIDs: non-steroidal anti-inflammatory drugs, COX-2: cyclooxygenase-2, SSRIs: selective serotonin reuptake inhibitors, SNRIs: norepinephrine reuptake inhibitors, TCAs: tricyclic antidepressants.

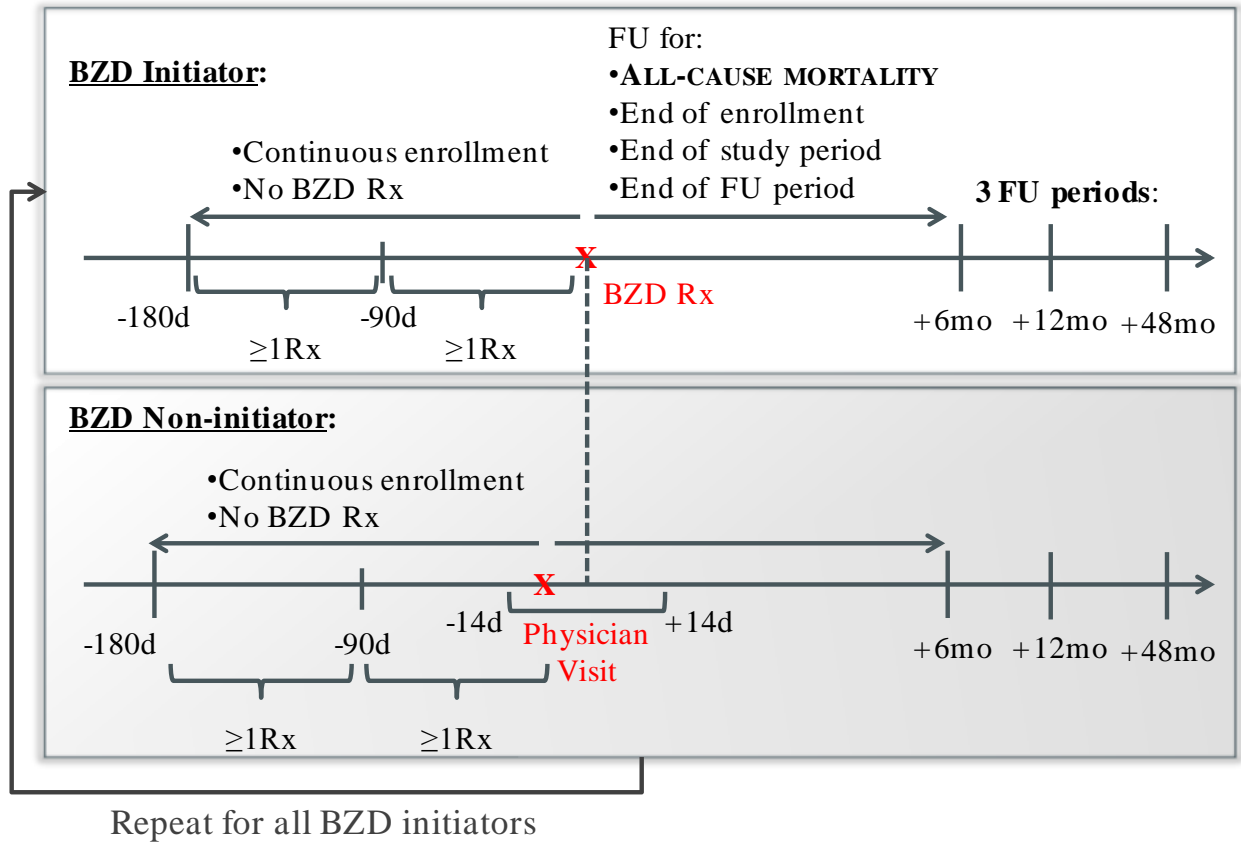
[†]Frailty was defined as a diagnostic code for urinary incontinence, decubitus ulcer, or oxygen use

eTable 3. Classification of Long-Acting and Short-Acting Benzodiazepines*

Long-acting agents	Short-acting agents
Chlordiazepoxide	Alprazolam
Clobazam	Midazolam
Clorazepate	Triazolam
Diazepam	Clonazepam
Flurazepam	Estazolam
Quazepam	Lorazepam
	Oxazepam
	Temazepam

*Long-acting BZDs are agents with half-life \geq 24 hours

eFigure 1. Study Diagram



BZD: Benzodiazepine, FU: Follow-up, Rx: Filled prescription, mo: Month