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 |
**eTable 2. Complete list of baseline characteristics of study participants before and after high-dimensional propensity score matching**

| Characteristic                     | Before PS-matching | After PS-matching |
|-----------------------------------|--------------------|-------------------|
|                                   | BZD Initiators     | BZD Non-initiators| ASD    | BZD Initiators     | BZD Non-initiators| ASD    |
|                                   | 1,686,410          | 1,930,159         | 1,252,988 | 1,252,988 |
| **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    |
| Characteristic                      | Before PS-matching | After PS-matching |
|------------------------------------|--------------------|-------------------|
|                                    | BZD Initiators 1,686,410 | BZD Non-initiators 1,930,159 | ASD | BZD Initiators 1,252,988 | BZD Non-initiators 1,252,988 | ASD |
| 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                            | 1.2                | 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|
| Characteristic                        | Before PS-matching | After PS-matching |
|--------------------------------------|--------------------|-------------------|
|                                      | BZD Initiators     | BZD Non-initiators | ASD | BZD Initiators | BZD Non-initiators | ASD |
|                                      | 1,686,410          | 1,930,159         |     | 1,252,988     | 1,252,988           |     |
|                                      | Mean (SD) or %     | Mean (SD) or %    |     | 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 | Before PS-matching | After PS-matching |
|--------------------------------------|--------------------|-------------------|
| Any hospitalization                  | 10.4 ± 6.9         | 0.12              |     | 8.1 ± 7.9     | 0.01               |
| No. hospital days                    | 0.8 (4.2)          | 0.09              |     | 0.6 (3.4)     | 0.00               |
| No. physician visits                 | 4.0 (3.6)          | 0.31              |     | 3.4 (3.2)     | 0.00               |
| No. prescription drugs               | 5.9 (4.0)          | 0.43              |     | 5.1 (3.6)     | 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)          | 0.35              |     | 8.0 (6.5)     | 0.00               |
| No. cardiograms                      | 0.3 (0.8)          | 0.15              |     | 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.

1Frailty 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 ≥ 24 hours
**Figure 1. Study Diagram**

**BZD Initiator:**
- Continuous enrollment
- No BZD Rx

FU for:
- ALl-CAUSE MORTALITY
- End of enrollment
- End of study period
- End of FU period

BZD Rx \( \geq 1 \text{Rx} \) \( -90 \text{d} \) \( +180 \text{d} + 6 \text{mo} \)

BZD Non-initiator:
- Continuous enrollment
- No BZD Rx

Repeat for all BZD initiators

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