

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time

Steps to estimate cumulative anticholinergic exposure are:

- 1) determine the defined daily dose (DDD) of all medications considered by the ACB scale;
- 2) calculate the standardized daily dose (SDD) of the medication for each anticholinergic dispensing, as follows:

$$\text{SDD} = [\text{Number of daily doses} \times \text{Unit dose}] / \text{DDD};$$
- 3) multiply the SDD by the ACB scale score of the medication dispensed to yield a drug and patient-specific measure of standardized daily anticholinergic exposure (SDACE);
- 4) add drug-specific SDACE at the patient level to account for coverage with multiple medications on a given day, to give a summated standardized daily anticholinergic exposure (SumSDACE);
- 5) calculate cumulative burden by summing SumSDACE for all days during the exposure period.

Drug 1:

ACB score 2, prescribed at 1.5 x defined daily dose
 → Adjusted score = 2 x 1.5 = 3

Drug 2:

ACB score 1, prescribed at defined daily dose
 → Adjusted score = 1 x 1 = 1

Example trajectory and calculation:

	Day 1: initiate drug 1				Day 5: initiate drug 2, continue drug 1				Day 9: Discontinue drugs
Day	1	2	3	4	5	6	7	8	9
Drug 1 (Adjusted score = 3)	X	X	X	X	X	X	X	X	
Drug 2 (Adjusted score = 1)					X	X	X	X	
SumSDACE	3	3	3	3	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	0
CumSDACE (Summed daily dose)	3	6	9	12	16	20	24	28	28

Supplementary Table 1: CPT, NDC, ICD-9 and HCPCS codes to identify OAB, comorbidities and risk factors, and study outcomes

Definition	References
Identify OAB	
By diagnosis code	
<p>Other functional disorders of bladder (ICD9: 596.5), Hypertonicity of the bladder (ICD9: 596.51) Urinary incontinence unspecified (ICD9: 788.3) Urge incontinence (ICD9: 788.31) Mixed incontinence (ICD9: 788.33) Urinary frequency (ICD9: 788.41) Nocturia (ICD9: 788.43) Urgency of urination (ICD9: 788.63) Functional urinary incontinence (ICD9: 788.91)</p>	<p>Chancellor MB, Migliaccio-Walle K, Bramley TJ, et al. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther. 2013;35(11):1744-1751. Pelletier EM, Vats V, Clemens JQ. Pharmacotherapy adherence and costs versus nonpharmacologic management in overactive bladder. Am J Manag Care. 2009;15(4 Suppl):S108-114. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clinical Therapeutics. 2005;27(2):144-153. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009;15(9):728-740.</p>
By drug code	
<p>Darifenacin (NDC: 0430-0170, 0430-0171, 0591-4375, 0591-4380, 10370-170, 10370-171, 13668-202, 13668-203, 35356-272, 42291-206, 42291-207, 54868-5363, 54868-5704, 59746-516, 59746-517, 65862-861, 65862-862, 69097-431, 69097-432)</p> <p>Fesoterodine (NDC: 0069-0242, 0069-0244, 54868-6156, 54868-6175, 55154-2737, 55154-2738, 63539-183, 63539-242, 69189-0242, 69189-0244)</p> <p>Flavoxate (NDC: 0574-0115, 24658-720, 42806-058, 50268-324, 51224-154, 54868-6326, 60429-290, 68151-3826)</p> <p>Oxybutynin (NDC: 0023-5812, 0023-5861, 0093-5206, 0093-5207, 0093-5208, 0121-0671, 0179-0187, 0378-6015, 0378-6605, 0378-6610, 0378-6615, 0603-1491, 0603-4975, 0615-3512, 0615-7519, 0615-7520, 0615-7521, 0832-0038, 0904-2821, 0904-6570, 10135-609, 10135-610, 10135-611, 10147-0761, 10147-0771, 10147-0781, 10544-518, 10544-559, 11523-4311, 11523-4322, 16729-317, 16729-318, 16729-319, 17856-1491, 21695-406, 33261-342, 35356-909, 35356-958, 35356-991, 42291-633, 42291-634, 42291-635, 43063-145, 43353-367, 43353-769, 43353-978, 50090-0317, 50090-0318, 50090-2049, 50111-456, 50268-627, 50268-628, 50268-629, 50436-4777, 50458-805, 50458-810, 50458-815, 51079-722, 51079-723, 52544-041, 52544-084, 52544-166, 52544-920, 53808-0618, 53808-0747, 53808-0873, 54569-1990, 54838-510, 54868-2157, 54868-4502, 54868-4835, 54868-5728, 54868-5742, 54868-5743, 54868-6171, 55154-0657, 55154-5537, 55154-6298, 55154-6647, 55154-7225, 60432-092, 60760-980, 61786-605, 62175-270, 62175-271, 62175-272, 63187-749, 63629-1354, 63629-5484, 63629-6355, 63629-6434, 63739-548, 64980-209, 64980-210, 64980-211, 65162-371, 65162-372, 65162-373, 66336-604, 67296-1175, 68071-1875, 68071-2013, 68084-400, 68084-480, 68084-610, 68151-3646, 68788-6402, 69189-0581, 69189-5206, 69189-6605, 69189-6610, 70518-0158, 70518-0202, 76237-216, 76237-217, 76237-218)</p> <p>Solifenacin (NDC: 50090-0972, 51248-150, 51248-151, 54569-5790, 54868-4705, 54868-5398, 55154-3875, 55154-3876, 55154-3877, 55154-3878)</p> <p>Tolterodine (NDC: 0009-4541, 0009-4544, 0009-5190, 0009-5191, 0093-0010, 0093-0018, 0093-2049, 0093-2050, 0093-2055, 0093-2056, 0093-7163, 0093-7164, 0378-3402, 0378-3404, 0378-5445, 0378-5446, 0904-6592, 0904-6593, 13668-189, 13668-190, 16590-959, 33342-097, 33342-098, 35356-417, 51079-197, 51079-198, 51079-235, 54868-4514, 54868-5126, 55154-3933, 55154-3935, 55289-132, 59762-0047, 59762-0048, 59762-0170, 59762-0800, 60429-825, 60429-826, 60505-3527, 60505-3528, 63629-5625, 68151-2049, 68151-4281, 69189-3404, 69189-5190)</p> <p>Trospium (NDC: 0574-0118, 0574-0145, 0591-3636, 23155-530, 42291-846, 60429-098, 60429-103, 60505-3454, 68001-228, 68462-461, 69097-912)</p> <p>Mirabegron/Myrbetriq (NDC: 00469-2601, 00469-2602)</p> <p>OnabotulinumtoxinA/Botox (CPT: 52287)</p>	<p>FDA-US Food and Drug administration. National Drug Code Directory. https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm</p>
Outcomes	
<p>Fall (ICD9: E880-E886, E888, E998.0, E888.1, E888.8, E888.9)</p> <p>Fracture (ICD9: 733.1,* 733.93-733.98,* 800.x-829.x, E887; ICD9: 79.0-79.6; CPT: 21800, 21805, 21810, 21820, 21825, 22305,22310, 22318, 22319, 22520, 22521, 22523, 22524, 23500, 23505, 23515, 23570, 23575, 23585, 23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565,</p>	<p>Afroz PN, Bykowski MR, James IB, et al. The Epidemiology of Mandibular Fractures in the United States, Part 1: A Review of 13,142 Cases from the US National Trauma Data Bank. Journal of oral and maxillofacial surgery. 2015;73(12):2361. Beydoun HA, Beydoun MA, Mishra NK, et al. Comorbid Parkinson's disease, falls and fractures in the 2010 National Emergency Department Sample. Parkinsonism & Related Disorders. 2017;35:30-35.</p>

24566, 24575, 24576, 24577, 24579, 24582, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600, 26605, 26607, 26608, 26615, 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27267, 27268, 27269, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27767, 27768, 27769, 27780, 27781, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 29850, 29851, 29855, 29856; HCPCS: S2360)

Clavijo-Alvarez JA, Deleyiannis FWB, Peitzman AB, Zenati MS. Risk factors for death in elderly patients with facial fractures secondary to falls. *The Journal of craniofacial surgery*. 2012;23(2):494-498.

Crispo JA, Willis AV, Thibault DP, et al. Associations between Anticholinergic Burden and Adverse Health Outcomes in Parkinson Disease. *PLoS one*. 2016;11(3):e0150621.

Curtis JR, Mudano AS, Solomon DH, et al. Identification and validation of vertebral compression fractures using administrative claims data. *Medical care*. 2009;47(1):69.

Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy*. 2005;25(4):511-519.

Ganz DA, Kim SB, Zingmond DS, et al. Effect of a Falls Quality Improvement Program on Serious Fall-Related Injuries. *Journal of the American Geriatrics Society*. 2015;63(1):63-70.

Kachroo S, Kawabata H, Colilla S, et al. Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: analysis of a US commercial database. *Journal of managed care & specialty pharmacy*. 2015;21(3):243-253.

Kalilani L, Asgharnejad M, Palokangas T, Durgin T. Comparing the Incidence of Falls/Fractures in Parkinson's Disease Patients in the US Population. *PLoS one*. 2016;11(9):e0161689.

Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. *The American journal of geriatric pharmacotherapy*. 2006;4(3):219-226.

Kruschinski C, Sheehy O, Hummers-Pradier E, Lelorier J. Fracture risk of patients suffering from dizziness: A retrospective cohort study. *European Journal of General Practice*. 2010;16(4):229-235.

Lapane KL, Jesdale BM, Dubé CE, et al. Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus. *Diabetes research and clinical practice*. 2015;109(2):411.

Miller M, Stürmer T, Azrael D, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. *Journal of the American Geriatrics Society*. 2011;59(3):430-438.

Pan H-H, Li C-Y, Chen T-J, Su T-P, Wang K-Y. Association of polypharmacy with fall-related fractures in older Taiwanese people: age-and gender-specific analyses. *BMJ open*. 2014;4(3):e004428.

Roudsari BS, Ebel BE, Corso PS, et al. The acute medical care costs of fall-related injuries among the US older adults. *Injury*. 2005;36(11):1316-1322.

Schiff. Pregnancy outcomes following hospitalisation for a fall in Washington State from 1987 to 2004. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2008;115(13):1648-1654.

Shah M, Chaudhari S, McLaughlin TP, et al. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. *Clinical therapeutics*. 2013;35(4):486.

Stevens JA, Powell KE, Smith SM, et al. Physical activity, functional limitations, and the risk of fall-related fractures in community-dwelling elderly. *Annals of epidemiology*. 1997;7(1):54-61.

Verma SK, Sorock GS, Pransky GS, Courtney TK, Smith GS. Occupational physical demands and same-level falls resulting in fracture in female workers: an analysis of workers' compensation claims. *Injury prevention*. 2007;13(1):32-36.

Wolinsky FD, Bentler SE, Liu L, et al. Recent hospitalization and the risk of hip fracture among older Americans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2009;64(2):249-255.

Comorbidities and falls/fractures risk factors

CV diseases

Hypertension, uncomplicated (ICD9: 401.x)

Cerebrovascular disease and Stroke (ICD9: 430.x-438.x)

Hypertension, complicated (ICD9: 402.x-405)

Hypotension (ICD9: 796.3)

Musculoskeletal problems

Arthritis (ICD9: 446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30)

Musculoskeletal problems (ICD9: 306.0, 723.9, 729.89)

Bynum JP, Rabins PV, Weller W, et al. The relationship between a dementia diagnosis, chronic illness, Medicare expenditures, and hospital use. *Journal of the American Geriatrics Society*. 2004;52(2):187-194.

Centers for Medicare & Medicaid Services. ICD-9-CM Diagnosis and Procedure Codes: Abbreviated and Full Code Titles. <https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html>. Accessed November 07 2016.

Forbes WF, McLachlan DR. Further thoughts on the aluminum-Alzheimer's disease link. *Journal of Epidemiology and Community Health*. 1996;50(4):401-403.

Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke; a journal of cerebral circulation*. 1998;29(8):1602-1604.

Osteoporosis (ICD9: 733.0x)

Neurologic impairments

Palmental reflex (ICD9: 796.1)

Parkinson's disease and other neurologic impairments (ICD9: 332.x, 331.9, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3)

Dementia (ICD9: 290.x, 294.1, 331.2)

Depression, neurotic disorders, or psychosis (ICD9: 293.8, 295-299, 300-309, 311, E937.x)

Alzheimer's disease (ICD9: 331.0)

Cognitive impairment (ICD9: 331.x)

Dizziness (ICD9: 780.4)

Syncope/fainting (ICD9: 780.2)

Endocrine, nutritional and metabolic diseases

Diabetes mellitus and diabetic peripheral neuropathy (ICD9: 250.x, 357.2)

Hyperparathyroidism (ICD9: 252.0x, 588.81)

Other

COPD (ICD9: 490.x, 491.x, 492.x, 494.x, 496.x)

Chronic kidney disease (ICD9: 403.x, 585.x)

Internal motility disorders (ICD9: 564.89)

Decreased vision (ICD9: 369.x)

Prior (serious) falls or fractures within the preceding year **Various:** (see outcomes listed above)

Leg and foot amputation (ICD9: 896.x, 897.x)

Lifestyle choices

Smoking (by proxy codes, and COPD (see below) (ICD9: 649.0x, 305.1x, V15.82)

Alcohol abuse (ICD9: 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3)

Medications

Opioids (NDC: codes for Opioids [full list available upon request])

Benzodiazepines (NDC: codes for Benzodiazepines [full list available upon request])

CPT: 1034F, 4000F, 4001F, 99406, 99407

HCPCS: D1320, G8402, G8403, G8453, G8454, G8455

Chronic use of inhaled or oral corticosteroids (NDC: codes for inhaled or oral corticosteroids [full list available upon request]) (Chronic was defined a days supply of ≥90 over one year)

Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation*. 2010;121(1):63-70

Johnston S, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2012;14(7):634-643.

Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299-308.

Mustard CA, Mayer T. Case-Control Study of Exposure to Medication and the Risk of Injurious Falls Requiring Hospitalization among Nursing Home Residents. *American Journal of Epidemiology*. 1997;145(8):738-745

Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J Urol*. 2010;184(4):1413-1418*

Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol*. 1991;46(5):M164-170

Pan H-H, Li C-Y, Chen T-J, Su T-P, Wang K-Y. Association of polypharmacy with fall-related fractures in older Taiwanese people: age-and gender-specific analyses. *BMJ open*. 2014;4(3):e004428.

Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care*. 2005;1130-1139.

Teng Z, Zhu Y, Wu F, et al. Opioids Contribute to Fracture Risk: A Meta-Analysis of 8 Cohort Studies: e0128232. *PLoS One*. 2015;10(6)

Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *New England journal of medicine*. 1988;319(26):1701-1707

Vaughan CP, Brown CJ, Goode PS, et al. The association of nocturia with incident falls in an elderly community-dwelling cohort. *Int J Clin Pract*. 2010;64(5):577-583.

NDC: National drug code; ICD-9: International Classification of Diseases (9th Edition); CPT: Common Procedural Code; HCPCS: Healthcare Common Procedure Coding System

*Pathophysiologic fractures, stress fractures, and fracture due to motor vehicle accident were excluded in the base case analysis.

Supplementary Table 2: Results from the (left) Cox model and (right) marginal structural model estimating the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449)

	Cox model results*		MSM results*	
	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden†				
Among those with OAB				
Low (1 – 89)	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.5)	<0.001
Medium (90 – 499)	1.3 (1.2, 1.4)	<0.001	1.4 (1.2, 1.5)	<0.001
High (500+)	1.4 (1.3, 1.5)	<0.001	1.5 (1.3, 1.6)	<0.001
Among those without OAB				
Low (1 – 89)	1.4 (1.3, 1.4)	<0.001	1.3 (1.3, 1.4)	<0.001
Medium (90 – 499)	1.4 (1.3, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
High (500+)	1.7 (1.6, 1.8)	<0.001	1.8 (1.6, 1.9)	<0.001
By age category vs. ≤45				
46 to 55	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.4)	<0.001
56 to 65	1.5 (1.4, 1.6)	<0.001	1.5 (1.3, 1.6)	<0.001
66 to 75	2.1 (2.0, 2.2)	<0.001	2.0 (1.9, 2.2)	<0.001
76 to 85	3.3 (3.1, 3.5)	<0.001	3.2 (2.9, 3.5)	<0.001
86+	4.6 (4.2, 5.0)	<0.001	4.8 (4.1, 5.5)	<0.001
Sex				
Female vs. male	1.5 (1.5, 1.6)	<0.001	1.5 (1.4, 1.6)	<0.001
Comorbidity categories at baseline				
Cardiovascular diseases‡	1.1 (1.1, 1.2)	<0.001	1.1 (1.0, 1.1)	0.017
Neurologic impairments	1.5 (1.4, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
Endocrine, nutritional and metabolic disease	1.2 (1.1, 1.3)	<0.001	1.1 (1.0, 1.3)	0.021
Cardiovascular disease X Neurologic impairments	1.0 (1.0, 1.1)	0.240	1.1 (1.0, 1.3)	0.041
Cardiovascular disease X Endocrine, nutritional, metabolic disease	0.9 (0.8, 1.0)	0.102	1.0 (0.8, 1.1)	0.715
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.0 (0.9, 1.2)	0.432	1.1 (0.9, 1.3)	0.491
No OAB vs. OAB at baseline				
Among those with no anticholinergic burden	0.8 (0.8, 0.9)	<0.001	0.8 (0.8, 0.9)	<0.001
Among those with low anticholinergic burden	0.9 (0.8, 0.9)	<0.001	0.9 (0.8, 1.0)	0.009
Among those with medium anticholinergic burden	0.8 (0.8, 0.9)	<0.001	0.8 (0.8, 0.9)	<0.001
Among those with high anticholinergic burden	1.0 (0.9, 1.0)	0.511	1.0 (0.9, 1.1)	0.908

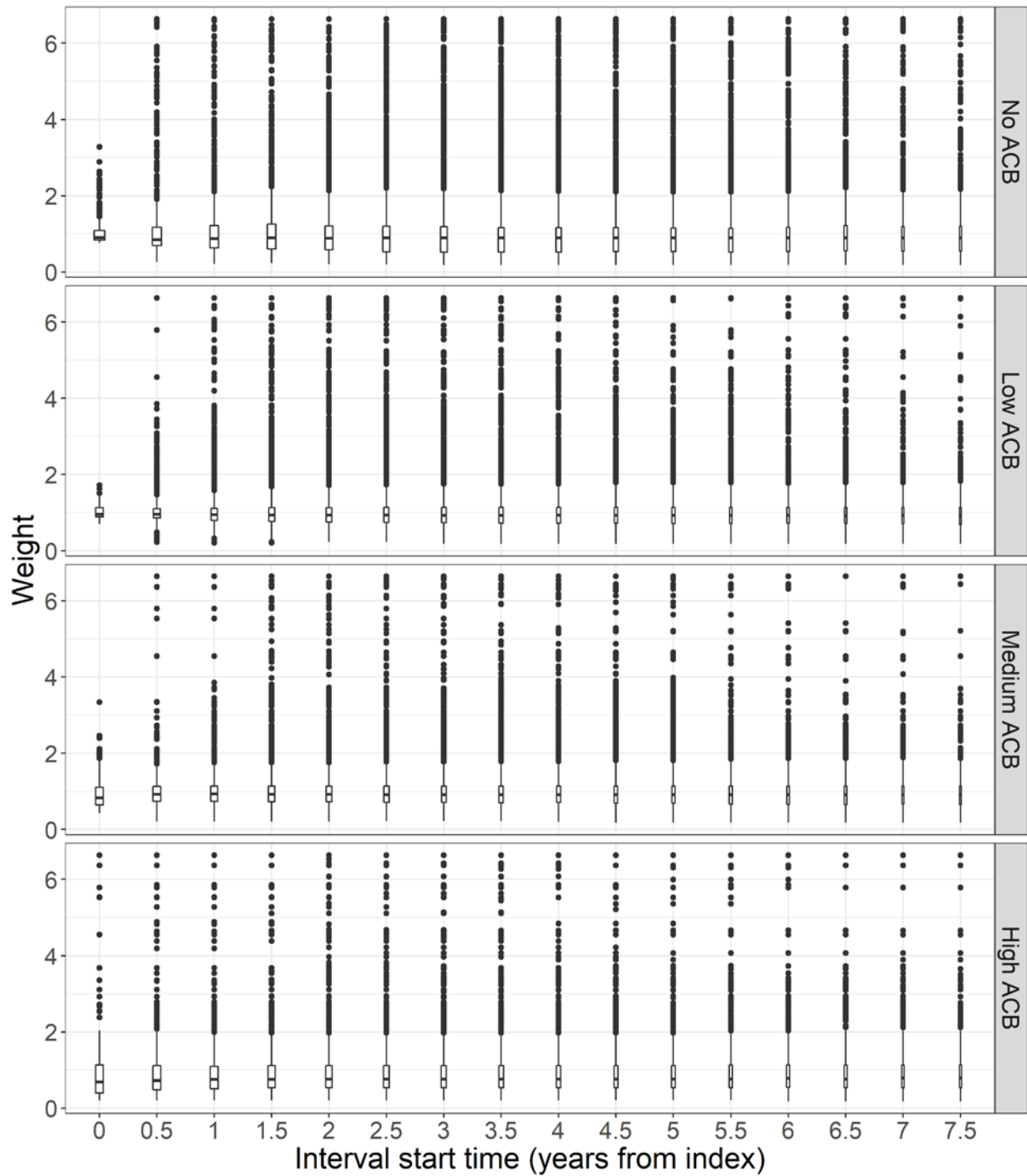
CI: confidence interval; HR: hazard ratio; OAB: overactive bladder; MSM: marginal structural model.

*The Cox model was implemented using function `coxph` from the R package `survival` version 2.41-3. The marginal structural model was implemented using function `coxph` from R package `survival` version 2.41-3, using the `weight` argument to apply time-varying weights, and setting a cluster term for enrolment id for robust variance estimation. Time-varying weights were calculated using function `ipwtm` from R package `ipw` version 1.0-11, and based on a multinomial logistic regression model (using a generalized logit link) with categorical time-varying anticholinergic burden as the outcome, where OAB at baseline, age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables.

†Level of anticholinergic burden assessed using the closest 6 month measure prior to the fall or fracture

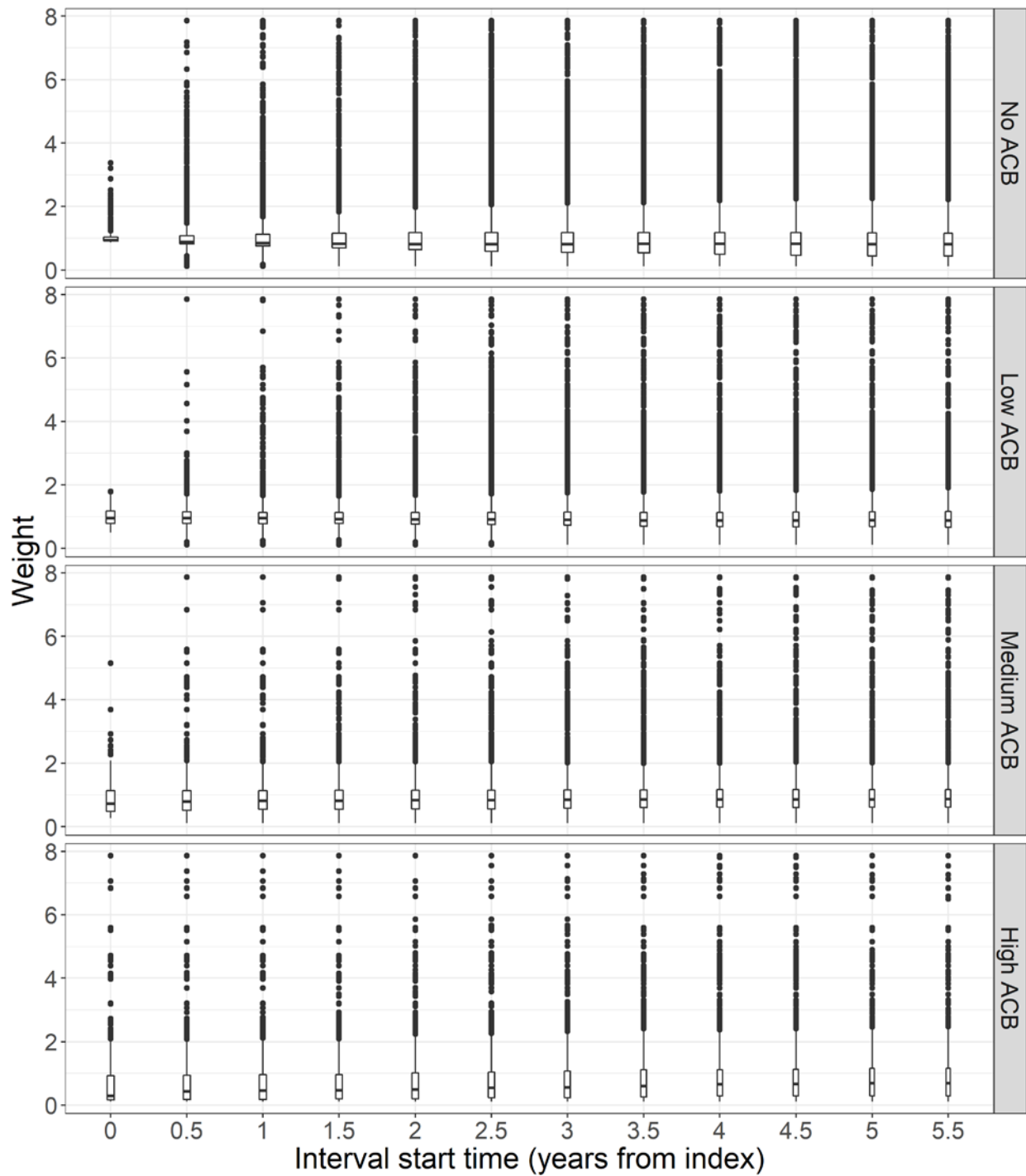
‡Cardiovascular disease = cerebrovascular disease + stroke.

Supplementary Figure 2: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.

Supplementary Figure 3: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.