

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. International Classification of Disease (ICD) Codes Used in the Study

Fractures

Vertebral

ICD-9-CM: 805.2-805.5,

ICD-10-CA: S22.0, S22.1, S32.0

Humerus

ICD-9-CM: 812.0, 812.1

ICD-10-CA: S42.2

Wrist

ICD-9-CM: 813

ICD-10-CA: S52

Hip

ICD-9-CM: 820

ICD-10-CA: S72.0-S72.2

Mental Disorders

Depression (unipolar):

ICD-9-CM: 296.2-296.3, 300.4, 309, 311

ICD-10-CA: F32, F33, F34.1, F43.2, F53.0

Anxiety:

ICD-9-CM: 300.0, 300.2, 300.3

ICD-10-CA: F40, F41, F42, F43.1

Schizophrenia:

ICD-9-CM: 295

ICD-10-CA: F20

eAppendix 2. Psychotropic Medications Examined in the Study, by Category, Specific Medication, and World Health Organization Anatomical Therapeutic Chemical (ATC) Classification Code

1. Selective serotonin reuptake inhibitors (N06AB)
2. Tricyclic antidepressants (N06AA)
3. Other antidepressants (mirtazapine, bupropion, venlafaxine, duloxetine, desvenlafaxine; N06AX11, N06AX12, N06AX16, N06AX21, N06AX23)
4. Lithium (N05AN)
5. Non-lithium mood stabilizers (carbamazepine, oxcarbazepine, valproic acid, lamotrigine, topiramate; N03AF01, N03AF02, N03AG01, N03AX09, N03AX11)
6. Antipsychotics (N05AA; N05AB, N05AC, N05AD, N05AE, N05AF; N05AG, N05AH, N05AX)
7. Benzodiazepines (N05BA)

eTable 1. Characteristics of the Sample Presented by Fracture Outcome

Characteristics	Total sample (n=68,730) N (%)	Major Osteoporotic Fracture (MOF) ¹			Hip Fracture		
		Yes (n=5750) N (%)	No (n=62,980) N (%)	<i>P</i> Value	Yes (n=1579) N (%)	No (n=67,151) N (%)	<i>P</i> Value
FRAX Risk Factors							
Age (years)	64.2 ± 11.2	68.8 ± 11.3	63.8 ± 11.1	<.001	74.4 ± 9.4	64.0 ± 11.2	<.001
Sex (male)	6455 (9.4)	405 (7.0)	6050 (9.6)	<.001	108 (6.8)	6347 (9.5)	<.001
Body mass index (kg/m ²)	27.1 ± 8.2	26.1 ± 5.0	27.2 ± 8.4	<.001	25.1 ± 4.6	27.1 ± 8.3	<.001
Prior fracture	10012 (14.6)	1486 (25.8)	8526 (13.5)	<.001	430 (27.2)	9582 (14.3)	<.001
Parental hip fracture	4060 (5.9)	182 (3.2)	3878 (6.2)	<.001	46 (2.9)	4014 (6.0)	<.001
Chronic obstructive pulmonary disease	5908 (8.6)	680 (11.8)	5228 (8.3)	<.001	207 (13.1)	5701 (8.5)	<.001
Recent glucocorticoid use	3781 (5.5)	392 (6.8)	3389 (5.4)	<.001	124 (7.9)	3657 (5.4)	<.001
Rheumatoid arthritis	2425 (3.5)	310 (5.4)	2115 (3.4)	<.001	100 (6.3)	2325 (3.5)	<.001
Alcohol or substance abuse	2080 (3.0)	237 (4.1)	1843 (2.9)	<.001	56 (3.5)	2024 (3.0)	.22
Femoral neck T-score	-1.4 ± 1.0	-1.9 ± 0.9	-1.3 ± 1.0	<.001	-2.3 ± 0.8	-1.3 ± 1.0	<.001
FRAX Risk Estimates							
MOF probability (%)	10.6 ± 7.8	16.0 ± 10.3	10.1 ± 7.4	<.001	20.5 ± 10.5	10.4 ± 7.6	<.001
Hip fracture probability (%)	2.6 ± 4.4	5.2 ± 6.3	2.4 ± 4.1	<.001	7.8 ± 7.0	2.5 ± 4.3	<.001
Mental Disorders							
None	55748 (81.1)	4562 (79.3)	51186 (81.3)	.003	1271 (80.5)	54477 (81.1)	.56
Depression	6604 (9.6)	620 (10.8)	5984 (9.5)		165 (10.4)	6439 (9.6)	

Anxiety	6187 (9.0)	549 (9.5)	5638 (9.0)		137 (8.7)	6050 (9.0)	
Schizophrenia	191 (0.3)	19 (0.3)	172 (0.3)		6 (0.4)	185 (0.3)	
Medication Use							
Osteoporosis medications	9531 (13.9)	869 (15.1)	8662 (13.8)	<.001	245 (15.5)	9286 (13.8)	<.001
SSRIs	4122 (6.0)	393 (6.8)	3729 (5.9)	<.001	100 (6.3)	4022 (6.0)	.005
Tricyclic Antidepressants	2913 (4.2)	273 (4.7)	2640 (4.2)	<.001	84 (5.3)	2829 (4.2)	.09
Other antidepressants	2007 (2.9)	136 (2.4)	1871 (3.0)	.004	27 (1.7)	1980 (2.9)	.01
Lithium	151 (0.2)	12 (0.2)	139 (0.2)	.78	² (<0.5)	148 (0.2)	.53
Mood stabilizers	711 (1.0)	76 (1.3)	635 (1.0)	.07	21 (1.3)	690 (1.0)	.32
Antipsychotics	898 (1.3)	104 (1.8)	794 (1.3)	<.001	41 (2.6)	857 (1.3)	<.001
Benzodiazepines	4126 (6.0)	494 (8.6)	3632 (5.8)	<.001	167 (10.6)	3959 (5.9)	<.001

¹Major Osteoporotic Fractures included one or more vertebral (N=1416, 2.1% of the total sample), humerus (N=1169, 1.7%), wrist (N=2253, 3.3%), and hip (N=1579, 2.3%).

²Suppressed due to small cell size.

eTable 2. Adjusted Hazard Ratios for Death in Subgroups Defined From Mental Disorders or Psychotropic Medications

Mental disorders and psychotropic medications	Death Hazard ratio ¹ (95% CI)
No mental disorders or psychotropic medications (referent)	1.00
Depression	0.88 (0.80-0.95)
Anxiety	0.85 (0.78-0.92)
Schizophrenia	1.27 (0.91-1.78)
SSRI	1.31 (1.19-1.44)
Tricyclic antidepressants	1.26 (1.15-1.38)
Other antidepressants	1.49 (1.29-1.72)
Lithium	1.45 (1.03-2.03)
Mood stabilizers	1.34 (1.11-1.60)
Antipsychotics	1.67 (1.42-1.96)
Benzodiazepines	1.48 (1.37-1.59)

¹Multivariable analyses adjusted for FRAX probability with BMD and prior osteoporosis drug use. Bolded results indicate p<0.05.

eTable 3. *c*-statistics (95% CI) for Fracture Discrimination According to FRAX Scores in Subgroups Defined From Mental Disorders or Psychotropic Medication Use

Subgroup	MOF <i>c</i> -statistic (95% CI)	Hip Fracture <i>c</i> -statistic (95% CI)
No mental disorders or psychotropic medication use (referent)	0.69 (0.69-0.70)	0.82 (0.81-0.83)
Depression	0.69 (0.67-0.71)	0.83 (0.81-0.86)
Anxiety	0.69 (0.67-0.71)	0.84 (0.81-0.87)
Schizophrenia	0.73 (0.60-0.85)	0.72 (0.52-0.92)
SSRIs	0.69 (0.66-0.72)	0.84 (0.81-0.87)
Tricyclic antidepressants	0.69 (0.66-0.72)	0.79 (0.75-0.83)
Other antidepressants	0.66 (0.61-0.70)	0.79 (0.71-0.86)
Lithium	0.75 (0.59-0.90)	-- ¹
Mood stabilizers	0.69 (0.63-0.76)	0.81 (0.73-0.89)
Antipsychotics	0.68 (0.63-0.74)	0.80 (0.74-0.86)
Benzodiazepines	0.70 (0.67-0.72)	0.77 (0.74-0.80)

¹Suppressed due to small cell size.

The *c*-statistic represents the concordance of the FRAX tool for predicting the outcome of fractures. It is a unitless index denoting the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur compared to a randomly selected subject who did not experience the event. It ranges from 0.5 (no better than chance) to 1.0 (perfect prediction).⁴³

eTable 4. Two-Way Interaction Analyses for Mental Disorders and Psychotropic Medication Use vs Sex, Age, FRAX Probability, WHO Category or Prior Hip/Spine Fracture, From Multivariable Cox Proportional Hazard Regression Models Which Also Included All Main Effect Covariates

Interactions with Sex		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
Sex * Mental disorder	.66	.99
Sex * SSRIs	.71	.81
Sex * Tricyclic antidepressants	.62	.24
Sex * Other antidepressants	.70	.69
Sex * Lithium	.83	NA
Sex * Mood stabilizers	.49	.90
Sex * Antipsychotics	.37	.65
Sex * Benzodiazepines	.54	.18
Interactions with age (<65 vs 65+ years)		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
Age * Mental disorder	.07	.74
Age * SSRIs	.39	.51
Age * Tricyclic antidepressants	.52	.34
Age * Other antidepressants	.71	.51
Age * Lithium	.89	NA
Age * Mood stabilizers	.93	.41
Age * Antipsychotics	.67	.94
Age * Benzodiazepines	.21	.51
Interactions with FRAX probability		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
FRAX * Mental disorder	.79	.30
FRAX * SSRIs	.44	.95
FRAX * Tricyclic antidepressants	.75	.45
FRAX * Other antidepressants	.83	.27
FRAX * Lithium	.41	NA
FRAX * Mood stabilizers	.65	.35
FRAX * Antipsychotics	.49	.89
FRAX * Benzodiazepines	.76	.41

Interactions with WHO category or prior hip/spine fracture		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
WHO category * Mental disorder	.78	.67
WHO category * SSRIs	.49	.54
WHO category * Tricyclic antidepressants	.49	.39
WHO category * Other antidepressants	.24	.26
WHO category * Lithium	.35	NA
WHO category * Mood stabilizers	.29	1.00
WHO category * Antipsychotics	.41	.72
WHO category * Benzodiazepines	.89	.54
Prior spine/hip fracture * Mental disorder	.08	.30
Prior spine/hip fracture * SSRIs	.59	.70
Prior spine/hip fracture * Tricyclic antidepressants	.90	.38
Prior spine/hip fracture * Other antidepressants	.23	.88
Prior spine/hip fracture * Lithium	.99	NA
Prior spine/hip fracture * Mood stabilizers	.76	.38
Prior spine/hip fracture * Antipsychotics	.17	.98
Prior spine/hip fracture * Benzodiazepines	.63	.72

Interactions with osteoporosis treatment prior to BMD		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
Osteoporosis treatment * Mental disorder	.94	.21
Osteoporosis treatment * SSRIs	.36	.90
Osteoporosis treatment * Tricyclic antidepressants	.12	.14
Osteoporosis treatment * Other antidepressants	.05	.73
Osteoporosis treatment * Lithium	.99	NA
Osteoporosis treatment * Mood stabilizers	.79	.96
Osteoporosis treatment * Antipsychotics	.49	.66
Osteoporosis treatment * Benzodiazepines	.77	.87

Interactions with osteoporosis treatment subsequent to BMD		
Interaction terms	Major Osteoporotic Fractures	Hip Fractures
	Type 3 Tests	Type 3 Tests
	<i>P</i> Value	<i>P</i> Value
Osteoporosis treatment * Mental disorder	.26	.19
Osteoporosis treatment * SSRIs	.002	.85
Osteoporosis treatment * Tricyclic antidepressants	.78	.45
Osteoporosis treatment * Other antidepressants	.96	.77
Osteoporosis treatment * Lithium	.98	NA
Osteoporosis treatment * Mood stabilizers	.89	.78
Osteoporosis treatment * Antipsychotics	.88	.21
Osteoporosis treatment * Benzodiazepines	.14	.22
Stratified analysis for SSRIs:	Major Osteoporotic Fractures	Hip Fractures
	HR (95% CI)	HR (95% CI)
For those without osteoporosis treatment:	1.21 (1.04-1.41)	1.42 (1.05-1.93)
For those with osteoporosis treatment:	1.81 (1.52-2.15)	1.57 (1.12-2.20)

NA: Results are not available due to insufficient hip fractures in the lithium subgroup.

eTable 5. Adjusted Hazard Ratios (aHR) With 95% CIs for Incident Fracture Associated With Mental Disorders and Psychotropic Medication Use

	MOF aHR (95% CI)		Hip Fracture aHR (95% CI)	
	Model 1	Model 2	Model 1	Model 2
Depression	1.40 (1.28-1.52)	1.07 (0.96-1.18)	1.52 (1.29-1.79)	1.09 (0.89-1.34)
Anxiety	1.20 (1.09-1.31)	1.06 (0.97-1.17)	1.10 (0.93-1.32)	0.96 (0.80-1.15)
Schizophrenia	1.92 (1.22-3.01)	1.22 (0.75-1.98)	2.84 (1.27-6.33)	1.18 (0.50-2.77)
SSRIs	1.42 (1.28-1.57)	1.38 (1.23-1.54)	1.42 (1.16-1.75)	1.37 (1.09-1.72)
Tricyclic antidepressants	1.05 (0.93-1.18)	1.04 (0.92-1.18)	1.16 (0.93-1.45)	1.15 (0.92-1.44)
Other antidepressants	1.24 (1.04-1.48)	1.21 (1.01-1.45)	1.02 (0.69-1.50)	0.98 (0.65-1.46)
Lithium	0.82 (0.47-1.46)	0.80 (0.45-1.43)	-- ¹	-- ¹
Mood stabilizers	1.55 (1.23-1.96)	1.55 (1.23-1.95)	1.75 (1.13-2.72)	1.73 (1.11-2.70)
Antipsychotics	1.56 (1.28-1.91)	1.50 (1.21-1.87)	2.52 (1.82-3.49)	2.43 (1.72-3.45)
Benzodiazepines	1.19 (1.08-1.31)	1.18 (1.07-1.30)	1.27 (1.08-1.50)	1.28 (1.08-1.51)

Model 1: Mental disorders and medications analyzed separately. Model 2: Mental disorders and medications analyzed in the same model. All models were adjusted for FRAX score computed without BMD and for prior osteoporosis medication use.

Bolded results indicate $P < 0.05$.

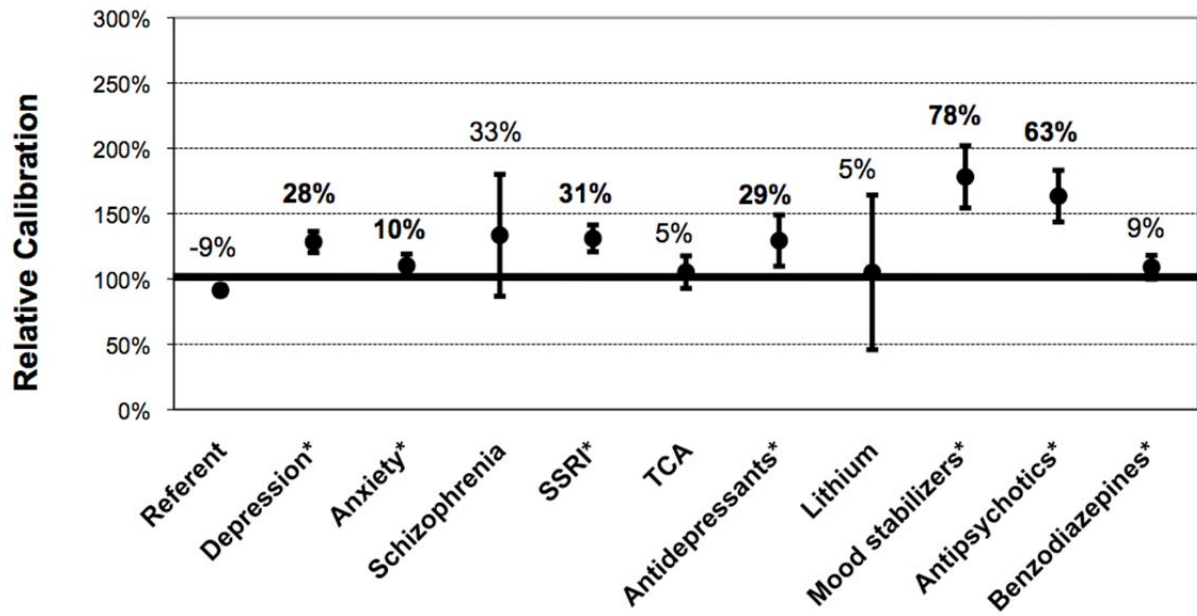
¹Suppressed due to small cell size.

eTable 6. Gradient of Risk in FRAX Scores Computed Without BMD (Adjusted Hazard Ratio per Standard Deviation) in Subgroups Defined From Mental Disorders or Psychotropic Medication Use

Subgroup	MOF Adjusted hazard ratio per standard deviation (95% CI)	Hip Fracture Adjusted hazard ratio per standard deviation (95% CI)
No mental disorders or psychotropic medication use (referent)	1.99 (1.91-2.06)	4.33 (3.95-4.74)
Depression	1.88 (1.74-2.04)	3.46 (2.91-4.11)
Anxiety	1.92 (1.76-2.09)	4.19 (3.37-5.22)
Schizophrenia	2.09 (1.29-3.38)	3.09 (1.10-8.65)
SSRIs	1.87 (1.69-2.06)	3.63 (2.88-4.58)
Tricyclic antidepressants	1.82 (1.60-2.08)	3.20 (2.45-4.20)
Other antidepressants	1.68 (1.42-1.98)	3.03 (2.02-4.53)
Lithium	2.32 (1.21-4.45)	-- ¹
Mood stabilizers	1.75 (1.40-2.18)	2.80 (1.73-4.54)
Antipsychotics	1.79 (1.47-2.17)	2.97 (2.08-4.23)
Benzodiazepines	1.94 (1.75-2.15)	3.26 (2.63-4.04)

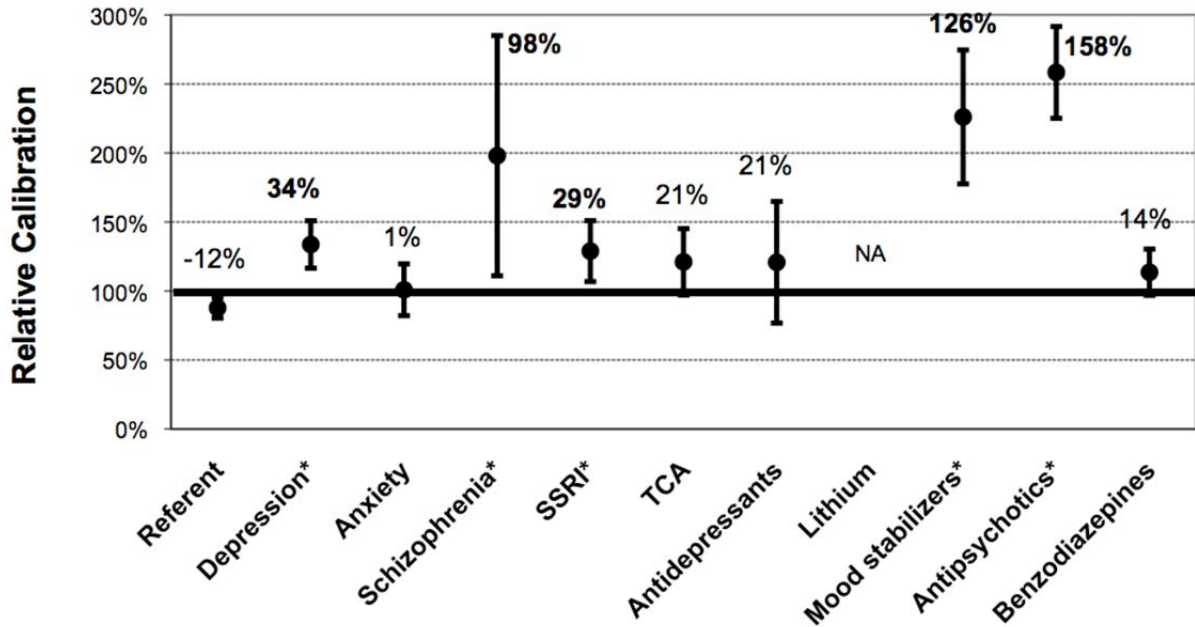
¹Suppressed due to small cell size.

eFigure 1. Relative Calibration of MOF FRAX Scores Without BMD With Mental Disorders or Psychotropic Medications Present



The solid line at 100% indicates perfect calibration. Results show the percentage change from perfect calibration based on the difference between the observed cumulative fracture probability at 10 years versus the expected 10-year fracture probability predicted by FRAX. (* denotes significant differences in calibration). Referent refers to those without mental disorders or psychotropic medication exposure. Error bars represent 95% CIs.

eFigure 2. Relative Calibration of Hip Fracture FRAX Scores Without BMD With Mental Disorders or Psychotropic Medications



The solid line at 100% indicates perfect calibration. Results show the percentage change from perfect calibration based on the difference between the observed cumulative fracture probability at 10 years versus the expected 10-year fracture probability predicted by FRAX. (* denotes significant differences in calibration). Referent refers to those without mental disorders or psychotropic medication exposure. Error bars represent 95% CIs. Lithium results are not available due to small cell size.