

Supplementary information

Predicting serum levels of lithium-treated patients: A supervised machine learning approach

Running Title: Machine learning to predict lithium concentration

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Appendix 1 (Supplementary Table S1). Detailed drug name with codes and diagnostic codes for mental disorders or medical diseases

Drug name	Detail drugs and their Anatomical Therapeutic Chemical (ATC) codes
Concomitant psychotropic medications	
Mood stabilizers	
Lithium	Lithium (N05AN01)
Carbamazepine	Carbamazepine (N03AF01)
Lamotrigine	Lamotrigine (N03AX09)
Valproic acid	Valproic acid (N03AG01)
Topiramate	Topiramate (N03AX11)
Antidepressants	
Selective serotonin reuptake inhibitor	Citalopram (N06AB04), Escitalopram (N06AB10), Fluoxetine (N06AB03), Paroxetine (N06AB05), Sertraline (N06AN06)
Serotonin norepinephrine reuptake inhibitor	Duloxetine (N06AX21), Milnacipran (N06AX17), Venlafaxine (N06AX16)
Trazodone	Trazodone (N06AX05)
Mirtazapine	Mirtazapine (N06AX11)
Bupropion	Bupropion (N06AX12)
Agomelatine	Agomelatine (N06AX22)
Antipsychotics	
Typical antipsychotics	Chlorpromazine (N05AA01), Haloperidol (N05AD01), Flupentixol (N05AF01), Fluphenazine (N05AB02), Loxapine (N05AH01), Prochlorperazine (N05AB04), Thioridazine (N05AC02), Zuclopenthixol (N05AF05)
The benzamides	Amisulpride (N05AL05), Sulpiride (N05AL01)
The -dones	Paliperidone (N05AX13), Risperidone (N05AX08), Ziprasidone (N05AE04)
The -pines	Clozapine (N05AH02), Olanzapine (N05AH03), Quetiapine (N05AH04), Zotepine (N05AX11)
Aripiprazole	Aripiprazole (N05AX12)
Anxiolytics, sedatives, or hypnotics	
Benzodiazepines	Alprazolam (N05BA12), Chlordiazepoxide (N05BA02), Clobazam (N05BA09), Clonazepam (N05AE01), Diazepam (N05BA01), Estazolam (N05CD04), Fludiazepam (N05BA17), Flurazepam (N05CD01), Lorazepam (N05BA06), Midazolam (N05CD08), Triazolam (N05CD05)
Non-benzodiazepines	Zaleplon (N05CF03), Zolpidem (N05CF02)
Antidementia	
Acetylcholinesterase inhibitors	Donepezil (N06DA02), Galantamine (N06DA04), Rivastigmine (N06DA03)
Concomitant medications (other)	
Lipid-lowering agents	
Statins	Statins (C10AA, C10BA)
Fibrates	Fibrates (C10AB)
Antidiabetic agents	
Insulins	Insulins (A10A)
Metformin	Metformin (A10BA02, A10BD)
Sodium-glucose cotransporter 2 inhibitors	Sodium-glucose cotransporter 2 inhibitors (A10BK)
Dipeptidyl peptidase 4 inhibitors	Dipeptidyl peptidase 4 inhibitors (A10BH)
Sulfonylureas	Sulfonylureas (A10BB, A10BD02)
Acarbose	Acarbose (A10BF)

Thiazolidinediones	Thiazolidinediones (A10BG)
Meglitinides	Meglitinides (A10BX)
Anti-hypertensive medications	
Angiotensin converting enzyme inhibitors	Angiotensin converting enzyme inhibitors (C09A, C09B)
Angiotensin receptor blockers	Angiotensin receptor blockers (C09C, C09D)
Diuretics	Diuretics (C03)
Beta blockers	Beta blockers (C07)
Calcium channel blockers	Calcium channel blockers (C08)
Antiplatelet drugs	
Aspirin	Aspirin (B01AC06)
Others	Others (B01AC07, B01AC22, B01AC30, B01AC91)
Antiarrhythmic drugs	
Amiodarone	Amiodarone (C01BD01, C01BD07)
Non-steroidal anti-inflammatory drugs	Non-steroidal anti-inflammatory drugs (M01AA, M01AX, M01AB, M01AC, M01AE, M01AG, M01AH)
Antacids	Antacids (A02BA, A02BC)
Mental disorders / Medical diseases	The International Classification of Diseases 9th (ICD-9) or 10th (ICD-10)
Mental disorders	
Neurodevelopmental disorders	299, 307.2, 307.3, 307.9, 314, 315, 317, 318, 319, F44.4, F63.3, F70, F71, F72, F73, F78, F79, F80.0, F80.1, F80.2, F80.4, F80.89, F80.9, F81, F82, F84.0, F84.3, F84.5, F84.8, F84.9, F88, F89, F90.1, F90.2, F90.8, F90.9, F95, F98.4, F98.8, H93.25, R41.840, R41.841, R41.843, R41.844, R45.1, R45.81, R45.82, R48.0
Disruptive, impulse-control, and conduct disorders	312.32, 312.33, 312.34, 312.8, 312.9, 313.81, F63.1, F63.2, F63.81, F9
Schizophrenia spectrum and other psychotic disorders	295, 297.0, 297.1, 297.2, 298.3, 298.4, 298.8, 298.9, F20, F22, F23, F25, F28, F2
Bipolar and related disorders	296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.80, 296.89, 301.13, F30.1, F30.2, F30.3, F30.4, F30.9, F31, F34
Depressive disorders	296.2, 296.3, 296.99, 300.4, 311, 625.4, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33, F34.1, F34.8, F34.9, G43.82, G43.83, N94
Anxiety disorders	300.00, 300.01, 300.02, 300.09, 300.2, 309.21, 313.23, F40, F41, F93.0, F94
Obsessive-compulsive and related disorders	300.3, 300.7, 312.39, 698.4, F42, F45.2, F63.3, F63.89, L98
Somatic symptom and related disorders	300.11, 300.19, 300.7, 300.8, 316, F44.2, F44.4, F44.5, F44.6, F44.7, F45.0, F45.1, F45.2, F45.8, F45.9, F48.8, F54, F68
Elimination disorders	307.6, 307.7, 787.60, 788.30, 788.39, F98.0, F98.1, N39.490, N39.498, R15, R32, R39.8
Sleep-wake disorders	307.4, 327, 347, 780.5, F51, G47.0, G47.1, G47.2, G47.3, G47.4, G47.5, G47.61, G47.69, G47.8, G47
Sexual dysfunctions	302.7, F52.0, F52.1, F52.2, F52.3, F52.4, F52.6, F52.8, F52.9, R3
Substance-related and addictive disorders	291.4, 291.81, 292.0, 292.2, 303, 304, 305, 312.31, F10.10, F10.120, F10.129, F10.20, F10.21, F10.220, F10.229, F10.230, F10.232, F10.239, F10.920, F10.929, F11.10, F11.120, F11.129, F11.20, F11.21, F11.220, F11.229, F11.23, F11.90, F11.920, F11.929, F11.93, F12.10, F12.120, F12.129, F12.20, F12.21, F12.220, F12.229, F12.90, F12.920, F12.929, F13.10, F13.120, F13.129, F13.20, F13.21, F13.220, F13.229, F13.23, F13.90, F13.920, F13.929, F13.93, F14.10, F14.120, F14.129, F14.20, F14.21, F14.220, F14.229, F14.23, F14.90, F14.920, F14.929, F15.10,

	F15.120, F15.129, F15.20, F15.21, F15.220, F15.229, F15.23, F15.90, F15.920, F15.929, F15.93, F16.10, F16.120, F16.129, F16.20, F16.21, F16.220, F16.229, F16.90, F16.920, F16.929, F17.200, F17.201, F17.203, F17.210, F17.211, F17.213, F17.220, F17.221, F17.223, F17.290, F17.291, F17.293, F18.10, F18.120, F18.129, F18.20, F18.21, F18.220, F18.229, F18.90, F18.920, F18.929, F19.10, F19.120, F19.129, F19.20, F19.21, F19.220, F19.229, F19.23, F19.90, F19.920, F19.929, F19.93, F55, F63
Neurocognitive disorders (Except vascular dementia)	F02, F05, G30, G31, G31.0, G31.1, G93.7, 290.1, 290.2, 290.3, 294.1, 294.2, 331.0, 331.1, 331.2, 331.8, 331.9, F03.90, G31.83, G31.85, G31.89, F03.90, G31.83, G31.85, G31.8
Personality disorders	301.0, 301.20, 301.22, 301.4, 301.50, 301.6, 301.7, 301.81, 301.82, 301.83, 301.89, 301.9, F21, F60, F6
Trauma- and stressor-related disorders	308.3, 309.0, 309.24, 309.28, 309.3, 309.4, 309.81, 309.89, 309.9, 313.89, F43.0, F43.1, F43.21, F43.22, F43.23, F43.24, F43.25, F43.8, F43.9, F93.8, F94.1, F94.2, F94.9, F98
Dissociative disorders	300.12, 300.13, 300.14, 300.15, 300.6, F44.0, F44.1, F44.81, F44.9, F48
Feeding and eating disorders	307.1, 307.5, F50, F98.2, F98
Gender dysphoria	302.6, 302.85, F64.1, F64.2, F64.8, F64
Paraphilic disorders	302.2, 302.3, 302.4, 302.81, 302.82, 302.83, 302.84, 302.89, 302.9, F65, F6
Medical diseases	
Myocardial infarct	410, 412, I21, I22, I25
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.6, 425.7, 425.8, 425.9, 428, I5
Peripheral vascular diseases	047.1, 093.0, 437.3, 440, 441, 443.1, 443.2, 443.3, 443.4, 443.5, 443.6, 443.7, 443.8, 443.9, 557.1, 557.9, I71, I73.9, I79.0, R02, Z95.8, Z95
Cerebrovascular diseases	362.34, 430, 431, 432, 433, 434, 435, 436, 437, 438, G45.0, G45.1, G45.2, G45.4, G45.8, G45.9, G46, I60, I61, I62, I63, I64, I65, I66, I67.0, I67.1, I67.2, I67.4, I67.5, I67.6, I67.7, I67.8, I67.9, I68.1, I68.2, I68.8, I6
Vascular dementia	290.4, F01
Hemiplegia	334.1, 342, 343, 344.0, 344.1, 344.2, 344.3, 344.4, 344.5, 344.6, 344.9, G04.1, G81, G82.0, G82.1, G82
Chronic pulmonary diseases	416.8, 416.9, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J6
Peptic ulcer diseases	531, 532, 533, 534, K25, K26, K27, K28
Liver diseases without sequelae	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, K70.2, K70.3, K71.7, K73, K74.0, K74.2, K74.3, K74.4, K74.5, K74.6, V42
Liver diseases with sequelae	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8, K72.1, K72.9, K76.6, K76
Renal diseases	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0, 583.1, 583.2, 583.3, 583.4, 583.5, 583.6, 583.7, 585, 586, 588.0, N01, N03, N05.2, N05.3, N05.4, N05.5, N05.6, N07.2, N07.3, N07.4, N18, N19, N25, V42.0, V45.1, V5
Connective tissue diseases	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 725, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.3, M06.9, M32, M33.2, M34, M35
Any cancer	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 174, 175, 176, 177, 178, 179, 180, 181, 182,

	183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 195.0, 195.1, 195.2, 195.3, 195.4, 195.5, 195.6, 195.7, 195.8, 200, 201, 202, 203, 204, 205, 206, 207, 208, 238.6, C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C88.3, C88.7, C88.9, C90.0, C90.1, C91, C92, C93, C94.0, C94.1, C94.2, C94.3, C94.51, C94.7, C95, C9
Metastatic solid tumor	196, 197, 198, 199, C77, C78, C79, C8
Acquired immune deficiency syndrome	042, 043, 044, B20, B21, B22, B23, B2
Hypertension	401, 402, 403, 404, 405, I10, I11, I12, I13, I15, N26
Hyperlipidemia	272, E75.2, E75.3, E75.5, E75.6, E77, E78, E88.1, E88.2, E88.8
Diabetes mellitus without end organ damage	250.0, 250.1, 250.2, 250.3, 250.8, 250.9, E10.1, E10.5, E10.9, E11.1, E11.5, E11.9, E13.1, E13.5, E13.9, E14.1, E14.5, E14
Diabetes mellitus with end organ damage	250.4, 250.5, 250.6, 250.7, E10.2, E10.3, E10.4, E11.2, E11.3, E11.4, E13.2, E13.3, E13.4, E14.2, E14.3, E14
Intracranial bleeding	430, 431, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0, I60, I61, I62, S06.340A, S06.341A, S06.342A, S06.343A, S06.344A, S06.345A, S06.346A, S06.347A, S06.348A, S06.349A, S06.350A, S06.351A, S06.352A, S06.353A, S06.354A, S06.355A, S06.356A, S06.357A, S06.358A, S06.359A, S06.360A, S06.361A, S06.362A, S06.363A, S06.364A, S06.365A, S06.366A, S06.367A, S06.368A, S06.369A, S06.4x0A, S06.4x1A, S06.4x2A, S06.4x3A, S06.4x4A, S06.4x5A, S06.4x6A, S06.4x7A, S06.4x8A, S06.4x9A, S06.5x0A, S06.5x1A, S06.5x2A, S06.5x3A, S06.5x4A, S06.5x5A, S06.5x6A, S06.5x7A, S06.5x8A, S06.5x9A, S06.6x0A, S06.6x1A, S06.6x2A, S06.6x3A, S06.6x4A, S06.6x5A, S06.6x6A, S06.6x7A, S06.6x8A, S06.6x9
Ocular bleeding	360.43, 362.81, 363.6, 364.4, 372.72, 376.32, 377.42, 379.23, H05.23, H11.3, H21.0, H31.3, H35.6, H43.1, H44.8, H47.0
Intraabdominal bleeding	568.81, 866.01, 866.02, 866.11, 866.12, K66.1, S31.001A, S37.011
Hemopericardium or pericardial bleeding	423.0, I31
Hematoma or compartment syndrome	599.7, M79.A, N30.01, N30.21, N30.31, N30.81, N30.91, R3
Gastrointestinal bleeding	530.7, 531, 531.2, 531.4, 531.6, 532, 533, 534, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578, K22.6, K25, K26, K27, K28, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K52.81, K55.21, K56.60, K56.60, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.81, K57.91, K57.93, K62.5, K92.0, K92.1, K92
Other bleeding	302.7, F52.0, F52.1, F52.2, F52.3, F52.4, F52.6, F52.8, F52.9, R3

Appendix 2 (Supplementary Table S2). Proportion of laboratory data with no missing test values in inpatient data

Features	Inpatient data (N = 2028)
White blood cell	699 (34.47)
Segment	599 (29.54)
Lymphocyte	599 (29.54)
Monocyte	599 (29.54)
Eosinophil	599 (29.54)
Basophil	599 (29.54)
Red blood cell	614 (30.28)
Hemoglobin	619 (30.52)
Hematocrit	619 (30.52)
Mean corpuscular volume	614 (30.28)
Mean corpuscular hemoglobin	614 (30.28)
Mean corpuscular hemoglobin concentration	614 (30.28)
Red cell distribution width-standard deviation	614 (30.28)
Red cell distribution width-coefficient of variation	468 (23.08)
Platelet	614 (30.28)
Blood urea nitrogen	584 (28.80)
Serum creatinine	638 (31.46)
Aspartate aminotransferase	522 (25.74)
Alanine aminotransferase	481 (23.72)
Sodium	455 (22.44)
Potassium	468 (23.08)

Data was expressed as N (percentage).

Appendix 3 (Supplementary Table S3). Characteristics of lithium-treated patients, comparing inpatient test data and outpatient test data

Characteristics	Inpatient (N = 204)	Outpatient (N = 7)	t or χ^2	p
Lithium serum levels, mmol/l	0.70 ± 0.22	0.59 ± 0.24	1.32	0.188
Basic information				
Age, year	42.95 ± 13.82	46.86 ± 6.79	-0.75	0.457
Sex, female	87 (42.65)	3 (42.86)	0.000	0.991
Clinical characteristics				
Height, m	1.64 ± 0.09	1.65 ± 0.07	-0.33	0.745
Weight, kg	70.35 ± 14.54	76.43 ± 20.98	-1.07	0.285
Systolic blood pressure, mmHg	122.30 ± 10.42	130.70 ± 18.74	-2.03	0.043
Diastolic blood pressure, mmHg	76.21 ± 7.76	76.14 ± 10.95	0.02	0.983
Lithium prescription				
Daily dose, mg/day	896.30 ± 257.20	857.10 ± 364.50	0.39	0.696
Dosing frequency, time/day	2.60 ± 0.73	2.43 ± 1.27	0.60	0.547
Last dose, mg	362.50 ± 131.30	385.70 ± 146.40	1.24	0.647
Time interval, hour	13.11 ± 1.32	13.43 ± 1.27	-0.63	0.527
Concomitant psychotropic drugs				
Mood stabilizers				
Carbamazepine	11 (5.39)	1 (14.29)	1.00	0.318
Lamotrigine	7 (3.43)	1 (14.29)	2.19	0.139
Topiramate	15 (7.35)	0 (0.00)	0.55	0.457
Valproic acid	67 (32.84)	5 (71.43)	4.48	0.034
Antidepressants				
SSRI	24 (11.76)	0 (0.00)	0.93	0.335
SNRI	10 (4.90)	0 (0.00)	0.36	0.548
Trazodone	4 (1.96)	0 (0.00)	0.14	0.708
Mirtazapine	7 (3.43)	0 (0.00)	0.25	0.618
Bupropion	8 (3.92)	0 (0.00)	0.29	0.593
Agomelatine	7 (3.43)	0 (0.00)	0.25	0.618
Antipsychotics				
Typical antipsychotics	23 (11.27)	0 (0.00)	0.89	0.347
The benzamides	7 (3.43)	0 (0.00)	0.25	0.618
The -dones	49 (24.02)	0 (0.00)	2.19	0.139
The -pines	129 (63.24)	0 (0.00)	11.39	0.001
Aripiprazole	23 (11.27)	0 (0.00)	0.89	0.347
Anxiolytics, sedatives, or hypnotics				
Benzodiazepines	169 (82.84)	0 (0.00)	29.13	<0.0001
Non-benzodiazepines	32 (15.69)	0 (0.00)	1.29	0.255
Acetylcholinesterase inhibitors	1 (0.49)	0 (0.00)	0.03	0.853
Mental disorders				
Bipolar disorders	150 (73.53)	5 (71.43)	0.02	0.902
Laboratory data				
Serum creatinine, mg/dL	0.80 ± 0.16	0.80 ± 0.12	-0.90	0.970
BUN, mg/dL	9.97 ± 2.58	10.86 ± 2.01	-0.04	0.368

Abbreviations: BUN; blood urea nitrogen; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Data was expressed as N (percentage) or mean ± standard deviation. Time interval is the time between the blood draw and last lithium dose.

Appendix 4 (Supplementary Table S4). Detail information of binary outcomes in inpatient test data and outpatient test data

Model	TP	TN	FP	FN	TPR (Sensitivity)	TNR (Specificity)	PPV (Precision)	NPV	AUC-ROC	F-score	Accuracy
LogR											
Inpatient (n = 204)	118 (112-124)	31 (25-36)	40 (35-46)	15 (9-21)	0.886 (0.839-0.932)	0.431 (0.356-0.506)	0.745 (0.726-0.764)	0.675 (0.600-0.750)	0.748 (0.732-0.764)	0.809 (0.792-0.826)	0.727 (0.707-0.748)
Outpatient (n = 7)	5 (5-5)	2 (2-2)	0 (0-0)	0 (0-0)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	1.000 (1.000-1.000)
SVM											
Inpatient (n = 204)	125 (121-129)	23 (17-29)	48 (42-54)	8 (4-12)	0.940 (0.911-0.969)	0.324 (0.241-0.407)	0.723 (0.702-0.744)	0.747 (0.675-0.819)	0.759 (0.744-0.774)	0.817 (0.806-0.828)	0.725 (0.706-0.745)
Outpatient (n = 7)	5 (4-5)	1 (1-2)	1 (0-1)	0 (0-1)	0.920 (0.784-1.056)	0.700 (0.360-1.040)	0.887 (0.757-1.016)	0.800 (0.460-1.140)	0.960 (0.892-1.028)	0.902 (0.778-1.026)	0.857 (0.680-1.035)
RF											
Inpatient (n = 204)	127 (126-129)	16 (10-22)	55 (49-61)	6 (4-7)	0.958 (0.947-0.969)	0.220 (0.134-0.305)	0.697 (0.676-0.719)	0.728 (0.659-0.797)	0.784 (0.754-0.814)	0.807 (0.794-0.820)	0.701 (0.675-0.727)
Outpatient (n = 7)	5 (5-5)	2 (1-2)	0 (0-1)	0 (0-0)	1.000 (1.000-1.000)	0.900 (0.622-1.178)	0.967 (0.874-1.059)	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.982 (0.931-1.032)	0.971 (0.892-1.051)
XGBoost											
Inpatient (n = 204)	120 (116-125)	27 (24-29)	44 (42-47)	13 (8-17)	0.904 (0.870-0.938)	0.377 (0.344-0.411)	0.731 (0.721-0.741)	0.681 (0.607-0.756)	0.775 (0.741-0.810)	0.808 (0.792-0.825)	0.721 (0.700-0.741)
Outpatient (n = 7)	4 (2-5)	2 (1-2)	0 (0-1)	1 (0-3)	0.720 (0.498-0.942)	0.900 (0.622-1.178)	0.950 (0.811-1.089)	0.600 (0.286-0.914)	0.960 (0.849-1.071)	0.811 (0.647-0.975)	0.771 (0.569-0.974)

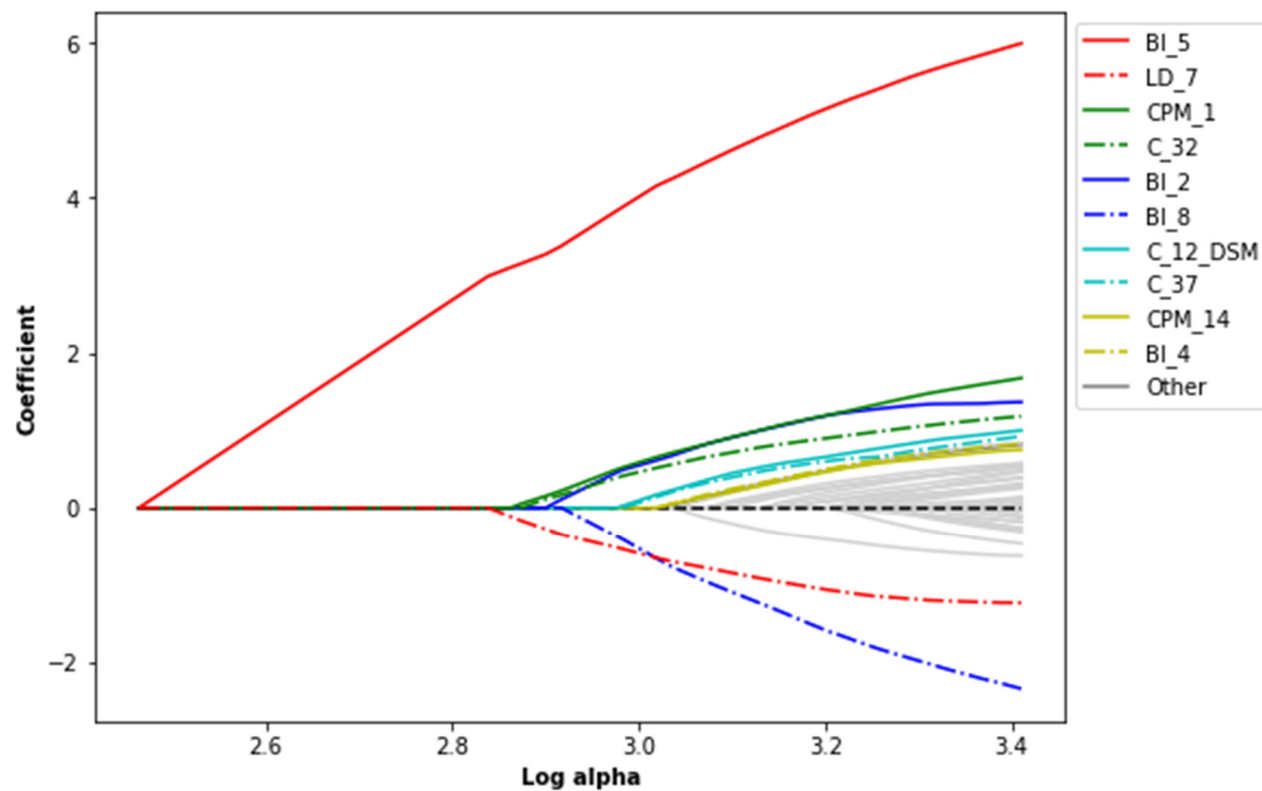
Abbreviations: AUC-ROC, area under the curve of receiver operator characteristic; FN, false negative; FP, false positive; LogR, logistic regression; NPV, negative predictive value; PPV, positive predictive value; RF, random forests; SVM, support vector machine; TN, true negative; TP, true positive; TNR, true negative rate; TPR, true positive rate; XGBoost, extreme gradient boosting.

Appendix 5 (Supplementary Table S5). Detail information of continuous outcomes in inpatient test data and outpatient test data

Model	MAE	MSE	RMSE	R ²	Accuracy
LinR					
Inpatient (n = 204)	0.159 (0.156-0.162)	0.038 (0.037-0.040)	0.196 (0.193-0.199)	0.209 (0.187-0.231)	0.690 (0.677-0.703)
Outpatient (n = 7)	0.144 (0.136-0.152)	0.031 (0.028-0.034)	0.175 (0.167-0.183)	0.227 (0.153-0.300)	0.667 (0.529-0.805)
SVM					
Inpatient (n = 204)	0.140 (0.134-0.145)	0.031 (0.028-0.033)	0.175 (0.167-0.183)	0.370 (0.312-0.427)	0.751 (0.710-0.792)
Outpatient (n = 7)	0.151 (0.143-0.159)	0.032 (0.029-0.035)	0.178 (0.170-0.187)	0.198 (0.122-0.274)	0.689 (0.538-0.840)
RF					
Inpatient (n = 204)	0.152 (0.147-0.156)	0.035 (0.034-0.037)	0.188 (0.184-0.192)	0.273 (0.245-0.301)	0.680 (0.665-0.696)
Outpatient (n = 7)	0.140 (0.129-0.151)	0.027 (0.022-0.033)	0.165 (0.149-0.180)	0.315 (0.181-0.448)	0.756 (0.640-0.871)
XGBoost					
Inpatient (n = 204)	0.155 (0.150-0.159)	0.037 (0.036-0.039)	0.193 (0.189-0.196)	0.236 (0.206-0.266)	0.683 (0.671-0.695)
Outpatient (n = 7)	0.121 (0.108-0.134)	0.022 (0.018-0.026)	0.149 (0.136-0.163)	0.436 (0.337-0.535)	0.778 (0.680-0.875)

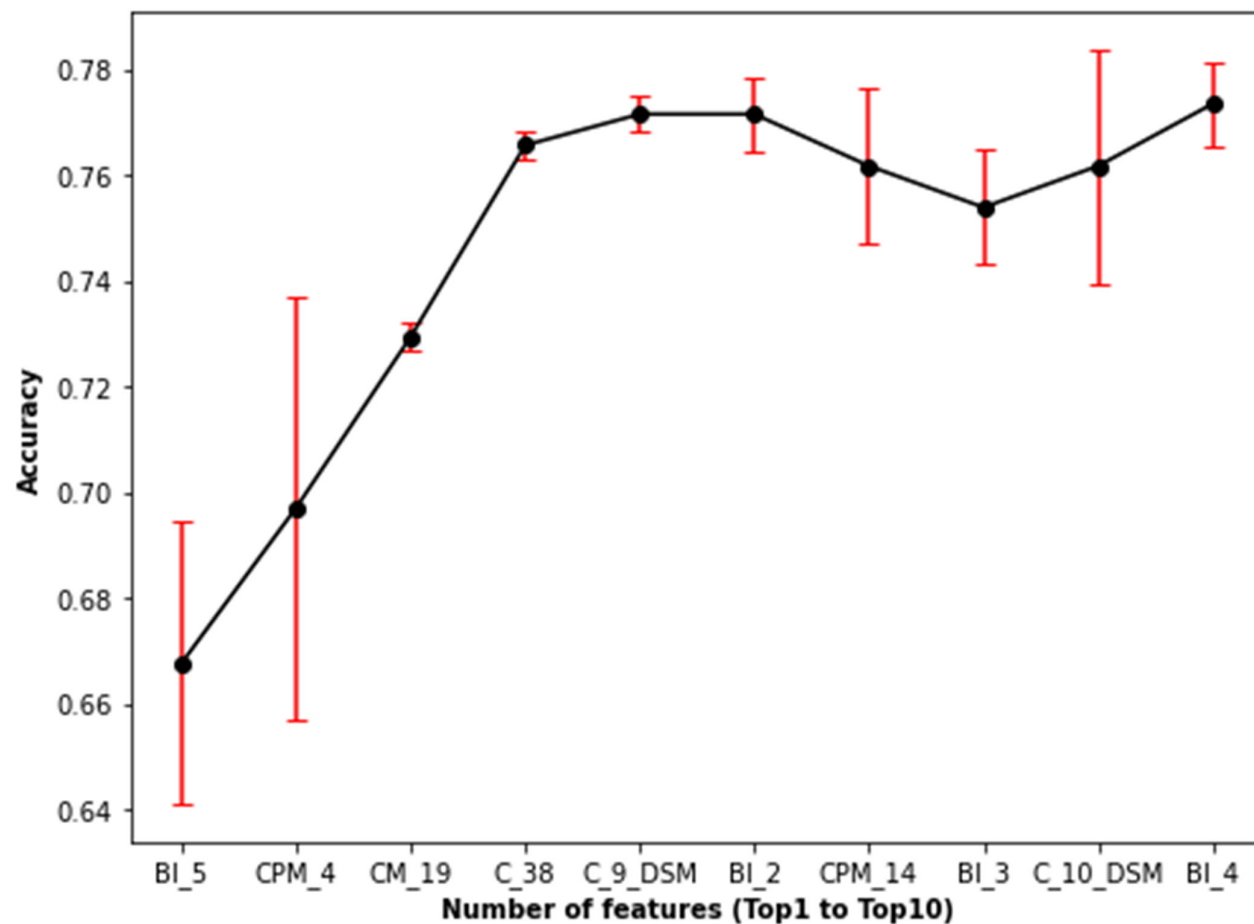
Abbreviations: LinR, linear regression; MAE, mean absolute error; MSE, mean-square error; RF, random forests; RMSE, root-mean-square error; SVM, support vector machine; XGBoost, extreme gradient boosting.

Appendix 6 (Supplementary Figure S1). LASSO method for selecting the top 10 features in logistic regression, binary outcomes



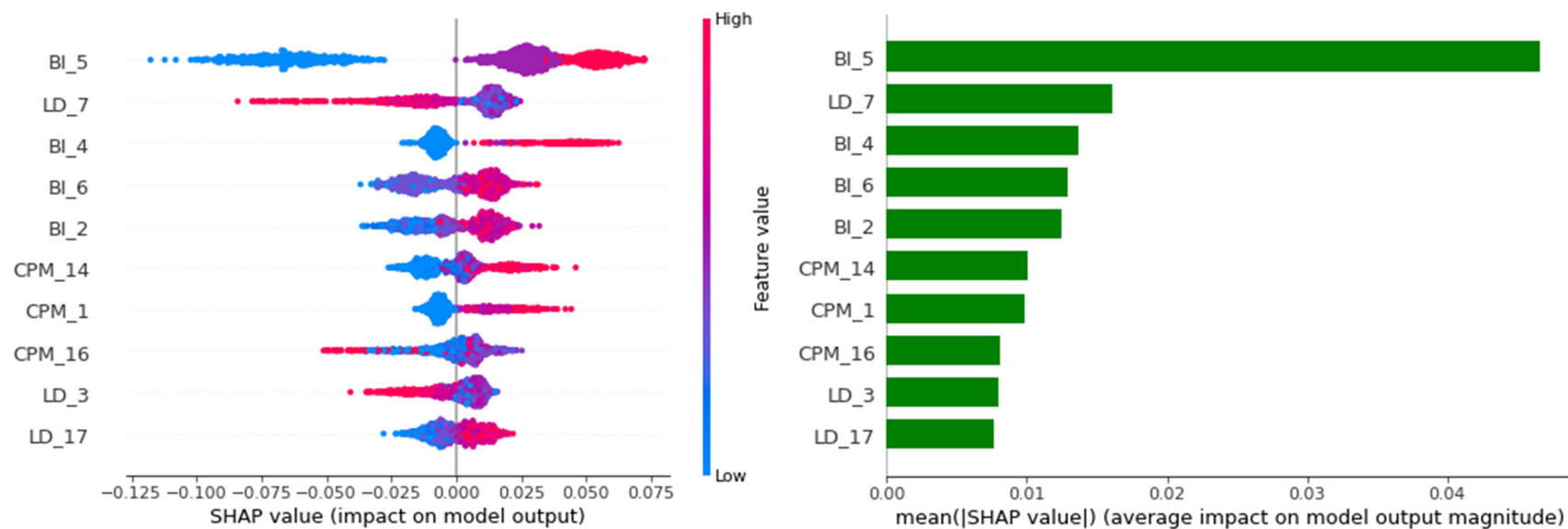
BI_5 = Daily dose, LD_7 = Mean corpuscular hemoglobin concentration, CPM_1 = Valproic acid, C_32 = Renal diseases, BI_2 = Age, BI_8 = Weight, C_12_DSM = Substance-related and addictive disorders, C_37 = Hypertension, CPM_14 = The -pines, BI_4 = Last dose.

Appendix 7 (Supplementary Figure S2). Backward stepwise method for selecting the top 10 features in support vector machine, binary outcomes



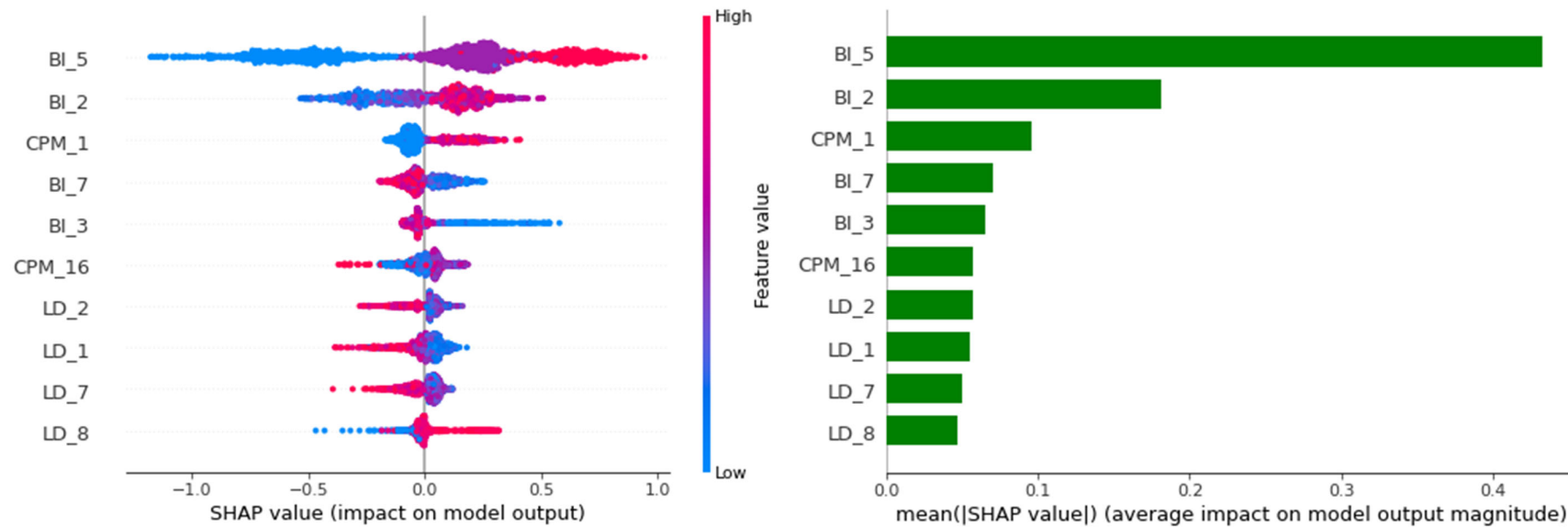
BI_5 = Daily dose, CPM_4 = Topiramate, CM_19 = Non-steroidal anti-inflammatory drugs, C_38 = Hyperlipidemia, C_9_DSM = Elimination disorders, BI_2 = Age, CPM_14 = The -pines, BI_3 = Time interval, C_10_DSM = Sleep-wake disorders, BI_4 = Last dose.

Appendix 8 (Supplementary Figure S3). Shapley additive explanations method for selecting the top 10 features in random forests, binary outcomes



BI_5 = Daily dose, LD_7 = Mean corpuscular hemoglobin concentration, BI_4 = Last dose, BI_6 = Dosing frequency, BI_2 = Age, CPM_14 = The -pines, CPM_1 = Valproic acid, CPM_16 = Benzodiazepines, LD_3 = Hemoglobin, LD_17 = Serum creatinine.

Appendix 9 (Supplementary Figure S4). Shapley additive explanations method for selecting the top 10 features in extreme gradient boost, binary outcomes



BI_5 = Daily dose, BI_2 = Age, CPM_1 = Valproic acid, BI_7 = Height, BI_3 = Time interval, CPM_16 = Benzodiazepines, LD_2 = Red blood cell, LD_1 = White blood cell, LD_7 = Mean corpuscular hemoglobin concentration, LD_8 = Red cell distribution width-standard deviation.

Appendix 10 (Supplementary Table S6). 114 feature importance ranking results of the 4 different machine learning algorithms in binary outcomes

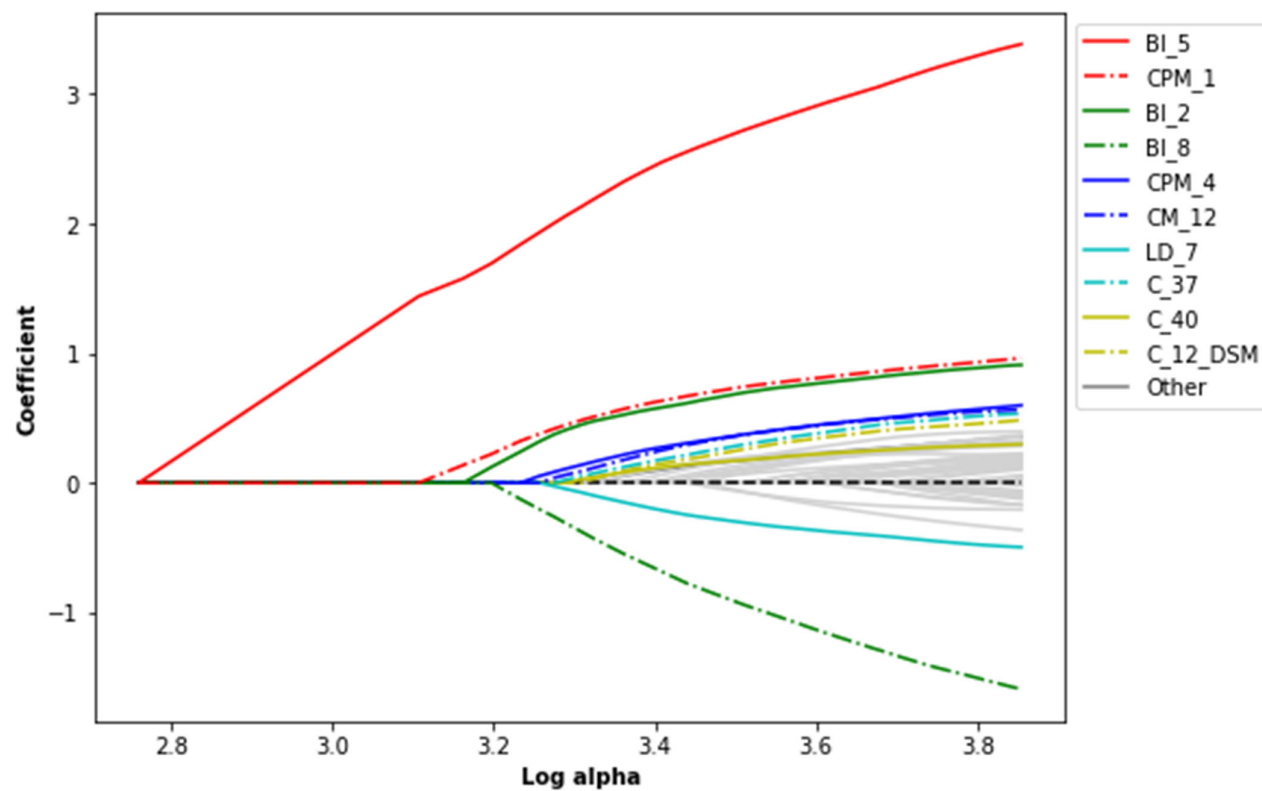
Rank	Logistic regression	Support vector machine	Random forests	Extreme gradient boosting
1	Daily dose	Daily dose	Daily dose	Daily dose
2	Mean corpuscular hemoglobin concentration (gHb/dL)	Topiramate	Mean corpuscular hemoglobin concentration (gHb/dL)	Age
3	Valproic acid	Non-steroidal anti-inflammatory drugs	Last dose	Valproic acid
4	Renal diseases	Hyperlipidemia	Dosing frequency	Height (m)
5	Age	Elimination disorders	Age	Time interval
6	Weight (Kg)	Age	The -pines	Benzodiazepines
7	Substance-related and addictive disorders	The -pines	Valproic acid	Red blood cell (count/uL)
8	Hypertension	Time interval	Benzodiazepines	White blood cell (count/uL)
9	The -pines	Sleep-wake disorders	Hemoglobin (g/dL)	Mean corpuscular hemoglobin concentration (gHb/dL)
10	Last dose	Last dose	Serum creatinine (mg/dL)	Red cell distribution width-standard deviation(fL)
11	Potassium (mg/dL)	Diabetes mellitus without end organ damage	Red blood cell (count/uL)	Last dose
12	Systolic blood pressure (mmHg)	Hypertension	Weight (Kg)	Weight (Kg)
13	Angiotensin receptor blockers	Bipolar and related disorders	Red cell distribution width-coefficient of variation (%)	The -dones
14	Serotonin norepinephrine reuptake inhibitor	Dosing frequency	White blood cell (count/uL)	Red cell distribution width-coefficient of variation (%)
15	Dipeptidyl peptidase 4 inhibitors	Systolic blood pressure (mmHg)	Height (m)	The -pines
16	Agomelatine	Cerebrovascular diseases	Hematocrit (%)	Topiramate
17	Trauma- and stressor-related disorders	Substance-related and addictive disorders	Serum creatinine (mg/dL)	Serum creatinine (mg/dL)
18	Elimination disorders	Gastrointestinal bleeding	Red cell distribution width-standard deviation(fL)	Natrium (mg/dL)
19	Non-steroidal anti-inflammatory drugs	Valproic acid	Potassium (mg/dL)	Blood urea nitrogen (mg/dL)
20	Selective serotonin reuptake inhibitor	Renal diseases	Systolic blood pressure (mmHg)	Non-steroidal anti-inflammatory drugs
21	Topiramate	Benzodiazepines	Hypertension	Substance-related and addictive disorders
22	Obsessive-compulsive and related disorders	Non-benzodiazepines	The -dones	Alanine aminotransferase (U/L)
23	The -dones	Neurodevelopmental disorders	White blood cell-segment (%)	Hemoglobin (g/dL)
24	Beta blockers	Selective serotonin reuptake inhibitor	Alanine aminotransferase (U/L)	Potassium (mg/dL)
25	Height (m)	Weight (Kg)	Aspartate aminotransferase (U/L)	Dosing frequency
26	Serum creatinine (mg/dL)	White blood cell-monocyte (%)	Blood urea nitrogen (mg/dL)	Systolic blood pressure (mmHg)
27	Trazodone	Personality disorders	Diastolic blood pressure (mmHg)	Platelet (count/uL)
28	Angiotensin converting enzyme inhibitors	Any cancer	White blood cell-monocyte (%)	White blood cell-segment (%)
29	Anxiety disorders	Anxiety disorders	Platelet (count/uL)	Depressive disorders
30	Dissociative disorders	Obsessive-compulsive and related disorders	White blood cell-lymphocyte (%)	Hypertension
31	Hematocrit (%)	Mean corpuscular hemoglobin concentration (gHb/dL)	White blood cell-eosinophil (%)	Aspartate aminotransferase (U/L)
32	Calcium channel blockers	Schizophrenia spectrum and other psychotic disorders	Mean corpuscular volume (fL)	Hyperlipidemia

33	Time interval	Beta blockers	Mean corpuscular hemoglobin (pg)	Aripiprazole
34	Acquired immune deficiency syndrome	Trauma- and stressor-related disorders	Renal diseases	Diastolic blood pressure (mmHg)
35	Ocular bleeding	Feeding and eating disorders	Bipolar and related disorders	Angiotensin receptor blockers
36	Disruptive, impulse-control, and conduct disorders	Intracranial bleeding	Substance-related and addictive disorders	White blood cell-eosinophil (%)
37	Hyperlipidemia	White blood cell-basophil (%)	Time interval	Beta blockers
38	White blood cell-eosinophil (%)	The -dones	White blood cell-basophil (%)	White blood cell-lymphocyte (%)
39	Sodium (mg/dL)	Mean corpuscular hemoglobin (pg)	Anxiety disorders	White blood cell-monocyte (%)
40	Acetylcholinesterase inhibitors	Angiotensin receptor blockers	Beta blockers	Schizophrenia spectrum and other psychotic disorders
41	White blood cell (count/uL)	Hematocrit (%)	Topiramate	Mean corpuscular volume (fL)
42	Other bleeding	Depressive disorders	Gastrointestinal bleeding	Gastrointestinal bleeding
43	Sodium-glucose cotransporter 2 inhibitors	White blood cell-lymphocyte (%)	Aripiprazole	Hematocrit (%)
44	Alanine aminotransferase (U/L)	Serum creatinine (mg/dL)	Trauma- and stressor-related disorders	White blood cell-basophil (%)
45	Diabetes mellitus without end organ damage	Sex	Typical antipsychotics	Mean corpuscular hemoglobin (pg)
46	Feeding and eating disorders	Metformin	Angiotensin converting enzyme inhibitors	Neurodevelopmental disorders
47	Fibrates	Acquired immune deficiency syndrome	Non-steroidal anti-inflammatory drugs	Renal diseases
48	Any cancer	Lamotrigine	Depressive disorders	Mirtazapine
49	Other antiplatelet	Diuretics	Hyperlipidemia	Non-benzodiazepines
50	Aripiprazole	Hemiplegia	Calcium channel blockers	Calcium channel blockers
51	Gastrointestinal bleeding	Hemopericardium or pericardial bleeding	Disruptive, impulse-control, and conduct disorders	Antacids
52	Hematoma or compartment syndrome	Dissociative disorders	Sex	Carbamazepine
53	Hemopericardium or pericardial bleeding	Ocular bleeding	Serotonin norepinephrine reuptake inhibitor	Serotonin norepinephrine reuptake inhibitor
54	Intraabdominal bleeding	Chronic pulmonary diseases	Lamotrigine	Feeding and eating disorders
55	Intracranial bleeding	Liver diseases with sequelae	Angiotensin receptor blockers	Bupropion
56	Metastatic solid tumor	Blood urea nitrogen (mg/dL)	Selective serotonin reuptake inhibitor	Disruptive, impulse-control, and conduct disorders
57	Liver diseases with sequelae	White blood cell (count/uL)	Schizophrenia spectrum and other psychotic disorders	Typical antipsychotics
58	Hemiplegia	Congestive heart failure	Non-benzodiazepines	Sleep-wake disorders
59	Diabetes mellitus with end organ damage	Carbamazepine	Liver diseases without sequelae	Anxiety disorders
60	Liver diseases without sequelae	Neurocognitive disorders (Except vascular dementia)	Vascular dementia	Selective serotonin reuptake inhibitor
61	Peptic ulcer diseases	Red cell distribution width-coefficient of variation (%)	Diabetes mellitus without end organ damage	Bipolar and related disorders
62	Connective tissue diseases	Sexual dysfunctions	Obsessive-compulsive and related disorders	Diabetes mellitus without end organ damage
63	Chronic pulmonary diseases	Intraabdominal bleeding	Neurodevelopmental disorders	Trauma- and stressor-related disorders
64	Vascular dementia	Metastatic solid tumor	Sleep-wake disorders	Chronic pulmonary diseases
65	Cerebrovascular diseases	Hemoglobin (g/dL)	Agomelatine	Vascular dementia
66	Peripheral vascular diseases	Agomelatine	Personality disorders	Metformin

67	Congestive heart failure	The benzamides	Chronic pulmonary diseases	Liver diseases without sequelae
68	Myocardial infarct	Potassium (mg/dL)	Antacids	Sex
69	Paraphilic disorders	Alanine aminotransferase (U/L)	Neurocognitive disorders (Except vascular dementia)	Intraabdominal bleeding
70	Gender dysphoria	Aripiprazole	Ocular bleeding	Hemopericardium or pericardial bleeding
71	Personality disorders	Hematoma or compartment syndrome	Feeding and eating disorders	Myocardial infarct
72	Neurocognitive disorders (Except vascular dementia)	Red cell distribution width-standard deviation(fL)	Carbamazepine	Any cancer
73	Sexual dysfunctions	Acarbose	Mirtazapine	Congestive heart failure
74	Sleep-wake disorders	Thiazolidinediones	Metformin	Peripheral vascular diseases
75	Somatic symptom and related disorders	Vascular dementia	Trazodone	Acquired immune deficiency syndrome
76	Depressive disorders	Diabetes mellitus with end organ damage	Statins	Cerebrovascular diseases
77	Bipolar and related disorders	Fibrates	Sulfonylureas	Hemiplegia
78	Schizophrenia spectrum and other psychotic disorders	Diastolic blood pressure (mmHg)	Dipeptidyl peptidase 4 inhibitors	Intracranial bleeding
79	Neurodevelopmental disorders	Peptic ulcer diseases	Other bleeding	Diabetes mellitus with end organ damage
80	Antacids	Serotonin norepinephrine reuptake inhibitor	Any cancer	Connective tissue diseases
81	Amiodarone	Bupropion	Hematoma or compartment syndrome	Ocular bleeding
82	Aspirin	Mirtazapine	Liver diseases with sequelae	Hematoma or compartment syndrome
83	Diuretics	Disruptive, impulse-control, and conduct disorders	Bupropion	Paraphilic disorders
84	Meglitinides	Paraphilic disorders	Fibrates	Peptic ulcer diseases
85	Thiazolidinediones	Gender dysphoria	The benzamides	Liver diseases with sequelae
86	Acarbose	Platelet (count/uL)	Cerebrovascular diseases	Metastatic solid tumor
87	Sulfonylureas	Height (m)	Somatic symptom and related disorders	Thiazolidinediones
88	Metformin	Aspirin	Elimination disorders	Gender dysphoria
89	Insulins	Red blood cell (count/uL)	Diabetes mellitus with end organ damage	Acarbose
90	Statins	Somatic symptom and related disorders	Insulins	Lamotrigine
91	Non-benzodiazepines	Antacids	Acarbose	Trazodone
92	Benzodiazepines	Calcium channel blockers	Aspirin	Agomelatine
93	The benzamides	Dipeptidyl peptidase 4 inhibitors	Acquired immune deficiency syndrome	The benzamides
94	Typical antipsychotics	Typical antipsychotics	Intracranial bleeding	Acetylcholinesterase inhibitors
95	Bupropion	White blood cell-segment (%)	Diuretics	Statins
96	Mirtazapine	White blood cell-eosinophil (%)	Hemiplegia	Fibrates
97	Lamotrigine	Statins	Sodium-glucose cotransporter 2 inhibitors	Insulins
98	Carbamazepine	Angiotensin converting enzyme inhibitors	Myocardial infarct	Sodium-glucose cotransporter 2 inhibitors
99	Aspartate aminotransferase (U/L)	Connective tissue diseases	Peripheral vascular diseases	Dipeptidyl peptidase 4 inhibitors
100	Blood urea nitrogen (mg/dL)	Myocardial infarct	Thiazolidinediones	Sulfonylureas
101	White blood cell-basophil (%)	Sodium-glucose cotransporter 2 inhibitors	Acetylcholinesterase inhibitors	Meglitinides

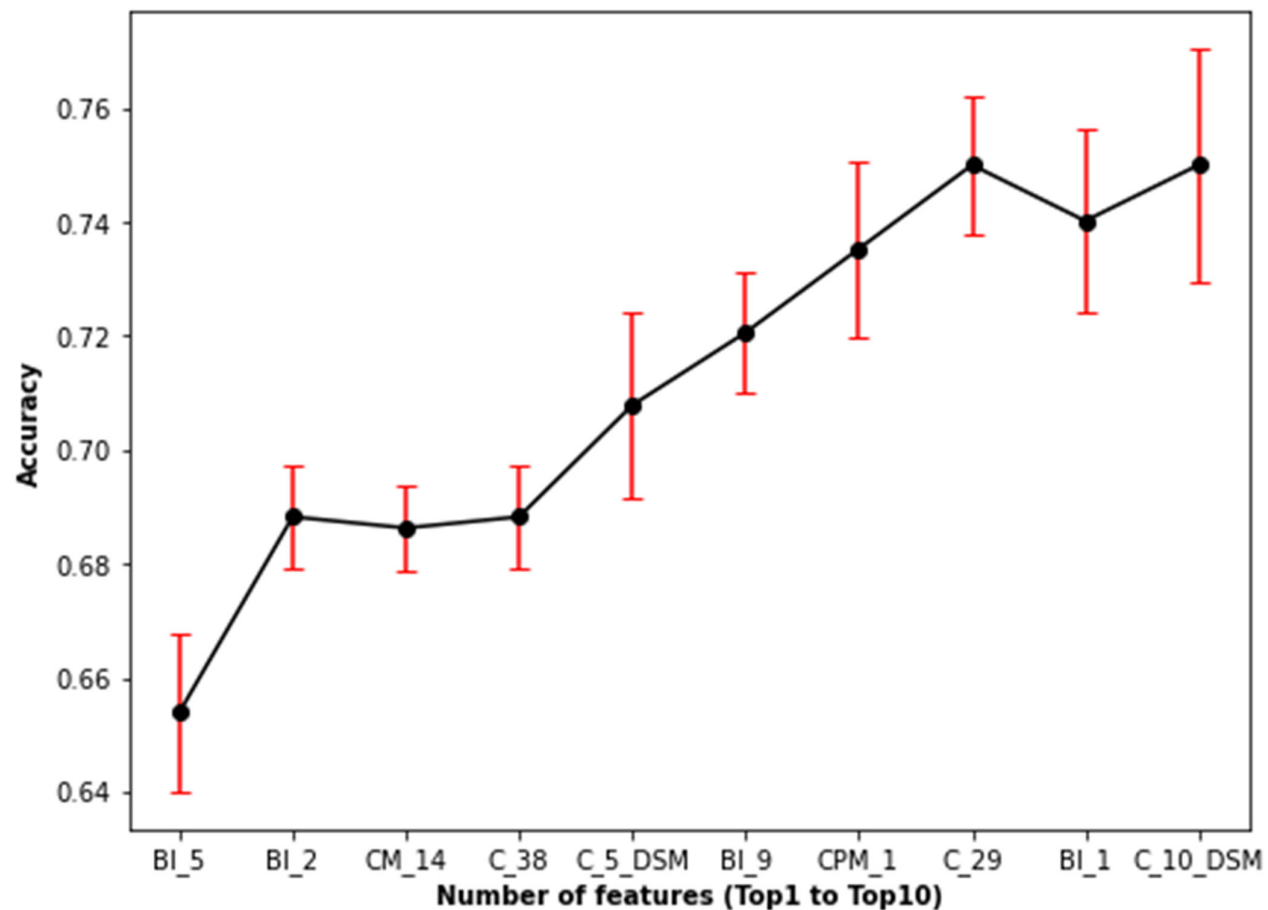
102	White blood cell-monocyte (%)	Amiodarone	Sexual dysfunctions	Dissociative disorders
103	White blood cell-lymphocyte (%)	Other antiplatelet	Connective tissue diseases	Angiotensin converting enzyme inhibitors
104	White blood cell-segment (%)	Other bleeding	Congestive heart failure	Diuretics
105	Red cell distribution width-coefficient of variation (%)	Meglitinides	Other antiplatelet	Aspirin
106	Platelet (count/uL)	Mean corpuscular volume (fL)	Peptic ulcer diseases	Other antiplatelet
107	Red cell distribution width-standard deviation(fL)	Sulfonylureas	Meglitinides	Amiodarone
108	Mean corpuscular hemoglobin (pg)	Trazodone	Metastatic solid tumor	Obsessive-compulsive and related disorders
109	Mean corpuscular volume (fL)	Aspartate aminotransferase (U/L)	Paraphilic disorders	Somatic symptom and related disorders
110	Hemoglobin (g/dL)	Peripheral vascular diseases	Gender dysphoria	Elimination disorders
111	Red blood cell (count/uL)	Acetylcholinesterase inhibitors	Dissociative disorders	Sexual dysfunctions
112	Diastolic blood pressure (mmHg)	Insulins	Intraabdominal bleeding	Neurocognitive disorders (Except vascular dementia)
113	Dosing frequency	Sodium (mg/dL)	Hemopericardium or pericardial bleeding	Personality disorders
114	Sex	Liver diseases without sequelae	Amiodarone	Other bleeding

Appendix 11 (Supplementary Figure S5). LASSO method for selecting the top 10 features in linear regression, continuous outcomes



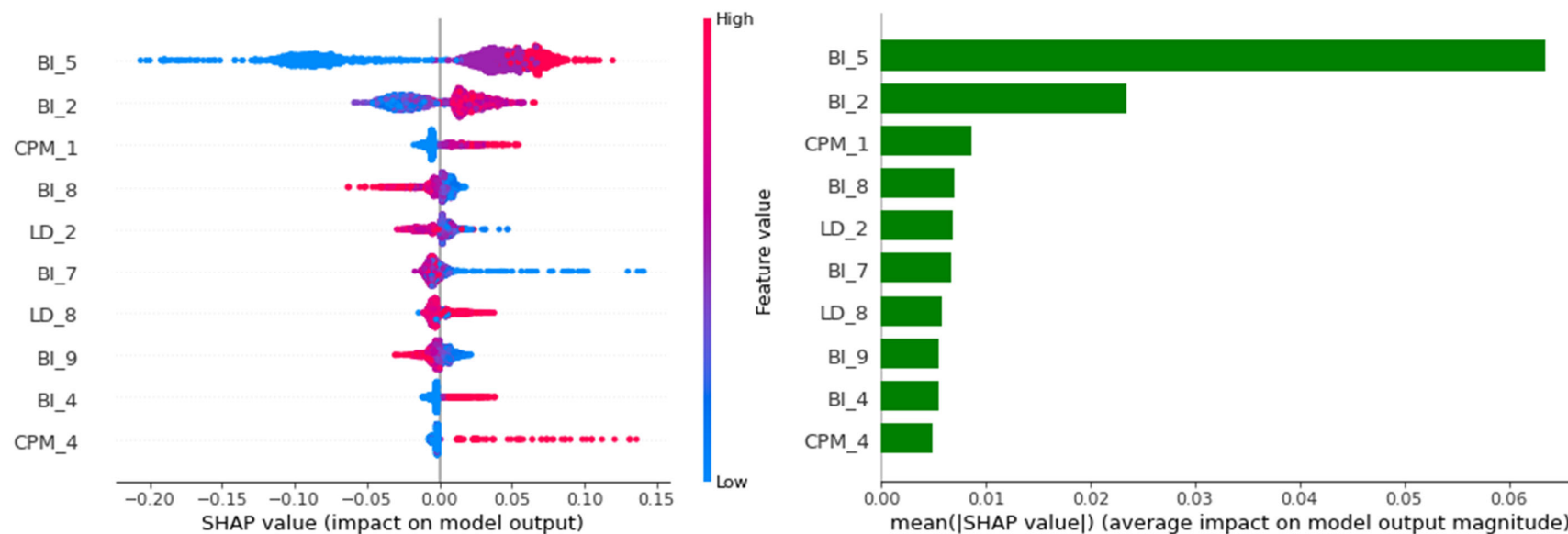
BI_5 = Daily dose, CPM_1 = Valproic acid, BI_2 = Age, BI_8 = Weight (Kg), CPM_4 = Topiramate, CM_12 = Angiotensin receptor blockers, LD_7 = Mean corpuscular hemoglobin concentration, C_37 = Hypertension, C_40 = Ocular bleeding, C_12_DSM = Substance-related and addictive disorders.

Appendix 12 (Supplementary Figure S6). Backward stepwise method for selecting the top 10 features in support vector machine, continuous outcomes



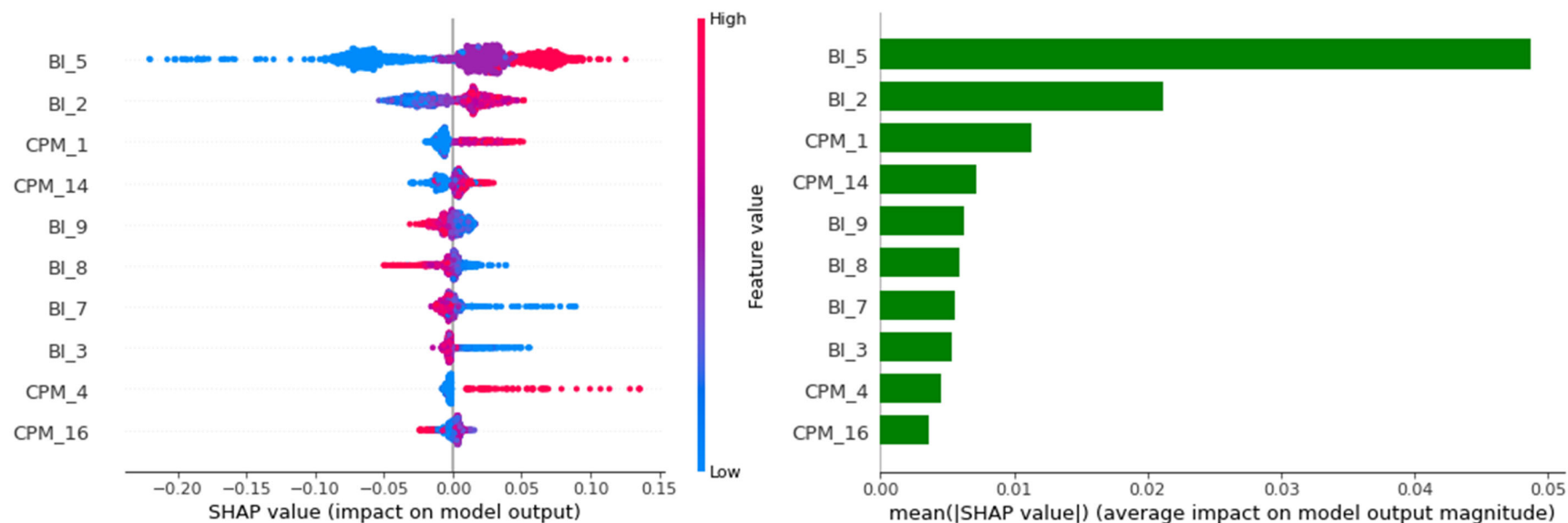
BI_5 = Daily dose, BI_2 = Age, CM_14 = Beta blockers, C_38 = Hyperlipidemia, C_5_DSM = Depressive disorders, BI_9 = Systolic blood pressure, CPM_1 = Valproic acid, C_29 = Diabetes mellitus without end organ damage, BI_1 = Sex, C_10_DSM = Sleep-wake disorders.

Appendix 13 (Supplementary Figure S7). Shapley additive explanations method for selecting the top 10 features in random forests, continuous outcomes



BI_5 = Daily dose, BI_2 = Age, CPM_1 = Valproic acid, BI_8 = Weight, LD_2 = Red blood cell, BI_7 = Height, LD_8 = Red cell distribution width-standard deviation, BI_9 = Systolic blood pressure, BI_4 = Last dose, CPM_4 = Topiramate.

Appendix 14 (Supplementary Figure S8). Shapley additive explanations method for selecting the top 10 features in extreme gradient boost, continuous outcomes



BI_5 = Daily dose, BI_2 = Age, CPM_1 = Valproic acid, CPM_14 = The -pines, BI_9 = Systolic blood pressure, BI_8 = Weight, BI_7 = Height, BI_3 = Time interval, CPM_4 = Topiramate, CPM_16 = Benzodiazepines.

Appendix 15 (Supplementary Table S7). 114 feature importance ranking results of the 4 different machine learning algorithms in continuous outcomes

Rank	Linear regression	Support vector machine	Random forests	Extreme gradient boosting
1	Daily dose	Daily dose	Daily dose	Daily dose
2	Valproic acid	Age	Age	Age
3	Age	Beta blockers	Valproic acid	Valproic acid
4	Weight (Kg)	Hyperlipidemia	Weight (Kg)	The -pines
5	Topiramate	Depressive disorders	Red blood cell (count/uL)	Systolic blood pressure (mmHg)
6	Angiotensin receptor blockers	Systolic blood pressure (mmHg)	Height (m)	Weight (Kg)
7	Mean corpuscular hemoglobin concentration (gHb/dL)	Valproic acid	Red cell distribution width-standard deviation(fL)	Height (m)
8	Hypertension	Diabetes mellitus without end organ damage	Systolic blood pressure (mmHg)	Time interval
9	Ocular bleeding	Sex	Last dose	Topiramate
10	Substance-related and addictive disorders	Sleep-wake disorders	Topiramate	Benzodiazepines
11	Acetylcholinesterase inhibitors	Dosing frequency	The -pines	Red cell distribution width-standard deviation(fL)
12	Depressive disorders	The -pines	Time interval	Red blood cell (count/uL)
13	The -pines	Substance-related and addictive disorders	Hypertension	Non-steroidal anti-inflammatory drugs
14	Neurocognitive disorders (Except vascular dementia)	Diabetes mellitus with end organ damage	Platelet (count/uL)	Platelet (count/uL)
15	Trauma- and stressor-related disorders	Obsessive-compulsive and related disorders	Benzodiazepines	Substance-related and addictive disorders
16	Renal diseases	Liver diseases with sequelae	Non-steroidal anti-inflammatory drugs	The -dones
17	Fibrates	Gastrointestinal bleeding	Substance-related and addictive disorders	Beta blockers
18	Last dose	Chronic pulmonary diseases	Red cell distribution width-coefficient of variation (%)	Serum creatinine (mg/dL)
19	Beta blockers	Vascular dementia	Mean corpuscular hemoglobin concentration (gHb/dL)	Last dose
20	Systolic blood pressure (mmHg)	White blood cell-eosinophil (%)	White blood cell (count/uL)	Hypertension
21	Potassium (mg/dL)	Non-benzodiazepines	The -dones	Mean corpuscular hemoglobin concentration (gHb/dL)
22	Acquired immune deficiency syndrome	The benzamides	Serum creatinine (mg/dL)	Red cell distribution width-coefficient of variation (%)
23	Agomelatine	Neurocognitive disorders (Except vascular dementia)	Hemoglobin (g/dL)	Dosing frequency
24	Metastatic solid tumor	Dipeptidyl peptidase 4 inhibitors	Beta blockers	Depressive disorders
25	Natrium (mg/dL)	Last dose	Natrium (mg/dL)	White blood cell-lymphocyte (%)
26	Trazodone	Potassium (mg/dL)	Aspartate aminotransferase (U/L)	Aspartate aminotransferase (U/L)
27	Obsessive-compulsive and related disorders	Hemoglobin (g/dL)	Mean corpuscular volume (fL)	Natrium (mg/dL)
28	Non-steroidal anti-inflammatory drugs	Neurodevelopmental disorders	Diastolic blood pressure (mmHg)	Hemoglobin (g/dL)
29	Anxiety disorders	Selective serotonin reuptake inhibitor	Blood urea nitrogen (mg/dL)	White blood cell (count/uL)
30	The benzamides	Blood urea nitrogen (mg/dL)	Hematocrit (%)	Mean corpuscular hemoglobin (pg)
31	Sulfonylureas	Diastolic blood pressure (mmHg)	Hyperlipidemia	Hyperlipidemia
32	Elimination disorders	Cerebrovascular diseases	Potassium (mg/dL)	Angiotensin receptor blockers

33	White blood cell-basophil (%)	Acquired immune deficiency syndrome	Alanine aminotransferase (U/L)	Alanine aminotransferase (U/L)
34	Other bleeding	Non-steroidal anti-inflammatory drugs	Mean corpuscular hemoglobin (pg)	Potassium (mg/dL)
35	Red cell distribution width-standard deviation(fL)	Liver diseases without sequelae	White blood cell-monocyte (%)	White blood cell-segment (%)
36	Serum creatinine (mg/dL)	Aripiprazole	White blood cell-eosinophil (%)	White blood cell-monocyte (%)
37	Somatic symptom and related disorders	White blood cell-basophil (%)	White blood cell-lymphocyte (%)	Blood urea nitrogen (mg/dL)
38	Time interval	Somatic symptom and related disorders	Anxiety disorders	Diastolic blood pressure (mmHg)
39	Dipeptidyl peptidase 4 inhibitors	Trauma- and stressor-related disorders	White blood cell-segment (%)	White blood cell-eosinophil (%)
40	Aripiprazole	Serum creatinine (mg/dL)	Angiotensin receptor blockers	Sex
41	Diabetes mellitus without end organ damage	Other bleeding	Depressive disorders	Non-benzodiazepines
42	Diuretics	The -dones	Liver diseases without sequelae	Diabetes mellitus without end organ damage
43	The -dones	Statins	White blood cell-basophil (%)	Hematocrit (%)
44	Acarbose	Height (m)	Trauma- and stressor-related disorders	Sleep-wake disorders
45	Any cancer	Red cell distribution width-standard deviation(fL)	Typical antipsychotics	Vascular dementia
46	White blood cell-eosinophil (%)	White blood cell (count/uL)	Diabetes mellitus without end organ damage	Antacids
47	Neurodevelopmental disorders	Platelet (count/uL)	Dosing frequency	Liver diseases without sequelae
48	Statins	Dissociative disorders	Selective serotonin reuptake inhibitor	Feeding and eating disorders
49	Angiotensin converting enzyme inhibitors	Hematocrit (%)	Mirtazapine	Neurocognitive disorders (Except vascular dementia)
50	Other antiplatelet	Hemopericardium or pericardial bleeding	Gastrointestinal bleeding	Selective serotonin reuptake inhibitor
51	Height (m)	Intraabdominal bleeding	Neurocognitive disorders (Except vascular dementia)	Carbamazepine
52	Gastrointestinal bleeding	Congestive heart failure	Non-benzodiazepines	Aripiprazole
53	Hematoma or compartment syndrome	Mean corpuscular hemoglobin (pg)	Neurodevelopmental disorders	White blood cell-basophil (%)
54	Hemopericardium or pericardial bleeding	Calcium channel blockers	Aripiprazole	Ocular bleeding
55	Intraabdominal bleeding	Antacids	Schizophrenia spectrum and other psychotic disorders	Mean corpuscular volume (fL)
56	Intracranial bleeding	Peptic ulcer diseases	Bipolar and related disorders	Anxiety disorders
57	Hyperlipidemia	Hemiplegia	Sex	Typical antipsychotics
58	Liver diseases with sequelae	Angiotensin converting enzyme inhibitors	Vascular dementia	Neurodevelopmental disorders
59	Hemiplegia	Sulfonylureas	Ocular bleeding	Personality disorders
60	Diabetes mellitus with end organ damage	Aspirin	Obsessive-compulsive and related disorders	Trauma- and stressor-related disorders
61	Liver diseases without sequelae	Paraphilic disorders	Antacids	Aspirin
62	Peptic ulcer diseases	Metformin	Agomelatine	Bipolar and related disorders
63	Connective tissue diseases	Renal diseases	Feeding and eating disorders	Calcium channel blockers
64	Chronic pulmonary diseases	Disruptive, impulse-control, and conduct disorders	Diuretics	Cerebrovascular diseases

65	Vascular dementia	Ocular bleeding	Sleep-wake disorders	Schizophrenia spectrum and other psychotic disorders
66	Cerebrovascular diseases	Mean corpuscular volume (fL)	Serotonin norepinephrine reuptake inhibitor	Diuretics
67	Peripheral vascular diseases	Elimination disorders	Calcium channel blockers	Renal diseases
68	Congestive heart failure	Red cell distribution width-coefficient of variation (%)	Carbamazepine	Acetylcholinesterase inhibitors
69	Myocardial infarct	Hematoma or compartment syndrome	Personality disorders	Liver diseases with sequelae
70	Paraphilic disorders	Feeding and eating disorders	Trazodone	Angiotensin converting enzyme inhibitors
71	Gender dysphoria	Connective tissue diseases	Disruptive, impulse-control, and conduct disorders	Sulfonylureas
72	Feeding and eating disorders	Agomelatine	Elimination disorders	Obsessive-compulsive and related disorders
73	Dissociative disorders	White blood cell-lymphocyte (%)	Aspirin	Any cancer
74	Personality disorders	Gender dysphoria	Fibrates	Chronic pulmonary diseases
75	Sexual dysfunctions	Metastatic solid tumor	Chronic pulmonary diseases	Elimination disorders
76	Sleep-wake disorders	Intracranial bleeding	Lamotrigine	The benzamides
77	Bipolar and related disorders	Acarbose	Myocardial infarct	Agomelatine
78	Schizophrenia spectrum and other psychotic disorders	Meglitinides	Insulins	Diabetes mellitus with end organ damage
79	Disruptive, impulse-control, and conduct disorders	Typical antipsychotics	Metformin	Lamotrigine
80	Antacids	Sodium-glucose cotransporter 2 inhibitors	Renal diseases	Sexual dysfunctions
81	Amiodarone	Myocardial infarct	Angiotensin converting enzyme inhibitors	Hematoma or compartment syndrome
82	Aspirin	Amiodarone	Sulfonylureas	Intracranial bleeding
83	Calcium channel blockers	Bupropion	Cerebrovascular diseases	Hemiplegia
84	Meglitinides	Serotonin norepinephrine reuptake inhibitor	The benzamides	Acquired immune deficiency syndrome
85	Thiazolidinediones	Carbamazepine	Other bleeding	Hemopericardium or pericardial bleeding
86	Sodium-glucose cotransporter 2 inhibitors	Hypertension	Statins	Gastrointestinal bleeding
87	Metformin	Benzodiazepines	Acetylcholinesterase inhibitors	Metastatic solid tumor
88	Insulins	Aspartate aminotransferase (U/L)	Acarbose	Peptic ulcer diseases
89	Non-benzodiazepines	Diuretics	Liver diseases with sequelae	Connective tissue diseases
90	Benzodiazepines	Thiazolidinediones	Any cancer	Intraabdominal bleeding
91	Typical antipsychotics	Sexual dysfunctions	Bupropion	Thiazolidinediones
92	Bupropion	Red blood cell (count/uL)	Acquired immune deficiency syndrome	Peripheral vascular diseases
93	Mirtazapine	Lamotrigine	Diabetes mellitus with end organ damage	Dipeptidyl peptidase 4 inhibitors
94	Serotonin norepinephrine reuptake inhibitor	Any cancer	Metastatic solid tumor	Serotonin norepinephrine reuptake inhibitor
95	Selective serotonin reuptake inhibitor	Angiotensin receptor blockers	Other antiplatelet	Trazodone
96	Lamotrigine	Insulins	Somatic symptom and related disorders	Mirtazapine
97	Carbamazepine	White blood cell-segment (%)	Dipeptidyl peptidase 4 inhibitors	Bupropion
98	Alanine aminotransferase (U/L)	Fibrates	Intracranial bleeding	Statins

99	Aspartate aminotransferase (U/L)	Alanine aminotransferase (U/L)	Hematoma or compartment syndrome	Fibrates
100	Blood urea nitrogen (mg/dL)	Sodium (mg/dL)	Dissociative disorders	Insulins
101	White blood cell-monocyte (%)	Other antiplatelet	Hemiplegia	Metformin
102	White blood cell-lymphocyte (%)	Peripheral vascular diseases	Connective tissue diseases	Sodium-glucose cotransporter 2 inhibitors
103	White blood cell-segment (%)	Mean corpuscular hemoglobin concentration (gHb/dL)	Gender dysphoria	Acarbose
104	Red cell distribution width-coefficient of variation (%)	Mirtazapine	Meglitinides	Congestive heart failure
105	Platelet (count/uL)	Topiramate	Peptic ulcer diseases	Meglitinides
106	Mean corpuscular hemoglobin (pg)	Trazodone	Sodium-glucose cotransporter 2 inhibitors	Other antiplatelet
107	Mean corpuscular volume (fL)	White blood cell-monocyte (%)	Amiodarone	Amiodarone
108	Hematocrit (%)	Personality disorders	Peripheral vascular diseases	Disruptive, impulse-control, and conduct disorders
109	Hemoglobin (g/dL)	Acetylcholinesterase inhibitors	Congestive heart failure	Somatic symptom and related disorders
110	Red blood cell (count/uL)	Bipolar and related disorders	Intraabdominal bleeding	Dissociative disorders
111	White blood cell (count/uL)	Time interval	Hemopericardium or pericardial bleeding	Gender dysphoria
112	Diastolic blood pressure (mmHg)	Anxiety disorders	Sexual dysfunctions	Paraphilic disorders
113	Dosing frequency	Weight (Kg)	Paraphilic disorders	Myocardial infarct
114	Sex	Schizophrenia spectrum and other psychotic disorders	Thiazolidinediones	Other bleeding

Appendix 16 (Supplementary Table S8). Detail information of binary outcomes of logistic regression algorithm under different feature combinations

Model (LogR)	TP	TN	FP	FN	TPR (Sensitivity)	TNR (Specificity)	PPV (Precision)	NPV	AUC-ROC	F-score	Accuracy
Model P	118 (112-124)	31 (25-36)	40 (35-46)	15 (9-21)	0.886 (0.839-0.932)	0.431 (0.356-0.506)	0.745 (0.726-0.764)	0.675 (0.600-0.750)	0.748 (0.732-0.764)	0.809 (0.792-0.826)	0.727 (0.707-0.748)
Model 1	125 (124-127)	21 (18-23)	50 (48-53)	8 (6-9)	0.941 (0.929-0.954)	0.290 (0.252-0.328)	0.713 (0.701-0.725)	0.725 (0.677-0.774)	0.753 (0.741-0.766)	0.811 (0.801-0.822)	0.715 (0.698-0.731)
Model 2	116 (113-119)	28 (24-32)	43 (39-47)	17 (14-20)	0.874 (0.852-0.895)	0.400 (0.343-0.457)	0.732 (0.715-0.749)	0.628 (0.588-0.669)	0.734 (0.721-0.747)	0.796 (0.785-0.808)	0.709 (0.691-0.726)
Model 3	121 (120-123)	27 (26-28)	44 (43-45)	12 (10-13)	0.913 (0.899-0.927)	0.380 (0.363-0.398)	0.734 (0.726-0.742)	0.700 (0.659-0.741)	0.761 (0.751-0.771)	0.814 (0.804-0.824)	0.727 (0.713-0.741)

Abbreviations: AUC-ROC, area under the curve of receiver operator characteristic; FN, false negative; FP, false positive; LogR, Logistic regression; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive; TNR, true negative rate; TPR, true positive rate.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 17 (Supplementary Table S9). Detail information of binary outcomes of support vector machine algorithm under different feature combinations

Model (SVM)	TP	TN	FP	FN	TPR (Sensitivity)	TNR (Specificity)	PPV (Precision)	NPV	AUC-ROC	F-score	Accuracy
Model P	125 (121-129)	23 (17-29)	48 (42-54)	8 (4-12)	0.940 (0.911-0.969)	0.324 (0.241-0.407)	0.723 (0.702-0.744)	0.747 (0.675-0.819)	0.759 (0.744-0.774)	0.817 (0.806-0.828)	0.725 (0.706-0.745)
Model 1	123 (120-126)	21 (17-24)	50 (47-54)	10 (7-13)	0.925 (0.901-0.949)	0.290 (0.238-0.342)	0.709 (0.690-0.728)	0.673 (0.576-0.770)	0.766 (0.747-0.786)	0.803 (0.783-0.823)	0.704 (0.673-0.735)
Model 2	120 (119-122)	26 (21-32)	45 (39-50)	13 (11-14)	0.904 (0.894-0.914)	0.369 (0.293-0.445)	0.729 (0.706-0.752)	0.669 (0.625-0.714)	0.775 (0.754-0.797)	0.807 (0.793-0.821)	0.718 (0.693-0.743)
Model 3	121 (119-122)	28 (23-32)	43 (39-48)	12 (11-14)	0.908 (0.896-0.920)	0.392 (0.327-0.456)	0.737 (0.718-0.756)	0.694 (0.671-0.717)	0.771 (0.762-0.779)	0.814 (0.805-0.823)	0.728 (0.711-0.746)

Abbreviations: AUC-ROC, area under the curve of receiver operator characteristic; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SVM, support vector machine; TN, true negative; TP, true positive; TNR, true negative rate; TPR, true positive rate.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 18 (Supplementary Table S10). Detail information of binary outcomes of random forests algorithm under different feature combinations

Model (RF)	TP	TN	FP	FN	TPR (Sensitivity)	TNR (Specificity)	PPV (Precision)	NPV	AUC-ROC	F-score	Accuracy
Model P	127 (126-129)	16 (10-22)	55 (49-61)	6 (4-7)	0.958 (0.947-0.969)	0.220 (0.134-0.305)	0.697 (0.676-0.719)	0.728 (0.659-0.797)	0.784 (0.754-0.814)	0.807 (0.794-0.820)	0.701 (0.675-0.727)
Model 1	122 (120-125)	24 (20-28)	47 (43-51)	11 (8-13)	0.920 (0.901-0.940)	0.341 (0.286-0.395)	0.723 (0.703-0.744)	0.694 (0.613-0.775)	0.767 (0.759-0.775)	0.810 (0.790-0.830)	0.719 (0.688-0.749)
Model 2	125 (124-127)	21 (17-25)	50 (46-54)	8 (6-9)	0.941 (0.929-0.954)	0.299 (0.244-0.353)	0.716 (0.701-0.731)	0.731 (0.688-0.773)	0.796 (0.786-0.806)	0.813 (0.803-0.823)	0.718 (0.700-0.735)
Model 3	119 (116-123)	26 (21-31)	45 (40-50)	14 (10-17)	0.896 (0.871-0.921)	0.369 (0.298-0.440)	0.727 (0.706-0.749)	0.655 (0.598-0.712)	0.785 (0.777-0.792)	0.803 (0.786-0.819)	0.713 (0.687-0.739)

Abbreviations: AUC-ROC, area under the curve of receiver operator characteristic; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; RF, random forests; TN, true negative; TP, true positive; TNR, true negative rate; TPR, true positive rate.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 19 (Supplementary Table S11). Detail information of binary outcomes of extreme gradient boosting algorithm under different feature combinations

Model (XGBoost)	TP	TN	FP	FN	TPR (Sensitivity)	TNR (Specificity)	PPV (Precision)	NPV	AUC-ROC	F-score	Accuracy
Model P	120 (116-125)	27 (24-29)	44 (42-47)	13 (8-17)	0.904 (0.870-0.938)	0.377 (0.344-0.411)	0.731 (0.721-0.741)	0.681 (0.607-0.756)	0.775 (0.741-0.810)	0.808 (0.792-0.825)	0.721 (0.700-0.741)
Model 1	120 (118-121)	25 (22-28)	46 (43-49)	13 (12-15)	0.899 (0.887-0.912)	0.346 (0.304-0.389)	0.721 (0.706-0.735)	0.647 (0.601-0.693)	0.756 (0.732-0.780)	0.800 (0.788-0.812)	0.707 (0.688-0.726)
Model 2	122 (118-126)	27 (23-31)	44 (40-48)	11 (7-15)	0.916 (0.887-0.944)	0.383 (0.326-0.440)	0.736 (0.716-0.755)	0.710 (0.629-0.791)	0.778 (0.750-0.806)	0.816 (0.797-0.835)	0.730 (0.702-0.759)
Model 3	116 (113-120)	31 (28-34)	40 (37-43)	17 (13-20)	0.875 (0.852-0.899)	0.434 (0.389-0.479)	0.743 (0.731-0.756)	0.651 (0.616-0.685)	0.766 (0.748-0.785)	0.804 (0.793-0.815)	0.722 (0.707-0.736)

Abbreviations: AUC-ROC, area under the curve of receiver operator characteristic; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive; TNR, true negative rate; TPR, true positive rate; XGBoost, extreme gradient boosting. Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 20 (Supplementary Table S12). Detail information of continuous outcomes of linear regression algorithm under different feature combinations

Model (LinR)	MAE	MSE	RMSE	R²	Accuracy
Model P	0.159 (0.156-0.162)	0.038 (0.037-0.040)	0.196 (0.193-0.199)	0.209 (0.187-0.231)	0.690 (0.677-0.703)
Model 1	0.159 (0.158-0.160)	0.039 (0.039-0.039)	0.197 (0.196-0.198)	0.199 (0.192-0.207)	0.670 (0.654-0.685)
Model 2	0.157 (0.155-0.159)	0.039 (0.038-0.039)	0.196 (0.195-0.198)	0.207 (0.197-0.217)	0.670 (0.658-0.681)
Model 3	0.157 (0.155-0.159)	0.038 (0.038-0.039)	0.196 (0.194-0.197)	0.211 (0.200-0.223)	0.691 (0.676-0.706)

Abbreviations: LinR, linear regression; MAE, mean absolute error; MSE, mean-square error; RMSE, root-mean-square error.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 21 (Supplementary Table S13). Detail information of continuous outcomes of support vector machine algorithm under different feature combinations

Model (SVM)	MAE	MSE	RMSE	R²	Accuracy
Model P	0.140 (0.134-0.145)	0.031 (0.028-0.033)	0.175 (0.167-0.183)	0.370 (0.312-0.427)	0.751 (0.710-0.792)
Model 1	0.150 (0.147-0.152)	0.036 (0.034-0.037)	0.189 (0.186-0.192)	0.266 (0.241-0.291)	0.716 (0.705-0.726)
Model 2	0.145 (0.139-0.150)	0.032 (0.031-0.034)	0.180 (0.175-0.185)	0.333 (0.294-0.372)	0.735 (0.713-0.758)
Model 3	0.160 (0.158-0.161)	0.040 (0.038-0.041)	0.200 (0.196-0.203)	0.179 (0.149-0.208)	0.690 (0.674-0.706)

Abbreviations: MAE, mean absolute error; MSE, mean-square error; RMSE, root-mean-square error; SVM, support vector machine.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 22 (Supplementary Table S14). Detail information of continuous outcomes of random forests algorithm under different feature combinations

Model (RF)	MAE	MSE	RMSE	R²	Accuracy
Model P	0.152 (0.147-0.156)	0.035 (0.034-0.037)	0.188 (0.184-0.192)	0.273 (0.245-0.301)	0.680 (0.665-0.696)
Model 1	0.154 (0.153-0.155)	0.037 (0.036-0.037)	0.191 (0.190-0.193)	0.246 (0.237-0.255)	0.696 (0.681-0.711)
Model 2	0.150 (0.146-0.155)	0.035 (0.033-0.036)	0.186 (0.182-0.190)	0.287 (0.259-0.315)	0.681 (0.660-0.703)
Model 3	0.155 (0.153-0.158)	0.038 (0.037-0.039)	0.194 (0.192-0.197)	0.222 (0.203-0.242)	0.687 (0.665-0.710)

Abbreviations: MAE, mean absolute error; MSE, mean-square error; RF, random forests; RMSE, root-mean-square error.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

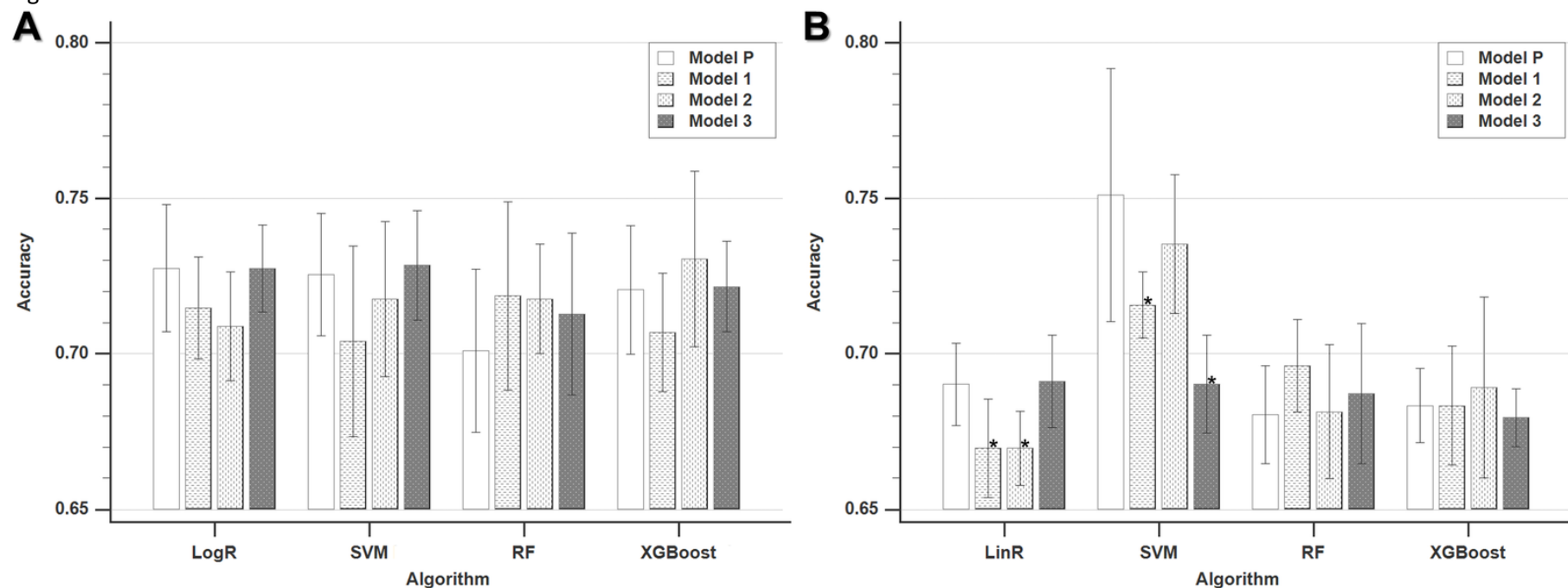
Appendix 23 (Supplementary Table S15). Detail information of continuous outcomes of extreme gradient boosting algorithm under different feature combinations

Model (XGBoost)	MAE	MSE	RMSE	R²	Accuracy
Model P	0.155 (0.150-0.159)	0.037 (0.036-0.039)	0.193 (0.189-0.196)	0.236 (0.206-0.266)	0.683 (0.671-0.695)
Model 1	0.155 (0.154-0.157)	0.038 (0.037-0.038)	0.195 (0.194-0.196)	0.220 (0.212-0.229)	0.683 (0.664-0.702)
Model 2	0.153 (0.149-0.158)	0.037 (0.035-0.038)	0.192 (0.188-0.195)	0.245 (0.215-0.274)	0.689 (0.660-0.718)
Model 3	0.159 (0.158-0.161)	0.039 (0.039-0.040)	0.198 (0.197-0.200)	0.191 (0.178-0.204)	0.679 (0.670-0.689)

Abbreviations: MAE, mean absolute error; MSE, mean-square error; RMSE, root-mean-square error; XGBoost, extreme gradient boosting.

Model P = primary model using all features; Model 1 = model using basic information as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features.

Appendix 24 (Supplementary Figure S9). Comparison of accuracy performance between the primary model and different new models under different algorithms.



(A) binary prediction, (B) continuous prediction. LinR = linear regression; LogR = logistic regression; Model P = primary model using all features; Model 1 = model using basic in-formation as features; Model 2 = model using basic information and concomitant psychotropic medications as features; Model 3 = model using the top 10 features of different algorithms as features; RF = random forests; SVM = support vector machine; XGBoost = extreme gradient boosting.