



# THE PRIMARY CARE COMPANION FOR CNS DISORDERS

## Supplementary Material

**Article Title:** Young Adult Depression, Antidepressant Prescriptions, and Therapy Intensification in People With Incident Depression in the United States

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# Supplementary Material

## METHODS

### **Rule-based Algorithm for identifying individuals with depression.**

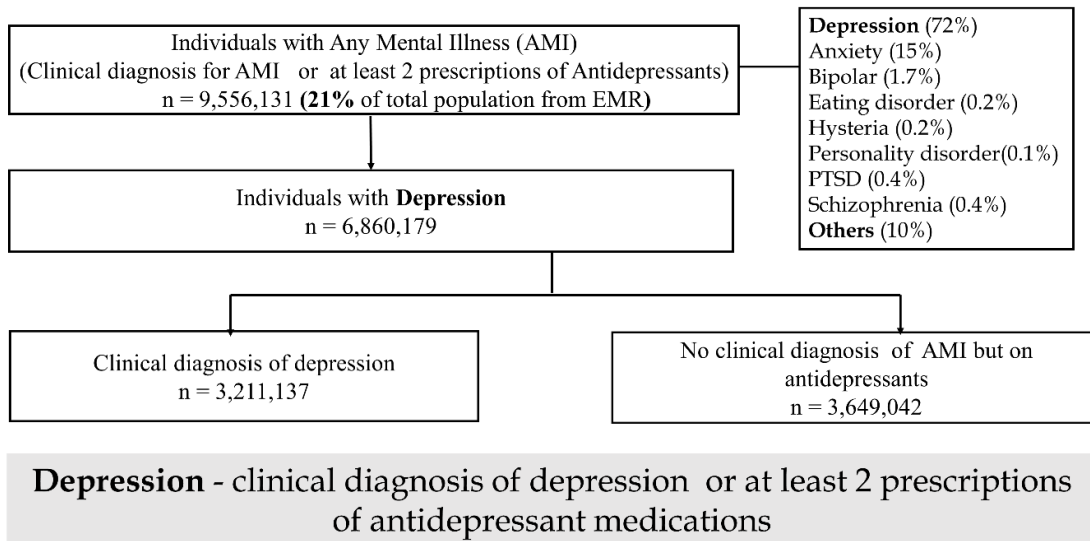
**Background:** Depression is the most common type of mental illness and among the leading cause of global disability. People with depression also tend to have other common medical conditions such as diabetes which are linked to worse outcomes. Depression exists in different types and its etiology poorly comprehended; thus, the identification of people with depression is urgently needed to better understand the causes and the course of the disease in order to design new and effective treatment strategies. The algorithm below describes in detail a rule-based approach developed to identify patients with depression from the CEMR database.

**Algorithm:** Any mental illness (AMI) comprises those mental illnesses that meet the diagnostic criteria specified within the 5<sup>th</sup> edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) excluding developmental and substance use disorder. These include **depression**, anxiety, bipolar, schizophrenia, posttraumatic stress disorder, eating disorder, gender identity disorder, personality disorder, and other unspecified mental illnesses. Patients with AMI were first identified with information from three domains: (1) AMI diagnosis disease codes (ICD 9(10) CM); (2) medications (use of antidepressant drugs for AMI); (3) key-word searching procedures for AMI related diseases from the clinical notes of every patient. Disease codes, search terms and list of antidepressants used for the identification of patients with AMI are indicated in Supplementary Tables 1 & 2. The process for the identification of patients with AMI was executed based on the following rule:

- **Inclusion criteria:** An initial cohort of patients with AMI were identified from the EMRs if the patient has at least one AMI specific diagnosis codes; **OR** use of antidepressants specifically used to treat AMI; **OR** having AMI related diagnostic codes from keywords. A patient was considered to use antidepressant if he / she has at least two prescriptions. The earliest date from either the first date of AMI occurrence or first prescription date was considered as the approximate date of diagnosis of AMI.
- **Classification of AMI and Depression identification:** Within the cohort of patients with AMI, patients with depression and other mental illnesses were formed in the following order:
  - a) **Patients with depression:** These include any patient with at least one of the following criteria: (1) has at least one clinical diagnosis code for depression; **OR** (2) has no clinical diagnosis of depression but taking antidepressants specifically used to treat depression; **OR** (3) has no clinical diagnosis of AMI but using other antidepressants used to treat depression (Supplementary Figure 1).
  - b) **Other mental illnesses:** These include all other patients not in the pool of patients with depression but have clinical diagnosis codes for anxiety, bipolar, schizophrenia, posttraumatic stress disorder, eating disorder, gender identity disorder, personality disorder, other unspecified mental illnesses or using antidepressant medications.

Among the people considered as having AMI, a total of 6,860,179 (72%) people were identified with depression (Supplementary Figure 1).

# Algorithm Design for Depression



**Supplementary Figure 1.** Methodological design with information to identify people with Depression. The information include ICD 9(10) CM codes and antidepressants mainly prescribed for common mental health disorders such as depression and anxiety.

## TABLES

**Supplementary Table 1.** Antidepressant generic (brand) drugs commonly prescribed for depression in US.

Drug class	Generic name	Brand name	Indications
Tricyclic antidepressants (TCAs)	amitriptyline	ALAVIL(Elavil), ENTRAVIL, LIMBITROL, TRIAVIL, VANATRIP, ETRAFON	major depressive disorder (MDD), anxiety disorders, and less commonly attention deficit hyperactivity disorder (ADHD) and bipolar disorder,
	amoxapine	ASENDIN	anxiety, depression
	clomipramine	ANAFRANIL	depression, anxiety, panic disorder
	doxepin	SILENOR, SINEQUAN	insomnia (low dose of doxepin), depression, anxiety
	trimipramine, desipramine, imipramine	SURMONTIL, NORPRAMIN, TOFRANIL,	depression
	nortriptyline	PAMELOR, AVENTYL	depression, ADHD
	protriptyline	VIVACTIL	depression, ADHD
Monoamine -oxidase inhibitors (MAOIs)	isocarboxazid	MARPLAN	depression
	Phenelzine	NARDIL	depression
	tranylcypromine	PARNATE	depression
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	Prozac, SYMBYAX, SARAFEM, SELFEMRA	MDD, obsessive compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder (PMDD), depression associated with

			bipolar, anxiety, Anorexia Nervosa, Posttraumatic Stress Syndrome (PTSD), Binge Eating Disorder
	sertraline	ZOLOFT	depression, OCD, panic disorder, PTSD, social anxiety disorder, and PMDD
	paroxetine	PAXIL, PEXEVA	depression, OCD, panic attacks, anxiety disorders, PTSD, and PMDD
	citalopram	CELEXA, CIPRAMIL	depression, anxiety, OCD, panic disorder, PTSD, and PMDD
	escitalopram	LEXAPRO, CIPRALEX	anxiety in adults and MDD
	fluvoxamine	LUVOX	OCD, depression
	vortioxetine	BRINTELLIX, TRINTELLIX	major depressive disorder
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine, desvenlafaxine	EFFEXOR, PRISTIQ, KHEDEZLA	anxiety, depression
	duloxetine	CYMBALTA, IRENKA	depression, anxiety
	levomilnacipran	FETZIMA	depression
Other antidepressants	bupropion	BUDEPRION, BUPROBAN, WELLBUTRIN, APLENZIN, APPBUTAMONE, FORFIVO, APLENZIN	depression
	trazodone	OLEPTRO, DESYREL	depression
	mirtazapine	REMERON	depression
	nefazodone	SERZONE	depression
	maprotiline	LUDIOMIL	depression, anxiety
	vilazodone	VIIIBRYD, TIANEPTINE	depression, anxiety

**Supplementary Table 2.** Clinical codes and terms used for the identification of patients with Any mental illness.

Disease	ICD09 CM	ICD10 CM	Search terms
Depression	290.13x, 290.2x, 290.21x, 290.43x, 296.[23]x, 96.82x, 298.0x, 300.4x, 301.12x, 309.[01]x, 309.28x, 311x	f3[23]x, 34.1x, f43.2[13]x, 25.1x, f41.8x	depressive, depression, Seasonal affective disorder, dysthymic, dysthymia
Anxiety	300.[023]x,	f4[01]x	anxiety, phobia, phobic, anxious, fear, obsess, panic, hypochondria
Bipolar	296.[01]x,	f3[01]x	bipolar, manic, mania
Schizophrenia	295x	f20x	Schizophrenia
Posttraumatic stress disorder	309.81x	f43.1x	Posttraumatic stress disorder, PTSD
Personality disorder	301x	f60x	personality disorder
Hysteria	300.[18]x	f45x	hysteria, somatization
Eating disorder	307.5x	f50	Eating disorder, bulimia nervosa, pica, anorexia nervosa, bulimia, anorexia
Other mental illness #	295-98, 300-302, 306-311	f20-f48, f50, f60, f63-f69, f99	paranoid, nerve pain, neuropathic pain mental disorder, mental illness, cyclothymic, delusion, cataplexy

All other mental illnesses in the list of disease codes specified for the row; [] = square bracket signifies either of the number or letter within, for example, f3[23] = f32, f33; x = represents a list of missing letter or number that completes the pattern of a particular disease codes.

**Supplementary Table 3.** Among all research-ready validated individuals registered in the EMR during the study periods, the prevalence of any mental illness (AMI) and depression are compared with diagnoses reported in the US National surveys.

Disease	Source	Size	Study period	Prevalence, % (95% CI)									
				Overall	Gender		Age					Race	
					Male	Female						Black	White
<b>Depression</b>							<b>18-29 yrs.</b>	<b>30-44 yrs.</b>	<b>45-64 yrs.</b>	<b>65+ yrs.</b>			
	NESARC-III [1]	36,309	2012-2013	20.6	14.7	26.1	20.2	22.0	22.9	14.4		15.2	23.1
	CEMR	14,818,513	2012-2013	18.2 (18.1, 18.2)	12.9 (12.8, 12.9)	22.0 (21.9, 22.0)	12.7 (12.6, 12.7)	17.7 (17.7, 17.8)	20.7 (20.6, 20.8)	18.6 (18.5, 18.6)		13.5 (13.4, 13.5)	21.7 (21.7, 21.8)
							<b>18-24 yrs.</b>	<b>25-34 yrs.</b>	<b>35-44 yrs.</b>	<b>44-54 yrs.</b>	<b>55+ yrs.</b>		
	BRFSS[2, 3]	91,377	2008	16.1	11.2	20.7	14.8	14.4	16.7	19.9	14.9	12.3	17.3
	CEMR	4,670,863	2008	12.2 (12.1, 12.2)	8.3 (8.3, 8.4)	14.9 (14.8, 15.0)	7.5 (7.4, 7.6)	10.1 (10.0, 10.2)	12.5 (12.4, 12.6)	14.0 (13.9, 14.1)	13.1 (13.0, 13.1)	7.7 (7.6, 7.8)	14.3 (14.2, 14.4)
	BRFSS[2, 3]	306,953	2006 & 2008	15.9	11.2	20.5	14.7	14.4	16.7	19.6	14.7	11.8	17.3
	CEMR	6,217,384	2006 & 2008	13.0 (12.4, 13.0)	8.4 (8.5)	15.3 (15.3, 15.4)	7.8 (7.7, 7.8)	10.4 (10.3, 10.5)	12.8 (12.7, 12.9)	14.4 (14.3, 14.4)	13.2 (13.1, 13.2)	8.1 (7.9, 8.2)	15.2 (15.1, 15.2)



							<b>18-25 yrs.</b>	<b>26-49 yrs.</b>	<b>50+ yrs.</b>				
<b>AMI</b>													
	NSDUH [4]	68,487	2010	20.0	16.8	23.0	29.9	22.1	14.3			19.7	20.6
	CEMR	8,171,102	2010	20.1 (20.1, 20.2)	16.1 (16.0, 16.1)	23.0 (22.9, 23.0)	14.6 (14.5, 14.6)	20.8 (20.7, 20.9)	20.8 (20.8, 20.9)			15.5 (15.4, 15.6)	23.7 (23.6, 23.8)
	NSDUH[5]	~ 67,500	2013	18.5	14.4	22.3	19.4	21.5	15.3			16.9	19.3
	CEMR	14,594,364	2013	24.3 (24.2, 24.3)	19.1 (19.0, 19.2)	27.9 (27.9, 28.0)	18.2 (18.1, 18.2)	25.3 (25.2, 25.3)	24.8 (24.8, 24.9)			19.9 (19.9, 20.1)	28.9 (28.9, 29.0)

NESARC -III: National Epidemiologic Survey on Alcohol and Related Conditions-III; BRFSS: Behavioral Risk Factor Surveillance System; NSDUH: National Survey on Drug Use and Health

**Supplementary Table 4.** Rates 1000 person-years (95% CI) of antidepressant drug class intensification from first-line AD monotherapy to second-line drugs by age groups and gender.

	<b>Male</b>				<b>Female</b>			
<b>Age groups</b>	<b>SSRI</b>	<b>SNRI</b>	<b>TCA</b>	<b>Others</b>	<b>SSRI</b>	<b>SNRI</b>	<b>TCA</b>	<b>Others</b>
18 to 29 years	67.4 (65.9 – 68.9)	15.9 (15.4 – 16.4)	8.1 (7.7 – 8.4)	36.6 (35.8 – 37.4)	84.2 (83.2 – 85.1)	20.2 (19.9 – 20.5)	11.3 (11.1 – 11.5)	35.9 (35.6 – 36.4)
30 to 39 years	59.5 (58.3 – 60.8)	18.8 (18.3 – 19.3)	9.8 (9.4 – 10.1)	37.7 (36.9 – 38.4)	71.9 (71.1 – 72.8)	23.8 (23.5 – 24.1)	12.8 (12.6 – 13.1)	37.9 (37.6 – 38.4)
40 to 49 years	49.8 (48.9 – 50.7)	18.7 (18.3 – 19.1)	10.8 (10.5 – 11.1)	36.4 (35.8 – 37.0)	59.7 (59.1 – 60.3)	25.9 (25.6 – 26.2)	13.4 (13.2 – 13.6)	36.2 (35.8 – 36.6)
50 to 59 years	42.4 (41.8 – 43.1)	17.6 (17.3 – 17.9)	10.1 (9.9 – 10.3)	32.2 (31.7 – 32.7)	50.5 (49.9 – 50.9)	23.4 (23.1 – 23.7)	11.8 (11.7 – 12.0)	30.8 (30.5 – 31.1)
60 to 70 years	37.2 (36.6 – 37.9)	13.6 (13.3 – 13.9)	7.4 (7.2 – 7.6)	25.5 (25.1 – 25.9)	45.7 (45.2 – 46.2)	171.7 (17.5 – 17.9)	9.2 (9.0 – 9.4)	25.1 (24.8 – 25.4)
Total	46.9 (46.5 – 47.31)	16.6 (16.5 – 16.8)	9.2 (9.1 – 9.3)	32.3 (32.0 – 32.5)	58.8 (58.6 – 59.1)	22.2 (22.0 – 22.3)	11.7 (11.6 – 11.7)	32.6 (32.4 – 32.7)

**Supplementary Table 5.** Intensification between antidepressant drug classes, by generic drugs. Only those generic drugs with a minimum of 10% change within each of the second-line antidepressant classes are presented.

First-line Antidepressants	Second-line Antidepressants			
	SNRI	TCA	Others	SSRI
<b>SSRI (1,003,822 (56))<sup>†</sup> &gt;</b>	62,925 (30)	30,522 (15)	114,299 (55)	<b>Not needed</b>
time (in months) to second-line for SSRI, <i>median (q1, q3)</i>	19 (8, 39)	18 (6, 39)	17 (6, 39)	
	citalopram > duloxetine 7,630 (12)	citalopram > amitriptyline 5,116 (17)	citalopram > bupropion 15,486 (14)	
	citalopram > venlafaxine 8,096 (13)	escitalopram > amitriptyline 3,545 (12)	citalopram > trazodone 11,230 (10)	
	escitalopram > duloxetine 7,698 (12)	fluoxetine > amitriptyline 3,737 (12)	escitalopram > bupropion 13,980 (12)	
	escitalopram > venlafaxine 7,479 (12)	sertraline > amitriptyline 5,055 (17)	fluoxetine > bupropion 10,991 (10)	
	sertraline > duloxetine 7,325 (12)		sertraline > bupropion 14,605 (13)	
	Sertraline > venlafaxine 7,532 (12)		sertraline > trazodone 10,995 (10)	
<b>SNRI (265,875 (15))<sup>†</sup> &gt;</b>	<b>Not needed</b>	10,992 (16)	25,298 (37)	32,595 (47)

time (in months) to second-line for SNRI, <i>median (q1, q3)</i>		14 (5, 32)	16 (5, 36)	18 (7, 37)
		duloxetine > amitriptyline 4,643 (42)	duloxetine > bupropion 5,607 (22)	venlafaxine > sertraline 3,622 (11)
		duloxetine > nortriptyline 1,601 (15)	duloxetine > trazodone 5,847 (23)	duloxetine > citalopram 3,996 (12)
		venlafaxine > amitriptyline 2,251 (20)	venlafaxine > bupropion 5,580 (22)	duloxetine > escitalopram 3,708 (11)
			venlafaxine > trazodone 4,887 (19)	duloxetine > fluoxetine 3,207 (10)
				venlafaxine > escitalopram 3,562 (11)
				venlafaxine > citalopram 4,015 (12)
				duloxetine > sertraline 3,749 (12)
<b>TCA (191,981 (11))<sup>†</sup> &gt;</b>	10,809 (25)	<b>Not needed</b>	10,037 (24)	21,903 (51)
time (in months) to second-line for TCA, <i>median (q1, q3)</i>	15 (6, 34)		18 (7, 39)	17 (6, 37)
				amitriptyline > citalopram 4,046 (18)
				amitriptyline > escitalopram 2,667 (12)

				amitriptyline > fluoxetine 2,606 (12)
				amitriptyline > sertraline 3,967 (18)
<b>Others (336,185 (19))<sup>†</sup> &gt;</b>	17,743 (22)	10,065 (12)	<b>Not needed</b>	53,158 (66)
time (in months) to second-line for Others, median (q1, q3)	14 (5, 32)	15 (6, 34)		14 (5, 32)
	bupropion > duloxetine 4,833 (27)	bupropion > amitriptyline 2,668 (27)		bupropion > citalopram 7,256 (14)
	bupropion > venlafaxine 4,281 (24)	trazodone > amitriptyline 2,930 (29)		bupropion > escitalopram 6,735 (13)
	trazodone > duloxetine 4,083 (23)			bupropion > fluoxetine 5,533 (10)
	trazodone > venlafaxine 2,515 (14)			bupropion > sertraline 7,402 (14)
				trazodone > citalopram 5,068 (10)
				trazodone > sertraline 5,122 (10)

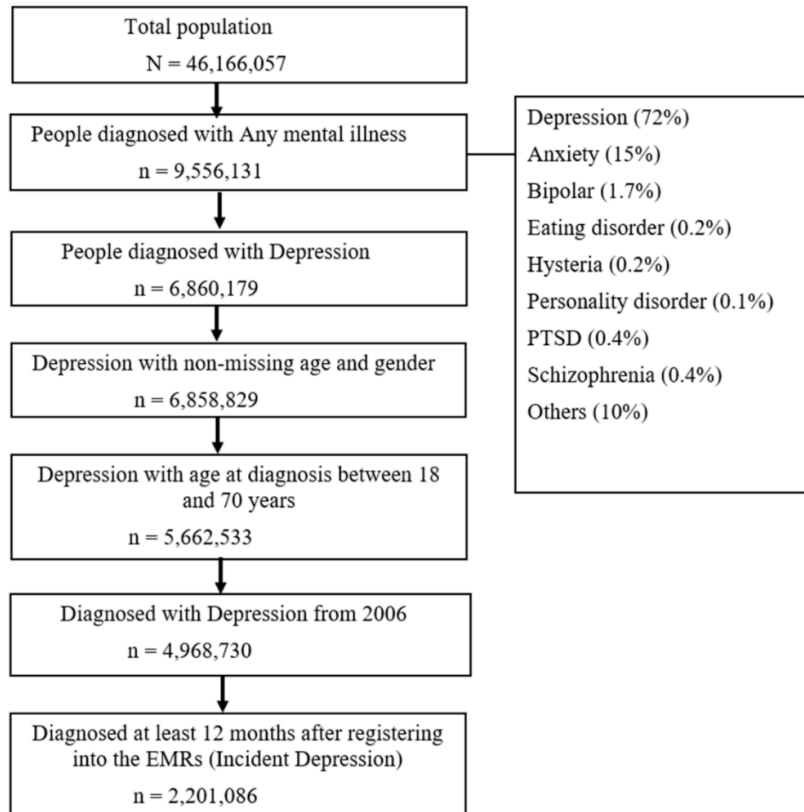
Data values in count (%) unless otherwise specified, **SNRI**: serotonin noradrenaline reuptake inhibitor, **TCA**: tricyclic antidepressant, **SSRI**: selective serotonin reuptake inhibitor, †: represents count (%) of first-line AD drug class from all those who initiated at least one AD drug class, > shows direction of intensification.

**Supplementary Table 6.** Rates per 1000 person-years (95% CI) of antidepressant drug class intensification from first-line AD monotherapy to second-line drugs by age groups and gender.

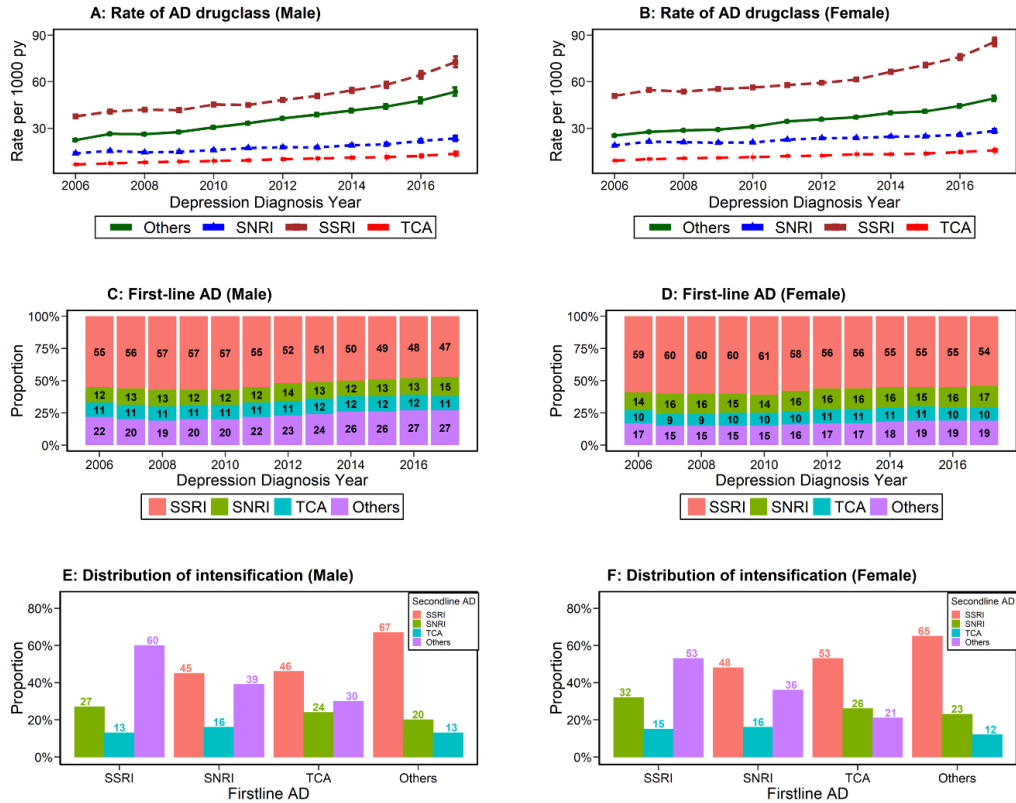
<b>Age groups</b>	<b>Male</b>	<b>Female</b>
18 to 29 years	62.14 (61.01 - 63.27)	71.97 (71.34 - 72.61)
30 to 39 years	65.66 (64.63 - 66.71)	75.53 (74.91 - 76.16)
40 to 49 years	63.77 (62.94 - 64.61)	73.48 (72.93 - 74.04)
50 to 59 years	56.90 (56.24 - 57.57)	63.84 (63.37 - 64.30)
60 to 70 years	45.36 (44.80 - 45.92)	52.26 (51.83 - 52.70)
Overall	56.37 (56.02 - 56.71)	66.21 (65.97 - 66.45)

## FIGURES

**Supplementary Figure 2.** Flow chart for the selection of study cohort of patients with incident depression.

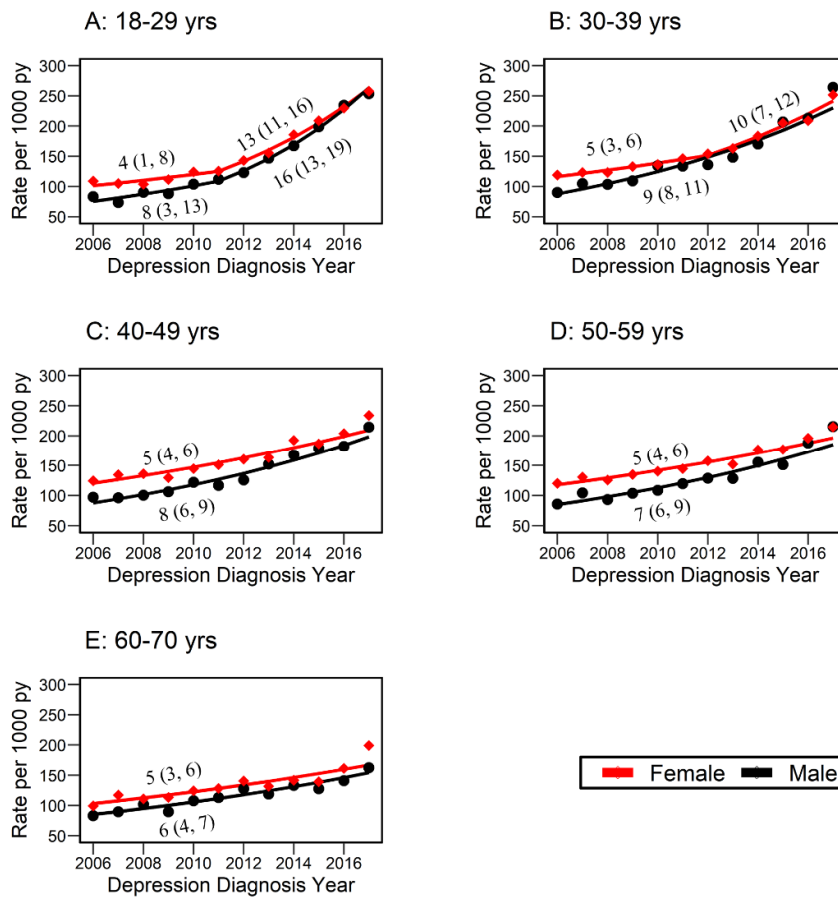


**Supplementary Figure 3.** Distribution of Antidepressant drug class prescriptions and intensifications by gender: (A) and (B) The rates / 1000 person-years of antidepressant drug class prescriptions; (C) and (D) Proportional share of first-line antidepressant (AD) prescriptions by drug class; (E) and (F) type of treatment intensification from first-line to second-line AD drug class.





**Supplementary Figure 4.** Observed and modelled trend in the overall antidepressant prescription rates (per 1000 person-years) among US adults with incident depression. The trends are represented separately by age (18-29, 30-39, 40-49, 50-59 and 60-70 years at diagnosis of depression) and gender. The dots and squares represent observed rates while the lines are the estimates from Join-Point Regression model. The numbers within the plots are the annual percent change (95% CI) of the trends.



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