

**Supplemental Digital Content**

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eTable 1. Inclusion and Exclusion Criteria, Definitions, and Cohort Derivation

<b>Criterion</b>	<b>Definition</b>	<b>Included n</b>
1. Age 13-73 in 2007	Birth years 1934-1993	6 433 559
2. No prior emigration	Emigration before 2007/01/01	6 035 233
3. Alive	Death before 2007/01/01	5 696 331
4. Residing in Sweden	Non-missing 2007 neighborhood	5 643 753
5. No prior opioids	Non-medication-assisted-treatment opioids dispensed in 2005-2006	5 144 305
6. No terminal cancer	Cancer cause of death (ICD-10 codes C00-C97 and D37-D48 through 2014/12/31)	5 094 583
7. No cancer opioids	Opioids from palliative/oncology practice or oncology practitioner	5 071 933
8. No invalid opioids	No invalid N02A or N07BC anatomical therapeutic chemical code 2007-2014	5 071 899
9. 6+ mo. follow-up	Last day eligible to initiate long-term opioid therapy on or after 2007/01/01	<b>5 071 193</b>
<b>Family data sub-cohort</b>		
10. Age 13-29 in 2007	Birth years 1978-1993	1 513 833
11. Any maternal data	Non-missing maternal identifier	1 508 310
12. Any paternal data	Non-missing paternal identifier	1 500 486
13. Socioeconomic data	Non-missing family-of-origin socioeconomic status <sup>a</sup>	<b>1 482 462<sup>b</sup></b>

<sup>a</sup> Maternal and paternal country of origin, maternal *and* paternal highest level of education through 2006, offspring-age-12 neighborhood deprivation, and offspring-age-12 maternal *or* paternal family disposable income.

<sup>b</sup> Complete-case family data sub-cohort; 97.9% of those eligible.

eTable 2. Anatomical Therapeutic Chemical Codes for Included Medications

Medication Group	Anatomical Therapeutic Chemical Codes <sup>a</sup>
Attention-deficit/hyperactivity disorder	<b>N06BA:</b> N06BA01, N06BA02, N06BA04, N06BA09
Antidepressant	<b>Selective serotonin reuptake inhibitor (N06AB):</b> N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10; <b>From other N06A:</b> N06AX16, N06AF03, N06AF04, N06AG02, N06AX02, N06AX03, N06AX06, N06AX11, N06AX12, N06AX18; <b>Other bupropion:</b> N07BA02
Antipsychotic	<b>From N05A:</b> N05AA01, N05AA02, N05AA06, N05AB01, N05AB02, N05AB03, N05AB04, N05AC01, N05AC02, N05AD01, N05AD03, N05AD05, N05AD08, N05AE03, N05AE04, N05AF01, N05AF03, N05AF05, N05AG02, N05AH02, N05AH03, N05AH04, N05AL01, N05AX08, N05AX12
Benzodiazepine	<b>N05BA:</b> N05BA01, N05BA02, N05BA04, N05BA05, N05BA06, N05BA09, N05BA12; <b>N05CD:</b> N05CD02, N05CD03, N05CD05, N05CD08; <b>Clonazepam:</b> N03AE01
Mood stabilizer	<b>Lithium:</b> N05AN01; <b>From N03A:</b> N03AF01, N03AF02, N03AG01, N03AX09
Opioid analgesic	<b>N02A:</b> N02AA01, N02AA03, N02AA05, N02AA55, N02AA59, N02AB01, N02AB02, N02AB03, N02AC04, N02AC54, N02AD01, N02AE01, N02AG01, N02AG02, N02AG04, N02AX02, N02AX06; <b>N07BC:</b> N07BC01, N07BC02, N07BC51; <b>Other codeine combination:</b> N02BE51
Opioid use disorder <sup>b</sup>	<b>From N02A:</b> N02AE01; <b>N07BC:</b> N07BC01, N07BC02, N07BC51
Other substance use disorder	<b>Nicotine (From N07BA):</b> N07BA01, N07BA03; <b>Alcohol (N07BB):</b> N07BB01, N07BB03, N07BB04
Z-hypnotic	<b>N05CF:</b> N05CF01, N05CF02, N05CF03

<sup>a</sup> We excluded duloxetine and all tricyclics from the antidepressants and included only select antiepileptic drugs as mood stabilizers [1] to avoid capturing psychoactive medications also used in pain management.

<sup>b</sup> See text for description of methods for distinguishing medication assisted treatment of opioid use disorder from analgesia.

## References

[1] Fazel S, Zetterqvist J, Larsson H, Långström N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet* 2014;384(9949):1206-1214.

eTable 3. *International Classification of Diseases* (ICD) Codes for Included Mental Health Conditions

<b>Diagnosis Group<sup>a</sup></b>	<b>ICD-10</b>	<b>ICD-9</b>	<b>ICD-8</b>
Anxiety disorder	F40-F43	300A, 300C, 300D, 308, 309	300.0, 300.2, 300.3, 307
Attention-deficit/hyperactivity disorder	F90	314	--
Bipolar disorder	F30, F31	296A, 296C, 296D, 296E, 296W	296.1, 296.3, 296.8
Depressive disorder	F32, F33, F34.1	296B, 300E, 311	296.2, 300.4
Opioid use disorder	F11	304A	304.0, 304.1
Other substance use disorder	F10, F12- F19 (except F17; tobacco)	291, 292, 303, 304 (except 304A), 305 (except 305B; tobacco)	291, 303, 304 (except 304.0, 304.1)
Schizophrenia spectrum disorder	F20-F25, F28, F29	295, 297, 298	295, 297, 298, 299
Suicide attempt/self-injury (definite or undetermined intent)	X60-X84, Y10-Y34, Y87.0, Y87.2	E950-E959, E980-E989	E950-E959, E980-E989

<sup>a</sup> In order to reduce the likelihood of inappropriate or invalid diagnoses, we required individuals to be at least 12 years of age at the time of diagnosis (5 years of age for attention-deficit/hyperactivity disorder, anxiety disorder, and depressive disorder).

eTable 4. Opioid Initiation, Long-Term Opioid Therapy, and Concurrent Benzodiazepine Therapy by Demographics

<b>Demographic</b>	<b>Included Cohort n (%)</b>	<b>Initiation % (95% CI)<sup>a</sup></b>	<b>Long-Term Opioid Therapy % (95% CI)<sup>a</sup></b>	<b>Concurrent Benzodiazepine % (95% CI)<sup>a</sup></b>
Sex				
Female	2 456 397 (48.4%)	12.3% (12.2%-12.3%)	7.6% (7.5%-7.6%)	6.4% (6.4%-6.5%)
Male	2 614 796 (51.6%)	10.5% (10.5%-10.6%)	7.7% (7.7%-7.8%)	5.0% (4.9%-5.0%)
Age group <sup>b</sup>				
13-18 years	606 534 (12.0%)	5.1% (5.1%-5.2%)	2.5% (2.3%-2.6%)	1.2% (1.0%-1.3%)
19-25 years	616 601 (12.2%)	8.2% (8.1%-8.2%)	4.3% (4.2%-4.4%)	3.2% (3.1%-3.3%)
26-35 years	841 168 (16.6%)	10.1% (10.0%-10.1%)	4.3% (4.2%-4.4%)	4.4% (4.3%-4.5%)
36-45 years	916 930 (18.1%)	11.3% (11.3%-11.4%)	5.1% (5.0%-5.2%)	4.9% (4.8%-5.0%)
46-55 years	822 515 (16.2%)	12.9% (12.8%-12.9%)	6.6% (6.5%-6.7%)	5.7% (5.6%-5.8%)
56-65 years	862 857 (17.0%)	14.9% (14.9%-15.0%)	8.7% (8.6%-8.8%)	6.4% (6.3%-6.5%)
66+ years	404 588 (8.0%)	17.7% (17.6%-17.9%)	15.1% (14.9%-15.2%)	8.7% (8.6%-8.8%)
County				
Skåne	629 596 (12.4%)	11.3% (11.2%-11.3%)	6.3% (6.1%-6.4%)	6.3% (6.1%-6.4%)
Stockholm	965 228 (19.0%)	13.9% (13.8%-14.0%)	7.0% (6.9%-7.1%)	5.0% (4.9%-5.1%)
Västra götaland	851 604 (16.8%)	10.7% (10.6%-10.8%)	6.7% (6.6%-6.8%)	6.7% (6.5%-6.8%)
Other counties <sup>c</sup>	2 624 765 (51.8%)	10.7% (10.6%-10.7%)	8.6% (8.5%-8.7%)	5.6% (5.6%-5.7%)

Kaplan Meier estimates of 3-year cumulative incidence of opioid initiation and, among those initiating opioids (n = 1 298 083), long-term opioid therapy and concurrent benzodiazepine therapy within 3 years of opioid initiation by demographics in 2007.

<sup>a</sup> Pointwise 95% confidence intervals.

<sup>b</sup> Age group is age at opioid initiation for long-term opioid therapy and concurrent benzodiazepine therapy.

<sup>c</sup> Grouped for analysis.

eTable 5. Opioid Prescriptions Dispensed to Cohort (n = 5 071 193 Individuals)

Opioid Drug	ATC Code	Dispensed Prescriptions	
		n	%
Buprenorphine	N02AE01	157 066	2.9%
	N07BC01	3775	0.1%
With naloxone	N07BC51	3487	0.1%
Codeine combinations <sup>a</sup>	N02AA59	1 749 118	32.4%
Paracetamol with codeine	N02BE51	758	0.0%
Dextropropoxyphene	N02AC04	222 359	4.1%
Fentanyl	N02AB03	57 940	1.1%
Hydromorphone	N02AA03	625	0.0%
With antispasmodics	N02AG04	166	0.0%
Ketobemidone	N02AB01	46 521	0.9%
With antispasmodics	N02AG02	5313	0.1%
Methadone	N07BC02	15 323	0.3%
Morphine	N02AA01	305 155	5.7%
With antispasmodics	N02AG01	90 401	1.7%
Oxycodone	N02AA05	907 673	16.8%
With naloxone	N02AA55	47 251	0.9%
Pentazocine	N02AD01	112	0.0%
Pethidine	N02AB02	101	0.0%
Tapentadol	N02AX06	11 178	0.2%
Tramadol	N02AX02	1 775 254	32.9%
Total		5 399 576	100.0%

Opioid analgesic prescriptions dispensed in 2007-2014.

<sup>a</sup> Acetylsalicylic acid, ibuprofen, or paracetamol.

ATC, Anatomical Therapeutic Chemical.

eTable 6. Associations of Psychoactive Medications with Opioid Initiation and Long-Term Opioid Therapy

<b>Psychoactive Medication</b>	<b>Medication Prevalence<sup>a</sup> n (%)</b>	<b>Association with Initiation HR<sup>b</sup> (95% CI)</b>	<b>Association with LTOT HR<sup>c</sup> (95% CI)</b>
Opioid use disorder <sup>d</sup>	992 (0.0%)	1.75 (1.59-1.93)	6.88 (5.82-8.12)
Antipsychotic	62 579 (1.2%)	1.15 (1.14-1.17)	2.16 (2.09-2.24)
Attention-deficit/hyperactivity disorder	9162 (0.2%)	1.61 (1.55-1.67)	2.12 (1.90-2.38)
Other substance use disorder	22 502 (0.4%)	1.85 (1.81-1.89)	2.01 (1.92-2.11)
Mood stabilizer	53 580 (1.1%)	1.29 (1.27-1.30)	1.89 (1.82-1.96)
Benzodiazepine	154 407 (3.0%)	1.57 (1.56-1.59)	1.71 (1.68-1.75)
Antidepressant	335 270 (6.6%)	1.56 (1.55-1.57)	1.57 (1.55-1.60)
Z-hypnotic	220 645 (4.4%)	1.69 (1.68-1.70)	1.51 (1.49-1.54)
<b>Included (n)</b>		5 071 193	1 298 083
<b>Opioid outcome (n)</b>		1 298 083	116 977

<sup>a</sup> Prevalence of medications dispensed in 2005-2006.

<sup>b</sup> Adjusted for county, sex, and age.

<sup>c</sup> Adjusted for county, sex, age at opioid initiation, and calendar year of initiation.

<sup>d</sup> Opioid use disorder medication models excluded all individuals aged less than 18 years (included n = 4 570 641 individuals overall, with 1 220 303 opioid recipients, of whom 113 447 received LTOT).

HR, hazard ratio. LTOT, long-term opioid therapy.

eTable 7. Sensitivity Analyses for Opioid Initiation

<b>Mental Health Condition</b>	<b>Past-6-Year Mental Health Diagnoses HR<sup>a</sup> (95% CI)</b>	<b>Excluding Buprenorphine and Methadone Recipients HR<sup>a</sup> (95% CI)</b>
Opioid use disorder	2.23 (2.12-2.35)	2.08 (1.98-2.19)
Other substance use disorder	1.85 (1.83-1.87)	1.69 (1.67-1.70)
Attention-deficit/hyperactivity disorder	1.57 (1.51-1.63)	1.53 (1.47-1.58)
Schizophrenia spectrum disorder	0.79 (0.77-0.81)	0.82 (0.80-0.84)
Suicide attempt or other self-injury	1.77 (1.75-1.80)	1.68 (1.66-1.70)
Depressive disorder	1.63 (1.61-1.65)	1.54 (1.52-1.55)
Anxiety disorder	1.61 (1.60-1.63)	1.56 (1.55-1.58)
Bipolar disorder	1.33 (1.29-1.37)	1.21 (1.18-1.24)
Number of conditions [reference: 0]		
1	1.44 (1.43-1.45)	1.41 (1.40-1.42)
2+	1.81 (1.79-1.84)	1.64 (1.63-1.66)
<b>Included (n)</b>	5 071 193	5 036 819
<b>Opioid initiation (n)</b>	1 298 083	1 267 383

<sup>a</sup> Adjusted for county, sex, and age.

HR, hazard ratio.



eTable 8. Sensitivity Analyses for Long-Term Opioid Therapy

<b>Mental Health Condition</b>	<b>Past-6-Year Mental Health Diagnoses HR<sup>a</sup> (95% CI)</b>	<b>Excluding Buprenorphine and Methadone Recipients HR<sup>a</sup> (95% CI)</b>	<b>LTOT Defined as Strong Opioids in 3 of 4 Quarters HR<sup>a,b</sup> (95% CI)</b>
Opioid use disorder	4.44 (4.01-4.91)	2.53 (2.23-2.88)	8.43 (7.44-9.55)
Other substance use disorder	2.37 (2.30-2.44)	2.04 (1.99-2.10)	3.54 (3.40-3.69)
Attention-deficit/hyperactivity disorder	2.16 (1.93-2.41)	1.78 (1.57-2.01)	3.76 (3.11-4.54)
Schizophrenia spectrum disorder	2.15 (2.02-2.28)	1.78 (1.69-1.88)	3.01 (2.79-3.25)
Suicide attempt or other self-injury	1.95 (1.87-2.03)	1.76 (1.70-1.81)	2.80 (2.66-2.94)
Depressive disorder	1.74 (1.69-1.80)	1.62 (1.57-1.66)	2.50 (2.39-2.61)
Anxiety disorder	1.71 (1.66-1.77)	1.60 (1.55-1.64)	2.54 (2.43-2.66)
Bipolar disorder	1.65 (1.53-1.78)	1.54 (1.43-1.66)	2.46 (2.21-2.75)
Number of conditions [reference: 0]			
1	1.73 (1.69-1.77)	1.54 (1.51-1.58)	2.32 (2.24-2.41)
2+	2.26 (2.19-2.33)	1.97 (1.92-2.02)	3.60 (3.46-3.75)
<b>Included (n)</b>	1 298 083	1 267 383	1 222 954
<b>LTOT (n)</b>	116 977	96 956	25 508

<sup>a</sup> Adjusted for county, sex, age at opioid initiation, and calendar year of initiation.

<sup>b</sup> Estimated among opioid recipients with at least one year (i.e., four quarters) of follow-up time.

HR, hazard ratio. LTOT, long-term opioid therapy.

eTable 9. Additional Analyses of Parental Mental Health and Opioid Initiation and Long-Term Opioid Therapy

<b>Parental Mental Health</b>	<b>Initiation</b>		<b>Long-Term Opioid Therapy</b>	
	<b>SES Adjusted HR<sup>a</sup> (95% CI)</b>	<b>+ Offspring MH HR<sup>b</sup> (95% CI)</b>	<b>SES Adjusted HR<sup>a</sup> (95% CI)</b>	<b>+ Offspring MH HR<sup>b</sup> (95% CI)</b>
Anxiety or depressive disorder	1.20 (1.18-1.22)	1.16 (1.14-1.17)	1.27 (1.20-1.34)	1.19 (1.13-1.26)
Substance use disorder	1.28 (1.26-1.30)	1.23 (1.21-1.25)	1.34 (1.26-1.42)	1.24 (1.17-1.32)
Suicide attempt or other self-injury	1.30 (1.28-1.33)	1.25 (1.23-1.27)	1.31 (1.23-1.40)	1.22 (1.14-1.30)
<b>Offspring<sup>c</sup> (n)</b>	1 482 462		273 824	
<b>Outcome (n)</b>	273 824		13 314	

<sup>a</sup> Adjusted for childhood SES (parental education, family income, neighborhood deprivation, parental immigration, and metropolitan residence), in addition to county, sex, age, and, for long-term opioid therapy, calendar year of initiation. For long-term opioid therapy, age is age at opioid initiation.

<sup>b</sup> Additionally adjusted for pre-existing offspring MH conditions.

<sup>c</sup> Sub-cohort of individuals aged 13-29 in 2007 with familial data.

HR, hazard ratio. MH, mental health. SES, socioeconomic status.