

Supplemental Materials

SUPPLEMENTAL TABLE 3 Inclusion and Exclusion Criteria, Definitions, and Cohort Derivation

Criterion	Definition	Included <i>n</i>
1. Age 9–29 by January 1, 2013	Births between January 1, 1984 and January 1, 2004	2 020 962
2. No prior emigration	Emigration before January 1, 2007 (or 9th birthday if later)	1 952 961
3. Alive	Death before January 1, 2007 (or 9th birthday)	1 945 206
4. Residing in Sweden	Nonmissing neighborhood of residence in 2007 (or year of 9th birthday)	1 941 632
5. Biological parents, identifiable	father No adoptive parents, nonmissing paternal identifier	1 929 139
6. No prior opioids	No opioid ^a dispensed before January 1, 2007 (or 9th birthday)	1 895 987
7. No invalid opioid prescription data	No invalid N02A or N07BC anatomical therapeutic chemical code before December 31, 2013	1 895 984
Demographically matched comparison (singleton births only)		
8. Singleton birth	Nontwin or greater multiple	1 846 548
9. Opioid recipient	Dispensed opioid after January 1, 2007 (or 9th birthday)	197 107
10. Matching	Matched 1:1 on demographics to non-recipient	197 107
11. Valid follow-up	Index date precedes censoring date (for both initiator and matched noninitiator)	193 216
12. No preexisting suicidal behavior	No outcome on or before index date (recipient and non-recipient)	180 808
Active comparator design (singleton births only)		
13. Incident opioid or NSAID user	First dispensed either drug after January 1, 2007 (or 9th birthday)	424 288
14. No simultaneous prescription	Index date is not identical for opioid and NSAID	397 613
15. Valid follow-up	Index date precedes censoring date	395 724
16. No preexisting suicidal behavior	No outcome on or before index date	383 488
17. Complete case	Nonmissing covariate values	341 731
Sibling comparison design		
18. Differentially opioid exposed	At least one sibling dispensed opioid after January 1, 2007 (or 9th birthday), but not simultaneously within family (1 family per each mother and father)	301 523
19. Valid follow-up	Index date precedes censoring date (in differentially exposed siblings)	298 015
20. No preexisting suicidal behavior	No outcome on or before index date (in differentially exposed siblings)	280 777
21. Complete case	Nonmissing covariate values (in differentially exposed siblings)	229 952

NSAID, nonsteroidal antiinflammatory drug.

^a Opioid analgesic or buprenorphine or methadone treatment for opioid use disorder.

SUPPLEMENTAL TABLE 4 Anatomical Therapeutic Chemical Codes for Included Medications

Medication Group	Anatomical Therapeutic Chemical Codes
Antidepressant (SSRI)	SSRI (N06AB): N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10
Antidepressant (cyclic)	N06AA: N06AA02, N06AA04, N06AA06, N06AA09, N06AA10, N06AA21
Antidepressant (other)	From other N06A: N06AF03, N06AF04, N06AG02, N06AX02, N06AX03, N06AX11, N06AX12, N06AX16, N06AX18, N06AX22
Antiepileptic/ mood stabilizer	Lithium: N05AN01; from N03A: N03AA02, N03AA03, N03AB02, N03AB05, N03AD01, N03AF01, N03AF02, N03AF03, N03AF04, N03AG01, N03AG04, N03AX03, N03AX09, N03AX10, N03AX11, N03AX14, N03AX15, N03AX17, N03AX18, N03AX21, N03AX22
Antipsychotic	From N05A: N05AA01, N05AA02, N05AB01, N05AB02, N05AB03, N05AB04, N05AC02, N05AD01, N05AD03, N05AE03, N05AE04, N05AF01, N05AF03, N05AF05, N05AG02, N05AH02, N05AH03, N05AH04, N05AL01, N05AL05, N05AX08, N05AX12, N05AX13
Anxiolytic	From N05B: N05BB01, N05BE01
ADHD medication	N06BA: N06BA01, N06BA02, N06BA04, N06BA07, N06BA09, N06BA12
Benzodiazepine	N05BA: N05BA01, N05BA04, N05BA06, N05BA09, N05BA12; N05CD: N05CD02, N05CD03, N05CD05, N05CD08; Clonazepam: N03AE01
Duloxetine	N06AX21
Gabapentin/pregabalin	N03AX12, N03AX16
Migraine medication	N02C: N02CA01, N02CA52, N02CA72, N02CC01, N02CC02, N02CC03, N02CC04, N02CC05, N02CC06, N02CX01, N02CX02
Nonsteroidal anti inflammatory drug	M01A: M01AB01, M01AB02, M01AB05, M01AB15, M01AB16, M01AB55, M01AC01, M01AC02, M01AC05, M01AC06, M01AE01, M01AE02, M01AE03, M01AE14, M01AE52, M01AH01, M01AH05, M01AX01, M01AX05
Opioid analgesic ^a	N02A: N02AA01, N02AA03, N02AA05, N02AA55, N02AA59, N02AB01, N02AB02, N02AB03, N02AC04, N02AC54, N02AD01, N02AE01, N02AG01, N02AG02, N02AG04, N02AX02, N02AX06; N07BC: N07BC01, N07BC02, N07BC51; other codeine combination: N02BE51
Paracetamol	N02BE01
Z-hypnotic	N05CF: N05CF01, N05CF02, N05CF03
Other sedative/hypnotic	From N05C: N05CC01, N05CH01, N05CM02, N05CM05, N05CM06, N05CM09

^a See text for references for method of distinguishing opioid analgesics from opioid use disorder medications.

SUPPLEMENTAL TABLE 5 International Classification of Diseases (ICD) Codes for Included Diagnoses

Diagnosis Group ^a	ICD-10	ICD-9	ICD-8
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
Cancer as cause of death only	C00-C97, D37-D48	—	—
Depressive disorder	F32, F33, F34.1	296B, 300E, 311	296.2, 300.4
Substance use disorder	F10-F19 (except F17; tobacco)	291, 292, 303, 304, 305 (except 305B; tobacco)	291, 303, 304
Schizophrenia spectrum disorder	F20-F25, F28, F29	295, 297, 298	295, 297, 298, 299
Suicidal behavior ^b	X60-X84, Y10-Y34, Y87.0, Y87.2	E950-E959, E980-E989	E950-E959, E980-E989

—, not applicable.

^a 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 of substance use disorder and bipolar disorder, and 5 years of age for attention-deficit/hyperactivity disorder, anxiety disorder, and depressive disorder.

^b Secondary ICD-10 suicidal behavior outcomes were: overdose outcomes (X60-X65, Y10-Y15), outcomes excluding overdose and other self-poisoning (X60-X69, Y10-Y19), and outcomes excluding injuries of undetermined intent (Y10-Y34, Y87.2).

SUPPLEMENTAL TABLE 6 Distribution of Covariates for Active Comparator Design

Variable	Opioid Initiators	NSAID Initiators
Overall		
Included, <i>n</i> (%)	86 635 (100)	255 096 (100)
Subsequent suicidal behavior, <i>n</i> (%)	1146 (1.3)	3128 (1.2)
Follow-up duration, y, median (IQR)	2.3 (1.0–4.1)	2.9 (1.3–4.8)
Demographics, <i>n</i> (%)		
Female	41 567 (48.0)	142 250 (55.8)
County of residence at start of eligibility		
Skåne	11 896 (13.7)	28 470 (11.2)
Stockholm	20 475 (23.6)	45 327 (17.8)
Västra Götaland	11 600 (13.4)	49 646 (19.5)
Other counties	42 664 (49.2)	131 653 (51.6)
Age at initiation, y, median (IQR)	20.2 (17.1–23.0)	19.3 (16.3–22.5)
Psychiatric diagnoses, <i>n</i> (%)		
Attention-deficit/hyperactivity disorder	2068 (2.4)	4873 (1.9)
Anxiety disorder	3696 (4.3)	8872 (3.5)
Bipolar disorder	256 (0.3)	566 (0.2)
Depressive disorder	2651 (3.1)	6474 (2.5)
Schizophrenia spectrum disorder	187 (0.2)	399 (0.2)
Substance use disorder	3345 (3.9)	6001 (2.4)
Psychoactive pharmacotherapies, <i>n</i> (%)		
Antidepressant, other	1770 (2.0)	3649 (1.4)
Antidepressant, SSRI	5588 (6.5)	13 130 (5.1)
Antidepressant, cyclic	363 (0.4)	721 (0.3)
Antiepileptic/mood stabilizer	1236 (1.4)	2669 (1.0)
Antipsychotic	934 (1.1)	2048 (0.8)
Anxiolytic	4352 (5.0)	10 347 (4.1)
Attention-deficit/hyperactivity disorder medication	1944 (2.2)	4552 (1.8)
Benzodiazepine	2187 (2.5)	3982 (1.6)
Duloxetine	216 (0.2)	453 (0.2)
Gabapentin/pregabalin	330 (0.4)	599 (0.2)
Migraine medication	1233 (1.4)	3886 (1.5)
Paracetamol	3518 (4.1)	8287 (3.2)
Z-hypnotic	2579 (3.0)	5041 (2.0)
Other sedative/hypnotic	2783 (3.2)	5972 (2.3)
Maternal pregnancy-related factors, <i>n</i> (%)		
Birth order		
First	35 409 (40.9)	104 021 (40.8)
Second	31 546 (36.4)	92 711 (36.4)
Third	13 688 (15.8)	41 051 (16.1)
Fourth or higher	5992 (6.9)	17 313 (6.8)
Maternal smoking during pregnancy		
None	62 950 (72.7)	191 115 (74.9)
Moderate	14 474 (16.7)	39 700 (15.6)
High	9211 (10.6)	24 281 (9.5)
Year of birth, median (IQR)	1990 (1987–1993)	1990 (1987–1994)
Maternal characteristics, <i>n</i> (%)		
Nordic country of origin	79 996 (92.3)	232 978 (91.3)
Age at childbirth, y		
Less than 20	1745 (2.0)	4594 (1.8)
20–29	50 355 (58.1)	146 984 (57.6)
30–39	32 619 (37.7)	97 632 (38.3)
At least 40	1916 (2.2)	5886 (2.3)
Highest level of education		
Less than 9 y	1589 (1.8)	5079 (2.0)
9 y	8950 (10.3)	24 812 (9.7)
Any upper secondary	45 709 (52.8)	136 788 (53.6)
Less than 2 y postsecondary	3428 (4.0)	10 427 (4.1)
At least 2 y postsecondary	26 439 (30.5)	76 599 (30.0)
Postgraduate	511 (0.6)	1391 (0.5)
Opioid receipt, 1.5 y before initiation	13 850 (16.0)	37 406 (14.7)

SUPPLEMENTAL TABLE 6 Continued

Variable	Opioid Initiators	NSAID Initiators
Psychiatric hospitalization		
Bipolar disorder	424 (0.5)	1098 (0.4)
Schizophrenia spectrum disorder	656 (0.8)	1817 (0.7)
Substance use disorder	2278 (2.6)	5451 (2.1)
Suicidal behavior	3072 (3.5)	7922 (3.1)
Anxiety disorder	3068 (3.5)	7981 (3.1)
Depressive disorder	2531 (2.9)	6830 (2.7)
Substance-related crime conviction	1935 (2.2)	4644 (1.8)
Violent crime conviction	1299 (1.5)	3207 (1.3)
Paternal characteristics, <i>n</i> (%)		
Nordic country of origin	78 676 (90.8)	229 801 (90.1)
Age at childbirth, y		
Less than 20	385 (0.4)	1047 (0.4)
20–29	35 601 (41.1)	102 215 (40.1)
30–39	42 588 (49.2)	126 965 (49.8)
40–49	7444 (8.6)	22 960 (9.0)
At least 50	617 (0.7)	1909 (0.7)
Highest level of education		
Less than 9 y	3301 (3.8)	10 054 (3.9)
9 y	13 946 (16.1)	39 704 (15.6)
Any upper secondary	46 295 (53.4)	137 599 (53.9)
Less than 2 y postsecondary	6221 (7.2)	19 097 (7.5)
At least 2 y postsecondary	15 816 (18.3)	45 623 (17.9)
Postgraduate	1056 (1.2)	3019 (1.2)
Opioid receipt, 1.5 y before initiation	10 988 (12.7)	29 836 (11.7)
Psychiatric hospitalization		
Bipolar disorder	280 (0.3)	807 (0.3)
Schizophrenia spectrum disorder	570 (0.7)	1608 (0.6)
Substance use disorder	4286 (4.9)	10 660 (4.2)
Suicidal behavior	2467 (2.8)	6552 (2.6)
Anxiety disorder	2212 (2.6)	6155 (2.4)
Depressive disorder	1903 (2.2)	5194 (2.0)
Substance-related crime conviction	11 640 (13.4)	29 893 (11.7)
Violent crime conviction	9668 (11.2)	25 276 (9.9)
Other socioeconomic factors, <i>n</i> (%)		
Parents not cohabitating at birth	4692 (5.4)	12 824 (5.0)
Family income in childhood		
Lowest income decile	9028 (10.4)	24 903 (9.8)
Decile 2	8706 (10.0)	25 373 (9.9)
Decile 3	8743 (10.1)	25 332 (9.9)
Decile 4	8438 (9.7)	25 845 (10.1)
Decile 5	8332 (9.6)	25 985 (10.2)
Decile 6	8314 (9.6)	25 938 (10.2)
Decile 7	8372 (9.7)	25 851 (10.1)
Decile 8	8640 (10.0)	25 654 (10.1)
Decile 9	8748 (10.1)	25 474 (10.0)
Highest income decile	9314 (10.8)	24 741 (9.7)
Neighborhood deprivation in childhood		
Least deprived decile	9401 (10.9)	24 664 (9.7)
Decile 2	8754 (10.1)	25 343 (9.9)
Decile 3	8382 (9.7)	25 818 (10.1)
Decile 4	8636 (10.0)	25 639 (10.1)
Decile 5	8451 (9.8)	25 743 (10.1)
Decile 6	8648 (10.0)	25 630 (10.0)
Decile 7	8566 (9.9)	25 680 (10.1)
Decile 8	8548 (9.9)	25 727 (10.1)
Decile 9	8630 (10.0)	25 452 (10.0)
Most deprived decile	8619 (9.9)	25 400 (10.0)

Unless otherwise noted, all variables assessed prior to date of initiation. Age and year of birth were centered at 9 years of age and year 2007, respectively, and modeled with linear and quadratic terms.

SUPPLEMENTAL TABLE 7 Opioid Prescriptions Dispensed to Birth Cohort (*N* = 201 433 Initiators) at Initiation

Opioid Drug	Anatomical Therapeutic Chemical Code	<i>n</i>	%
Buprenorphine	N02AE01	145	< 0.1
	N07BC01	15	< 0.1
With naloxone	N07BC51	14	< 0.1
Codeine combinations ^a	N02AA59	112 810	56.0
Paracetamol with codeine	N02BE51	2669	1.3
Dextropropoxyphene	N02AC04	8894	4.4
Fentanyl	N02AB03	37	<0.1
Hydromorphone	N02AA03	<10	<0.1
Ketobemidone	N02AB01	649	0.3
With antispasmodics	N02AG02	76	<0.1
Methadone	N07BC02	<10	<0.1
Morphine	N02AA01	3241	1.6
With antispasmodics	N02AG01	3804	1.9
Oxycodone	N02AA05	16 389	8.1
With naloxone	N02AA55	358	0.2
Tapentadol	N02AX06	<10	<0.1
Tramadol	N02AX02	49 998	24.8
>1 drug	—	2314	1.1
Total	—	201 433	100.0

Ns of size less than 10 masked. —, not applicable.

^a Acetylsalicylic acid, ibuprofen, or paracetamol.

SUPPLEMENTAL TABLE 8 Weighted Covariate Balance for Active Comparator Design

Variable	Opioid Initiators	NSAID Initiators
Overall		
Weighted <i>N</i> (%)	86 061.2 (100.0)	255 114.8 (100.0)
Subsequent suicidal behavior	1.3	1.2
Follow-up duration, y, median (IQR)	2.4 (1.0–4.3)	2.9 (1.3–4.8)
Demographics		
Female	53.1	53.8
County of residence at start of eligibility		
Skåne	11.9	11.8
Stockholm	19.3	19.2
Västra Götaland	17.3	17.9
Other counties	51.4	51.0
Age at initiation, y, median (IQR)	19.7 (16.6–22.7)	19.5 (16.5–22.6)
Psychiatric Diagnoses		
Attention-deficit/hyperactivity disorder	2.1	2.0
Anxiety disorder	3.8	3.7
Bipolar disorder	0.3	0.2
Depressive disorder	2.8	2.7
Schizophrenia spectrum disorder	0.2	0.2
Substance use disorder	2.9	2.7
Psychoactive Pharmacotherapies		
Antidepressant (other)	1.7	1.6
Antidepressant (SSRI)	5.6	5.5
Antidepressant (cyclic)	0.3	0.3
Antiepileptic/mood stabilizer	1.2	1.1
Antipsychotic	0.9	0.9
Anxiolytic	4.4	4.3
Attention-deficit/hyperactivity disorder medication	2.0	1.9
Benzodiazepine	1.9	1.8
Duloxetine	0.2	0.2
Gabapentin/pregabalin	0.3	0.3
Migraine medication	1.5	1.5
Paracetamol	3.5	3.5
Z-hypnotic	2.4	2.2
Other sedative/hypnotic	2.7	2.6
Maternal Pregnancy-Related Factors		
Birth order		
First	40.8	40.8
Second	36.4	36.4
Third	16.0	16.0
Fourth or higher	6.8	6.8
Maternal smoking during pregnancy		
None	74.2	74.3
Moderate	16.0	15.9
High	9.9	9.8
Year of birth, median (IQR)	1990 (1987–1993)	1990 (1987–1994)
Maternal Characteristics		
Nordic country of origin	91.8	91.6
Age at childbirth, y		
Less than 20	1.9	1.9
20–29	57.8	57.7
30–39	38.1	38.1
At least 40	2.3	2.3
Highest level of education		
Less than 9 y	1.9	2.0
9 y	9.9	9.9
Any upper secondary	53.3	53.4
Less than 2 y post-secondary	4.0	4.1
At least 2 y post-secondary	30.3	30.2
Postgraduate	0.6	0.6
Opioid receipt, 1.5 y before initiation	15.1	15.0

SUPPLEMENTAL TABLE 8 Continued

Variable	Opioid Initiators	NSAID Initiators
Psychiatric hospitalization		
Bipolar disorder	0.4	0.4
Schizophrenia spectrum disorder	0.7	0.7
Substance use disorder	2.3	2.3
Suicidal behavior	3.3	3.2
Anxiety disorder	3.3	3.2
Depressive disorder	2.8	2.7
Substance-related crime conviction	1.9	1.9
Violent crime conviction	1.3	1.3
Paternal Characteristics		
Nordic country of origin	90.5	90.3
Age at childbirth, y		
Less than 20	0.4	0.4
20–29	40.4	40.3
30–39	49.6	49.6
40–49	8.9	8.9
At least 50	0.7	0.7
Highest level of education		
Less than 9 y	3.9	3.9
9 y	15.7	15.7
Any upper secondary	53.8	53.8
Less than 2 y postsecondary	7.4	7.4
At least 2 y postsecondary	18.0	18.0
Postgraduate	1.2	1.2
Opioid receipt, 1.5 y before initiation	12.0	11.9
Psychiatric hospitalization		
Bipolar disorder	0.3	0.3
Schizophrenia spectrum disorder	0.6	0.6
Substance use disorder	4.4	4.4
Suicidal behavior	2.6	2.6
Anxiety disorder	2.5	2.5
Depressive disorder	2.1	2.1
Substance-related crime conviction	12.2	12.2
Violent crime conviction	10.3	10.2
Other Socioeconomic Factors		
Parents not cohabitating at birth	5.1	5.1
Family income in childhood		
Lowest income decile	10.0	9.9
Decile 2	9.9	10.0
Decile 3	10.0	10.0
Decile 4	10.0	10.0
Decile 5	10.0	10.0
Decile 6	10.0	10.0
Decile 7	10.0	10.0
Decile 8	10.1	10.0
Decile 9	10.0	10.0
Highest income decile	10.0	10.0
Neighborhood deprivation in childhood		
Least deprived decile	10.0	10.0
Decile 2	10.0	10.0
Decile 3	10.0	10.0
Decile 4	10.1	10.0
Decile 5	10.0	10.0
Decile 6	10.1	10.0
Decile 7	10.0	10.0
Decile 8	10.0	10.0
Decile 9	10.0	10.0
Most deprived decile	9.8	9.9

Values are percent (%) unless otherwise indicated. Unless otherwise noted, all variables assessed prior to date of initiation.

SUPPLEMENTAL TABLE 9 Results of Sensitivity Analyses

Model	<i>N</i> , Individuals	<i>N</i> With Outcome	Hazard Ratio (95% CI)
Adjusted model from main analysis	341 731	4274	1.19 (1.11–1.28)
Opioid drug, strength, and formulation			
Immediate-release, weak	329 633	4128	1.18 (1.10–1.27)
Extended-release or long-acting, strong	260 953	3193	1.25 (0.98–1.61)
Any, strong	265 333	3234	1.24 (1.02–1.52)
Excluding buprenorphine/methadone	341 671	4274	1.19 (1.11–1.28)
Age at initiation			
Youth and adolescents (age <19 y)	155 314	2419	1.16 (1.05–1.28)
Young adults (age 19 y or older)	186 417	1855	1.30 (1.18–1.44)
Active comparator specifications			
Covariates rather than weights	341 731	4274	1.22 (1.14–1.30)
Nontruncated, stabilized weights	341 731	4274	1.19 (1.10–1.27)
Nontruncated, non-stabilized weights	341 731	4274	1.18 (1.10–1.27)
Unadjusted models			
Complete case only	341 731	4274	1.25 (1.17–1.34)
Including those with missingness on covariates	383 488	4859	1.23 (1.16–1.31)
Dental initiation	18 603	180	1.56 (1.13–2.14)
Without cancer	339 846	4246	1.18 (1.10–1.27)
Depressive disorder outcome	332 606	8410	0.99 (0.94–1.04)

SUPPLEMENTAL TABLE 10 Descriptive Statistics for the Sibling Comparison Design

Variable	Opioid Initiators	Noninitiator Siblings
Included, <i>n</i>	97 366	132 586
Subsequent suicidal behavior, <i>n</i> (%)	1696 (1.7)	1117 (0.8)
Female, <i>n</i> (%)	51 641 (53.0)	62 681 (47.4)
Age at initiation, <i>y</i> , median (IQR)	19.96 (17.27–22.68)	19.14 (15.62–22.29)
Follow-up duration, <i>y</i> , median (IQR)	3.07 (1.55–4.82)	2.85 (1.36–4.61)

Initiation is date of first opioid prescription receipt or corresponding date for noninitiator siblings. For the sibling comparison design, families must vary on the suicidal behavior outcome to contribute to the stratified Cox regression (informative *N* = 6451 individuals in 2617 families). Within-family covariates were maternal and paternal age at childbearing, neighborhood deprivation, family income, parental cohabitation, maternal smoking during pregnancy, birth order, county of residence, sex, linear and quadratic age and year of birth, substance use disorder, schizophrenia, bipolar disorder, anxiety disorder, attention-deficit/hyperactivity disorder, depressive disorder, and psychoactive medications.