

Supplementary Material

Contents

eTable 1 Summary of Previous Systematic Reviews exploring Predictors of Opioid Overdose	4
eTable 2 Baseline characteristics of 28 eligible studies and 7 studies with overlapped population	6
eTable 3 Risk of bias assessment of 28 eligible studies and 7 studies with overlapped population	12
eTable 4 GRADE evidence profile of prevalence of fatal or non-fatal overdose	14
eTable 5 Dose-response relationship between opioid dose and fatal/nonfatal overdose	15
eTable 6 GRADE evidence profile of opioid prescribing factors associated with opioid overdose	16
eTable 7 GRADE evidence profile of co-prescription factors associated with opioid overdose	17
eTable 8 GRADE evidence profile of psychological factors associated with opioid overdose	18
eTable 9 GRADE evidence profile of medical factors associated with opioid overdose	19
eTable 10 GRADE evidence profile of socio-demographic factors associated with opioid overdose ..	22
eTable 11 Consistency of results of predictors between pooled and unpooled studies	24
eTable 12 Summary table of opioid tapering or discontinuation	26
eTable 13 Significant associations of six unpooled predictors with opioid overdose	30
eTable 14 Non-significant associations of 23 unpooled predictors with opioid overdose	32
eTable 15 Subgroup analyses of pre-defined factors for opioid overdose #	33
eTable 16 Sensitivity analyses to test robustness of results *,#	44
eFigure 1 Meta-analysis of the prevalence of opioid overdose	52
eFigure 1A Pooled prevalence of fatal overdose.....	52
eFigure 1B Pooled prevalence of non-fatal overdose.....	53
eFigure 2 Meta-analysis of the association of opioid prescribing factors	54
eFigure 2A Dose-response relationship between opioid dose and fatal/nonfatal overdose	54
eFigure 2B Predictor of opioid dose (every 50mg increment on a morphine equivalent dose)	55
eFigure 2C Predictor of opioid dispensing at multiple pharmacies: ≥ 3 vs. less	56
eFigure 2D Predictor of multiple opioid prescribers: ≥ 4 vs. less	56
eFigure 2E Predictor of fentanyl (including both transmucosal and transdermal fentanyl).....	57
eFigure 2F Predictor of long- vs. short-acting opioids	57
eFigure 2G Predictor of number of naloxone prescriptions	58
eFigure 3 Meta-analysis of the association of co-medication factors	59
eFigure 3A Predictor of use of benzodiazepines: current vs history	59
eFigure 3B Predictor of anticonvulsants	60
eFigure 3C Predictor of sedatives and hypnotics	60
eFigure 3D Predictor of muscle relaxants	61

eFigure 4 Meta-analysis of the association of psychological factors	62
eFigure 4A Predictor of depression or use of antidepressants: current vs history.....	62
eFigure 4B Predictor of bipolar disorder.....	63
eFigure 4C Predictor of psychotic disorders or use of antipsychotics: current vs history.....	64
eFigure 4D Predictor of tobacco use or use disorder: tobacco use vs. tobacco use disorder	65
eFigure 4E Predictor of anxiety.....	66
eFigure 5 Meta-analysis of the association of medical factors	67
eFigure 5A Predictor of previous overdose.....	67
eFigure 5B Predictor of pancreatitis.....	67
eFigure 6 Meta-analysis of the association of socio-demographic factors	68
eFigure 6A Predictor of age (every 10-year decrement)	68
eFigure 6B Predictor of sex (Male vs. Female).....	69
eFigure 6C Predictor of marital status: non-married vs. married	70
eFigure 6D Predictor of White race vs others	70
eFigure 6E Predictor of geographic region in United States	71
eFigure 6F Predictor of insurance	72
eFigure 7 Funnel plots with pseudo 95% confidence limits for opioid dose, current substance use disorder, age and sex	73
eFigure 7A Funnel plots for opioid dose, current substance use disorder, any mental health disorders and use of benzodiazepines	73
eFigure 7B Funnel plots for age, sex and race	74
Section 1 Search strategies	75
MEDLINE.....	75
EMBASE.....	76
PsycInfo.....	78
CINAHL.....	79
Web of Science.....	80
Section 2 Risk of bias assessment criteria	82
Section 3 Excluded studies	83
Excluded studies for conference abstracts: n=29	83
Excluded studies for non-observational studies: n=4.....	84
Excluded studies for unclear or non-chronic pain conditions: n=58.....	84
Excluded studies for unclear or non-prescriptions of opioids: n=38.....	87
Excluded studies without outcome of interest (fatal or non-fatal overdose): n=35.....	88
Excluded studies without adjusted analysis: n=18	90

Excluded studies with significant postbaseline factors: n=2	91
Excluded studies with patients exclusively having prior opioid overdose: n=2:.....	91
Section 4 Credibility assessment of subgroup effects for substance use disorder	92

eTable 1 Summary of Previous Systematic Reviews exploring Predictors of Opioid Overdose

Systematic review	No. of primary studies considered	Predictors of opioid overdose
Zullo AR, et al., 2020	3 studies	<p><u>Strong associations</u></p> <ul style="list-style-type: none"> • age (direction not reported) • disability status • opioid amount • substance misuse • long-term opioid use • opioid misuse • number of prescribers • number of pharmacies <p><u>Weak associations</u></p> <ul style="list-style-type: none"> • race (not defined), • comorbidities • mental health • low income • area-level percentage of unemployment • insurance status • opioid type (not defined) • nonpain treatments (antidepressants) • non-opioid substance misuse • benzodiazepine use
Van Draanen et al., 2020	37 studies	<ul style="list-style-type: none"> • criminal justice system involvement (11 of 13 studies*) • poverty (8 of 13 studies) • unemployment (2 of 11 studies) • low social support (6 of 9 studies) • health insurance status (6 of 8 studies) • homelessness and housing status (4 of 8 studies) • lower level of education (6 of 8 studies) • lower socioeconomic status (5 of 6 studies)
Adewumi et al., 2018	10 studies	<ul style="list-style-type: none"> • larger doses of opioids: <ul style="list-style-type: none"> (1) ≤ 20 versus ≥ 21 MME/day: RR 2.81, 95% CI 1.09-7.22 (2) ≤ 50 versus > 50 MME/day: RR 3.87, 95% CI 2.36-6.33 (3) ≤ 100 versus > 100 MME/day: RR 4.28, 95% CI 2.61-7.1 (4) ≤ 50 versus $> 50-100$ MME/day: RR 3.09, 95% CI 1.84-5.18
Elzey et al., 2016	24 studies	<ul style="list-style-type: none"> • higher dose of opioids • specific opioid medications (i.e., oxycodone, hydrocodone, methadone) • cocaine and heroin use • co-prescription with benzodiazepines • alcohol consumption • non-medical use of prescription opioids • history of prescription opioid overdose • a lifetime suicide attempt

Systematic review	No. of primary studies considered	Predictors of opioid overdose
		<ul style="list-style-type: none"> • middle age (40-49 years) • lack of a high school education • recent prescription for sedative-hypnotics • living in a rural area • poverty • bipolar disorder in women • depressive disorder
King et al., 2014	47 studies	<ul style="list-style-type: none"> • high-volume prescribing • opioid prescription or sales • opioid dosage • prescription of oxycodone • prescription of methadone • history of substance abuse • diversion • doctor or pharmacy shopping • drug substitution • polydrug toxicity (e.g., benzodiazepines and other sedatives---hypnotics, antidepressants, and sleep aids, alcohol, or illicit drugs) • sociodemographic characteristics (e.g., men, non-Hispanic Whites and American Indian/Alaska Natives, middle-aged individuals, those living in rural areas, and those of lower SES) • area urbanization or socioeconomic status • geography • guidelines, policies, and consensus statements supportive of opioids for chronic pain • interventions (i.e., co-prescription of naloxone, Prescription Pain Medication Program) • media coverage • prescription drug monitoring programs (1 of 2 studies)
van Draanen et al., 2021	38 studies	<ul style="list-style-type: none"> • mood disorders • anxiety disorders • thought disorders (e.g., schizophrenia, bipolar disorder) • any mental disorder

* The number of studies supporting the association (e.g., 11 of 13 studies exploring criminal system involvement found a positive association with opioid overdose)

eTable 2 Baseline characteristics of 28 eligible studies and 7 studies with overlapped population

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
28 eligible studies for primary analysis									
Hartung, 2007	Cohort study	USA	5684	52.5 \pm 16	1354 (23.8%)	Mixed CNCP and cancer	NR	SUD 186 (3.3%)	NR
Dunn, 2010	Cohort study	USA	9940	54 \pm 16.8	5924 (59.6%)	CNCP	NR	SUD 616 (6.2%)	Depression diagnosis 2674 (26.9%)
Bohnert, 2011 #†	Case-control study	USA	155434	\geq 18	10430 (6.7%)	Mixed CNCP and cancer	NR	SUD 15491 (10%)	Psychiatric disorder 52427 (33.7%)
Gwira Baublatt, 2014	Case-control study	USA	12432	43 \pm 12.3	NR	CNCP	NR	NR	NR
Zedler, 2014	Case-control study	USA	8987	62 \pm 11.5	706 (7.9%)	Mixed CNCP and cancer (12% acute pain)	1578 (17.6%)	SUD 1181 (13.1%); TUD 1567 (17.4%)	PTSD 1340 (14.9%); Anxiety disorder 861 (9.6%); Bipolar disorder 325 (3.6%); Schizophrenia 150 (1.7%); ADHD 65 (0.7%); OCD 24 (0.3%)
Kaplovich, 2015	Cohort study	Canada	32449	45 \pm 8.2	18809 (58%)	CNCP	8365 (25.8%)	AUD 3505 (10.8%)	SSRIs/SNRIs 7123 (22.0%); other antidepressants 4656 (14.3%)
Miller, 2015	Cohort study	USA	820616	60 \pm 14.8	52177 (6.5%)	CNCP	98814 (12%)	AUD 69241 (8.6%); Drug-related disorders 42210 (5.1%)	Depression 174049 (21.2%)
Ray, 2015	Cohort study	USA	38756	48 \pm 3	22434 (57.9%)	CNCP (1.5% acute pain)	24619 (63.5%)	AUD 764 (1.97%); Drug abuse was excluded	Heterocyclic antidepressant 10184 (26.3%); SSRI or other antidepressant 24865 (64.2%);

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
									Antipsychotic 6328 (16.3%)
Turner, 2015	Cohort study	USA	206869	44.1 \pm 12	117472 (56.8%)	CNCP	40802 (19.7%)	Alcohol abuse 4637 (2.2%); Other substance abuse 4420 (2.1%)	Anxiety or posttraumatic stress disorder 30887 (14.9); Depression 26,223 (12.7); Psychosis 5,603 (2.7)
Garg, 2017	Cohort study	USA	150821	18 to 64	102134 (67.7%)	CNCP	38069 (25.2%)	OD 6354 (4.3%)	NR
Carey, 2018	Cohort study	USA	627391	\geq 18	NR	CNCP (including acute pain) [¶]	NR	NR	NR
Chung, 2018	Cohort study	USA	50658	48.3 \pm 10.1	30094 (59.4%)	CNCP (2.6% acute pain)	19939 (39.4%)	Patients with SUD were excluded	SSRI or other antidepressant 16168 (31.9%)
Glanz, 2018 [†]	Cohort study	USA	53536	53.6 \pm 17.0	30815 (57.6%)	CNCP (16.8% no chronic pain)	NR	SUD 2711 (6.3%); TUD 9937 (23.2%)	Mental health disorder 17778 (33.2%); Psychotropic prescription 27357 (51.1%)
Gomes, 2018 [#]	Case-control study	Canada	6514	48.78 \pm 8.89	2892 (44.4%)	CNCP (including acute pain) [¶]	3808 (58.5%)	AUD 1376 (21.1%);	SSRIs 2370 (36.4%), other antidepressants 2681 (41.2%), other psychotropic drugs/CNS depressants 1714 (26.3%)
Nadpara, 2018	Case-control study	USA	27179	51 \pm 14.8	20910 (57.8%)	Mixed CNCP and cancer	10098 (27.9%)	SUD 3672 (10.2%); TUD 4539 (12.6%)	Anxiety 6153 (17%); Depression 6007 (16.6%); Bipolar disorder 1298 (3.6%); ADHD 814 (2.3%); PTSD 426 (1.2%); Schizophrenia 132 (0.4%); OCD 138 (0.4%)

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
Bedson, 2019	Cohort study	UK	98140	61 \pm 19.3	57937 (59%)	CNCP	NR	NR	Depression consultation 6615 (6.7%)
Glanz, 2019	Case-control study	USA	14898	56.3 \pm 16	8988 (60.3%)	CNCP	5468 (36.7%)	Drug or alcohol use disorder 4816 (32.3%)	Mental health disorder 10885 (73.1%)
James, 2019	Cohort study	USA	572	54.9 \pm 10.1	261 (45.6%)	Mixed CNCP and cancer	7 (1.2%)	AUD 110 (19.2%); History of other SUD 197 (34.4%)	Mental health disorders 420 (73.4%)
Young, 2019	Cohort study	USA	372038	53.5 \pm 13.8	200770 (54%)	Mixed CNCP and cancer (13% no chronic pain)	158282 (43%)	Drug dependence 55420 (15%); Alcohol 7511 (2%); Tobacco 50359 (14%)	Depression 83087 (22%)
El-Akkad, 2020	Cohort study	Canada	9272	38 \pm 10.4	1676 (18.1%)	CNCP	283 (3.1%)	SUD 1365 (14.7%)	NR
Fonda, 2020	Cohort study	USA	49014	29.6 \pm 4.93	7741 (15.8%)	CNCP	NR	SUD 4064 (8.3%); Alcohol (6.16%); other (4.15%)	Depression 10208 (20.82%); PTSD (28.44%); Anxiety (11.72%)
Li, 2020	Cohort study	USA	19678250	40.1 \pm 13.38	10690039 (54.3%)	CNCP	2345456 (11.9%)	SUD was excluded	Depression 1168964 (5.9%); Anxiety or PTSD 1007276 (5.1%); Bipolar disorder 203460 (1%); Schizophrenia 28587 (0.1%)
Qeadan, 2021 †	Cohort study	USA	869097	51.95 \pm 18.31	510331 (58.7%)	CNCP	NR	SUD excluding OUD 51819 (5.96%); OUD 19268 (2.22%)	Mental health disorder 270961 (31.18%)
Salkar, 2021	Case-control study	USA	266	76.27 \pm 7.55	95 (71.4%)	CNCP	55 (20.7%)	SUD 6 (2.3%); Hypnotic medication	Mental health disorder 151 (56.8%)

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
								dependence 7 (2.6%)	
DiPrete, 2022	Cohort study	USA	19443	49 \pm 10.4	13980 (71.9%)	Mixed CNCP and cancer pain (10.9% acute pain)	7873 (40.5%)	SUD 1782 (9.2%)	Depression 6399 (32.9%), Anxiety 6427 (33.1%), PTSD 420 (2.2%)
Hayes, 2022a #	Cohort study	USA	405631	57.3 \pm 14.4	32931 (8.1)	CNCP	71325 (17.58%)	Any SUD 53717 (13.24%): including OUD 4016 (0.99%), DUD 24888 (6.14%), AUD 40001 (9.86%), TUD 49256 (12.14%),	Any Mental health conditions 223884 (55.2%): including Anxiety 14361 (3.54%), Bipolar disorder 2625 (0.65%), Major depressive disorder 34312 (8.46%), PTSD 18113 (4.47%), Schizophrenia 1632 (0.40%), Multiple mental health conditions 103585 (25.54%)
Larochelle, 2022 #	Cohort study	USA	199836	56.9 \pm 12.4	109659 (54.9)	CNCP	69470 (34.8%)	OD (medication for OD, opioid overdose, detoxification) was excluded	Depression 39280 (19.7%); Anxiety 36052 (18.0%); ADHD 3590 (1.8%); PTSD 3126 (1.6%); Bipolar disorder 4218 (2.1%); Psychosis 2057 (1.0%)
Lo-Ciganic, 2022	Cohort study	USA	37879	59.3% \geq 65yr	27235 (71.9)	CNCP	12311 (32.5%)	Opioid use disorder 379 (1%), DUD 568 (1.5%), AUD 492 (1.3%);	Anxiety 7159 (18.9%), Mood disorders 6970 (18.4%), Sleep disorders 18864 (33.9%)
7 studies with overlapped population									

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
Gomes, 2011 [#]	Case-control study	Canada	2212	44.67 \pm 8.21	1287 (58.2)	CNCP	531 (24%)	History of AUD 592 (26.8%)	SSRIs 910 (41.1%); other antidepressants 926 (41.9%)
Ilgen, 2016 [#]	Case-control study	USA	123946	\geq 18	8994 (7.3)	Mixed CNCP and cancer	NR	SUD 12765 (10.3%)	Depression; bipolar; mood NOS 33852 (27.3%); Other anxiety 11505 (9.3%); PTSD 15721 (12.7%); Psychotic disorders 4588 (3.7%)
Gomes, 2017 [#]	Case-control study	Canada	5875	47.74 \pm 9.92	2540 (43.2)	CNCP (including acute pain) [†]	3575 (60.9%)	History of AUD 1401 (23.8%);	Anxiety/sleep disorders 4806 (81.8%); Affective disorder 1158 (19.7%), psychoses 752 (12.8%); Other mental health diagnosis 4193 (71.4%)
Hayes, 2020 [#]	Cohort study	USA	53187	57.18 \pm 12.98	5130 (9.6%)	CNCP	38087 (71.6%)	SUD 4633 (8.7%); including OUD 903 (1.7%), DUD 2544 (4.8%), AUD 2495 (4.7%)	Any Mental Health Conditions 27614 (51.9%)
Agnoli, 2021 [#]	Cohort study	USA	113618	58.1	60772 (53.5%)	CNCP (including acute pain) [†]	31821 (28%)	Drug use disorder 16356 (14.4%); AUD 2807 (2.5%)	Depression/anxiety 60605 (53.3%)
Hayes, 2021 [#]	Cohort study	USA	151462	56.38 \pm 13.36	13046 (8.6%)	CNCP	38148 (25.2%)	SUD 10522 (7.8%); including OUD 1983 (1.4%), DUD 5755 (4.2%), AUD 5768 (4.3%)	Any Mental Health Condition 79796 (52.7%)

Study	Study design	Country	Sample size	Age, mean \pm SD*	Female n(%)	Chronic pain conditions	Benzo-diazepine co-prescription n(%)	Substance use disorder n(%)	Mental health disorder n(%)
Hayes, 2022b [#]	Cohort study	USA	99111	58.07 \pm 13.35	10156 (10.2%)	CNCP	26535 (26.8%)	SUD 8090 (8.2%); including OUD 1403 (1.4%), DUD 4449 (4.5%), AUD 4489 (4.5%)	Any Mental Health Condition 51104 (51.6%)

ADHD: attention deficit hyperactivity disorder, AUD: alcohol use disorder, CNCP: chronic noncancer pain, DUD: Non-Opioid Drug Use Disorder, NR: not reported, OCD: Obsessive-compulsive disorder, OUD: opioid use disorder, PTSD: Post-traumatic stress disorder, SD: standard deviation, SNRIs: serotonin and norepinephrine reuptake inhibitors, SSRIs: selective serotonin reuptake inhibitors, SUD: substance use disorder, TUD: tobacco use disorder, UK: United Kingdom, USA: United States of America

*If age was reported as median and interquartile range or range, mean and SD of age were estimated.

[¶] Patients with acute pain were included; however, the proportion was not reported.

[#] Studies with \geq 50% overlapped study populations, the largest studies with longest follow-up were chosen as primary analysis

- Bohnert 2011 reported unintentional opioid overdose as primary analysis; Ilgen 2016 reported intentional opioid overdose for subgroup analysis of intentional vs unintentional overdose only
- Gomes 2011, 2017 and 2018: Gomes 2018 with largest sample size for primary analysis
- Larochelle 2022 and Agnoli 2021: Larochelle 2022 with largest sample size for primary analysis
- Hayes, 2020, 2021, 2022 a and b: Hayes 2022 a with largest sample size for primary analysis

[†] Studies reported regression models among two subpopulations in the same article

- Bohnert 2011: chronic cancer-related pain and chronic non-cancer pain
- Glanz 2018: two data sets: derivation and validation sets
- Qeadan 2021: chronic pain syndrome or low back pain

eTable 3 Risk of bias assessment of 28 eligible studies and 7 studies with overlapped population

Study	Representativeness of study population	Overdose type	Intentional or unintentional overdose	Valid outcome measure	Model appropriately adjusted	Proportion of loss to follow-up (%)	Model variables selected before the analysis	All variables reported in the final model	Industry-funded
28 eligible studies for primary analysis									
Hartung, 2007	Yes	Non-fatal	Mixed	No	No	NR	No	No	NR
Dunn, 2010	Yes	Mixed	Mixed	No	Yes	NR	Yes	Yes	No
Bohnert, 2011 # †	No, Veterans	Fatal	Unintentional	Yes	Yes	NR	Yes	Yes	No
Gwira Baumblatt, 2014	Yes	Fatal	Unintentional	Yes	No	NR	Yes	Yes	NR
Zedler, 2014	No, Veterans	Non-fatal	Unintentional	No	Yes	0.2	Yes	Yes	Yes
Kaplovich, 2015	Yes	Fatal	Mixed	Yes	Yes	NR	No	No	Yes
Miller, 2015	No, Veterans	Non-fatal	Unintentional	No	Yes	2.4	Yes	No	No
Ray, 2015	No, Mental illness>60%	Fatal	Mixed	No	Yes	NR	Yes	NA	No
Turner, 2015	Yes	Non-fatal	Mixed	No	Yes	NR	Yes	Yes	No
Garg, 2017	Yes	Fatal	Unintentional	Yes	No	NR	Yes	Yes	No
Carey, 2018	No, Disabled>50%	Non-fatal	Mixed	Yes	No	NR	Yes	Yes	No
Chung, 2018	Yes	Fatal	Unintentional	Yes	Yes	NR	Yes	No	No
Glanz, 2018 †	Yes	Mixed	Mixed	No	Yes	NR	No	No	No
Gomes, 2018 #	Yes	Fatal	Unintentional	Yes	No	NR	Yes	Yes	No
Nadpara, 2018	Yes	Non-fatal	Unintentional	Yes	Yes	NR	Yes	Yes	Yes
Bedson, 2019	Yes	Non-fatal	Intentional	Yes	No	NR	Yes	Yes	No
Glanz, 2019	No, Mental illness>70%	Mixed	Unintentional	No	Yes	NR	Yes	Yes	No
James, 2019	No, Mental illness>60%	Fatal	Mixed	No	No	NR	Yes	No	No
Young, 2019	No, High-dose opioid (≥90 mg/daily)	Non-fatal	Unintentional	No	Yes	NR	Yes	Yes	Yes
El-Akkad, 2020	Yes	Fatal	Mixed	No	No	14	Yes	Yes	No
Fonda, 2020	No, Veterans	Non-fatal	Mixed	Yes	No	NR	Yes	Yes	No
Li, 2020	Yes	Non-fatal	Unintentional	No	Yes	NR	Yes	Yes	No
Qeadan, 2021 †	Yes	Non-fatal	Unintentional	No	Yes	NR	Yes	Yes	No
Salkar, 2021	No, Elderly(≥65yr)	Mixed	Mixed	Yes	No	NR	Yes	Yes	No

Study	Representativeness of study population	Overdose type	Intentional or unintentional overdose	Valid outcome measure	Model appropriately adjusted	Proportion of loss to follow-up (%)	Model variables selected before the analysis	All variables reported in the final model	Industry-funded
DiPrete, 2022	No, High-dose opioid (≥ 90 mg/daily)	Mixed	Unintentional	No	Yes	NR	Yes	Yes	No
Hayes, 2022a #	No, Veterans	Non-fatal	Unintentional	No	No	NR	Yes	Yes	No
Larochelle, 2022 #	No, High-dose opioid (≥ 50 mg/daily)	Mixed	Mixed	No	Yes	NR	Yes	Yes	No
Hartung, 2007	Yes	Non-fatal	Mixed	No	Yes	NR	Yes	Yes	No
7 studies with overlapped population									
Gomes, 2011 #	Yes	Fatal	Mixed	Yes	No	NR	Yes	Yes	Yes
Ilgen, 2016 #	No, Veterans	Fatal	Intentional	Yes	Yes	NR	Yes	No	No
Gomes, 2017 #	No, Mental illness >80%	Fatal	Unintentional	Yes	No	NR	Yes	Yes	No
Hayes, 2020 #	No, Veterans	Non-fatal	Unintentional	No	No	NR	Yes	Yes	No
Agnoli, 2021 #	No, High-dose opioid (≥ 50 mg/daily)	Mixed	Unintentional	No	Yes	NR	Yes	Yes	No
Hayes, 2021 #	No, Veterans	Non-fatal	Unintentional	No	No	NR	Yes	Yes	No
Hayes, 2022b #	No, Veterans	Non-fatal	Unintentional	No	No	NR	Yes	Yes	No

NR: not reported, NA: not applicable (due to use of propensity score matching)

Studies with $\geq 50\%$ overlapped study populations, the largest studies with longest follow-up were chosen as primary analysis

- Bohnert 2011 reported unintentional opioid overdose as primary analysis; Ilgen 2016 reported intentional opioid overdose for subgroup analysis of intentional vs unintentional overdose only
- Gomes 2011, 2017 and 2018: Gomes 2018 with largest sample size for primary analysis
- Larochelle 2022 and Agnoli 2021: Larochelle 2022 with largest sample size for primary analysis
- Hayes, 2020, 2021, 2022 a and b: Hayes 2022 a with largest sample size for primary analysis

† Studies reported regression models among two subpopulations in the same article

- Bohnert 2011: chronic cancer-related pain and chronic non-cancer pain
- Glanz 2018: two data sets: derivation and validation sets
- Qeadan 2021: chronic pain syndrome or low back pain

eTable 4 GRADE evidence profile of prevalence of fatal or non-fatal overdose

Outcomes	Study characteristics		Quality assessment					Summary of Findings	Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	prevalence of overdose (95% CI), per 1000	
Fatal overdose	10	1,199,105	No [†]	No Tau ² <0.01	No	Yes [‡]	Undetected	1.3 (0.6 to 2.3)	Moderate
Non-fatal overdose	17	23,094,194	No [†]	No Tau ² <0.01	No	Yes [‡]	Undetected	3.2 (2.0 to 4.7)	Moderate

95% CI: 95% confidence interval

[†] We did not rate down for risk of bias as subgroup analysis showed no significant difference in low vs. high risk of bias on a component-by-component basis (subgroup analysis results are available upon request).

[‡] We rated down for imprecision as the 95%CI included the thresholds of 2‰ for fatal overdose and 4‰ for non-fatal overdose

eTable 5 Dose-response relationship between opioid dose and fatal/nonfatal overdose

Dose (mg on MED)	Adjusted OR (95%CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000
10	1.11 (1.08-1.14)	1.1 (1.1-1.1)	2.2 (2.2-2.3)
50	1.70 (1.48-1.96)	1.7 (1.5-2)	3.4 (3-3.9)
90	2.56 (1.94-3.38)	2.6 (1.9-3.4)	5.1 (3.9-6.8)
100	2.84 (2.08-3.87)	2.8 (2.1-3.9)	5.7 (4.2-7.7)
150	4.95 (3.26-7.51)	5 (3.3-7.5)	9.9 (6.5-15)
200	8.06 (4.34-14.99)	8.1 (4.3-15)	16.1 (8.7-30)
250	14.36 (7.16-28.82)	14.4 (7.2-28.8)	28.7 (14.3-57.6)

MED: morphine equivalent dose, OR: odds ratio, 95%CI: 95% confidence interval

* We estimated the absolute risk of fatal or non-fatal overdose for each dose using a baseline risk of 1% for fatal overdose or 2% for non-fatal overdose and the adjusted OR

eTable 6 GRADE evidence profile of opioid prescribing factors associated with opioid overdose

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Dose (50-mg increment)	14	1,315,173	No [†]	No	No	No	Undetected Egger's p=0.23	1.69 (1.50 to 1.90)	1.7 (1.5 to 1.9)	3.4 (3 to 3.8)	High
Long- vs. short- acting opioids	9	978,745	No [†]	No	No	Yes [‡]	NA	1.92 (1.51 to 2.45)	1.9 (1.5 to 2.5)	3.8 (3 to 4.9)	Moderate
Number of naloxone prescriptions (per each prescription increase)	2	869,097	Yes [#]	No	No	No	NA	1.81 (1.71 to 1.93)	1.8 (1.7 to 1.9)	3.6 (3.4 to 3.9)	Moderate
As needed + regularly scheduled vs. regularly scheduled	2	148,562	No	No	Yes [§]	No	NA	1.29 (1.07 to 1.55)	1.3 (1.1 to 1.6)	2.6 (2.1 to 3.1)	Moderate
Duration of opioid use (every 90-day increment from day 1)	2	153,033	Yes [#]	No	No	No	NA	1.01 (1.003 to 1.03)	1 (1 to 1)	2 (2 to 2.1)	Moderate
Route of administration: oral vs. non-oral (parenteral or transdermal)	2	45,153	No	No	No	No	NA	1.13 (0.88 to 1.46)	1.1 (0.9 to 1.5)	2.3 (1.8 to 2.9)	High
Long-acting methadone vs. long-acting morphine	2	30,727	Yes [#]	No	No	Yes [‡]	NA	2.25 (1.52 to 3.31)	2.3 (1.5 to 3.3)	4.5 (3 to 6.6)	Low

OR: odds ratio, 95%CI: 95% confidence interval, NA: not applicable

* We estimated the absolute risk of fatal or non-fatal overdose for each predictor using a baseline risk of 1‰ for fatal overdose or 2‰ for non-fatal overdose and the adjusted OR

[†] We did not rate down for risk of bias as subgroup analysis showed no significant difference in studies at low vs. high risk of bias on a component-by-component basis.

[§] We rated down for indirectness as the evidence was drawn indirectly from high-risk population (e.g., veterans, ≥60% study population with mental disorders, or use of high dose opioids)

[#] We rated down for risk of bias because of at least 20% of the total weight from studies with high-risk of bias.

[‡] We rated down for imprecision because the lower and upper limits of 95%CI associated with the adjusted OR included both large and small associations with opioid overdose (95%CI of adjusted OR included the threshold of large association of OR=2 or OR=0.5).

eTable 7 GRADE evidence profile of co-prescription factors associated with opioid overdose

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Co-prescription of benzodiazepines	12	1,246,864	No [†]	No	No	Yes [‡]	Undetected; Egger's p=0.72	1.79 (1.46 to 2.19)	1.8 (1.5 to 2.2)	3.6 (2.9 to 4.4)	Moderate
Co-prescription of anticonvulsants	3	12,655	Yes [#]	No	No	No	NA	1.56 (1.30 to 1.88)	1.6 (1.3 to 1.9)	3.1 (2.6 to 3.8)	Moderate
Co-prescription of sedatives and hypnotics	6	337,924	No [†]	No	No	No	NA	1.37 (1.2 to 1.56)	1.4 (1.2 to 1.6)	2.7 (2.4 to 3.1)	High
Co-prescription of muscle relaxants	5	19,776,855	No [†]	No	No	No	NA	1.28 (1.10 to 1.50)	1.3 (1.1 to 1.5)	2.6 (2.2 to 3)	High
Co-prescription of stimulants	2	45,153	No	No	No	No [*]	NA	1.06 (0.9 to 1.26)	1.1 (0.9 to 1.3)	2.1 (1.8 to 2.5)	High
Use of non-opioid analgesics	3	98,340	Yes [#]	Yes [¶]	No	No [*]	NA	0.79 (0.58 to 1.09)	0.8 (0.6 to 1.1)	1.6 (1.2 to 2.2)	Low
Co-prescription of NSAIDs	3	104,920	Yes [#]	Yes [¶]	No	No [*]	NA	0.94 (0.78 to 1.14)	0.9 (0.9 to 1.1)	1.9 (1.6 to 2.3)	Low
Co-prescription of warfarin	2	45,153	Yes [#]	Yes [¶]	No	No [*]	NA	0.96 (0.81 to 1.13)	1 (0.8 to 1.1)	1.9 (1.6 to 2.3)	Low
Number of drugs	3	132,801	Yes [#]	No	No	No [*]	NA	0.99 (0.94 to 1.04)	1 (0.9 to 1)	2 (1.9 to 2.1)	Moderate

OR: odds ratio, 95%CI: 95% confidence interval, NA: not applicable

* We estimated the absolute risk of fatal or non-fatal overdose for each predictor using a baseline risk of 1‰ for fatal overdose or 2‰ for non-fatal overdose and the adjusted OR

We rated down for risk of bias because of at least 20% of the total weight from studies with high-risk of bias.

† We did not rate down for risk of bias as subgroup analysis showed no significant difference in studies at low vs. high risk of bias on a component-by-component basis.

‡ We rated down for imprecision because the lower and upper limits of 95%CI associated with the adjusted OR included both large and small associations with opioid overdose (95%CI of adjusted OR included the threshold of large association of OR=2 or OR=0.5).

¶ Although the estimate of precision included no significant association, we did not rate down for imprecision because the 95%CI did not include important association (i.e., OR ≥2.0 or ≤0.5).

¶ We rated down for inconsistency because of large heterogeneity across studies.

eTable 8 GRADE evidence profile of psychological factors associated with opioid overdose

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Psychotic disorders or use of antipsychotics	6	410,629	No †	No	No	Yes ‡	NA	1.59 (1.16 to 2.19)	1.6 (1.2 to 2.2)	3.2 (2.3 to 4.4)	Moderate
Tobacco use or use disorder (including smoking & tobacco use disorder)	7	210,544	No †	No	No	No	NA	1.57 (1.37 to 1.81)	1.6 (1.4 to 1.8)	3.1 (2.7 to 3.6)	High
History of substance use disorder	4	46,628	No †	No	No	Yes ‡	NA	1.47 (1.03 to 2.09)	1.5 (1 to 2.1)	2.9 (2.1 to 4.2)	Moderate
Anxiety	5	271,300	No †	No	Yes §	No	NA	1.28 (1.02 to 1.61)	1.3 (1 to 1.6)	2.6 (2 to 3.2)	Moderate
Attention-deficit/hyperactivity disorder (ADHD)	2	45,153	No	Yes ¶	No	No **	NA	0.88 (0.69 to 1.13)	0.9 (0.7 to 1.1)	1.8 (1.4 to 2.3)	Moderate
Obsessive-Compulsive Disorder (OCD)	2	45,153	No	No	No	No **	NA	0.76 (0.49 to 1.2)	0.8 (0.5 to 1.2)	1.5 (1 to 2.4)	High
Schizophrenia	3	98,340	No	No	Yes §	Yes ‡	NA	1.78 (1.2 to 2.65)	1.8 (1.2 to 2.7)	3.6 (2.4 to 5.3)	Low
Post-traumatic stress disorder (PTSD)	5	271,300	No †	Yes ¶	Yes §	No **	NA	1.08 (0.78 to 1.5)	1.1 (0.8 to 1.5)	2.2 (1.6 to 3)	Low

OR: odds ratio, 95%CI: 95% confidence interval, NA: not applicable; ED: emergency department; COPD: Chronic obstructive pulmonary disease

* We estimated the absolute risk of fatal or non-fatal overdose for each predictor using a baseline risk of 1% for fatal overdose or 2% for non-fatal overdose and the adjusted OR

† We did not rate down for risk of bias as subgroup analysis showed no significant difference in studies at low vs. high risk of bias on a component-by-component basis.

‡ We rated down for inconsistency because of large heterogeneity across studies.

§ We rated down for indirectness as the evidence was drawn indirectly from high-risk population (e.g., veterans, ≥60% study population with mental disorders, or use of high dose opioids)

¶ We rated down for imprecision because the lower and upper limits of 95%CI associated with the adjusted OR included both large and small associations with opioid overdose (95%CI of adjusted OR included the threshold of large association of OR=2 or OR=0.5).

** Although the estimate of precision included no significant association, we did not rate down for imprecision because the 95%CI did not include important association.

eTable 9 GRADE evidence profile of medical factors associated with opioid overdose

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Heart failure	3	672,544	No	No	No	Yes ‡	NA	1.67 (1.39 to 2)	1.7 (1.4 to 2)	3.3 (2.8 to 4)	Moderate
Hemiplegia or paraplegia	3	672,544	No	No	Yes §	No	NA	1.45 (1.21 to 1.75)	1.5 (1.2 to 1.8)	2.9 (2.4 to 3.5)	Moderate
Injury or acute pain	5	203,655	No †	No	Yes §	No	NA	1.42 (1.27 to 1.59)	1.4 (1.3 to 1.6)	2.8 (2.5 to 3.2)	Moderate
ED visit	2	45,153	No	Yes ¶	No	No	NA	1.39 (1.28 to 1.5)	1.4 (1.3 to 1.5)	2.8 (2.6 to 3)	Moderate
Renal disease	5	726,080	Yes #	No	No	No	NA	1.35 (1.01 to 1.79)	1.4 (1 to 1.8)	2.7 (2 to 3.6)	Moderate
COPD	8	1,595,443	No †	No	No	No	NA	1.34 (1.19 to 1.49)	1.3 (1.2 to 1.5)	2.7 (2.4 to 3)	High
Liver diseases	6	726,346	No †	No	No	No	NA	1.24 (1.13 to 1.36)	1.2 (1.1 to 1.4)	2.5 (2.3 to 2.7)	High
Cancer	5	786,330	No †	No	No	No	NA	1.2 (1.02 to 1.4)	1.2 (1 to 1.4)	2.4 (2 to 2.8)	High
Hypertension	2	45,153	No	No	No	No	NA	1.18 (1.08 to 1.28)	1.2 (1.1 to 1.3)	2.4 (2.2 to 2.6)	High
Diabetes	2	45,153	No	No	Yes §	No	NA	1.18 (1.07 to 1.29)	1.2 (1.1 to 1.3)	2.4 (2.1 to 2.6)	Moderate
Charlson comorbidity index	4	76,174	Yes #	No	No	No	NA	1.14 (1.02 to 1.27)	1.1 (1 to 1.3)	2.3 (2 to 2.5)	Moderate
Headache	7	463,711	No †	Yes ¶	No	No *	NA	1.18 (0.95 to 1.47)	1.2 (1 to 1.5)	2.4 (1.9 to 2.9)	Moderate
Neck/Back pain	6	317,176	Yes #	No	No	No *	NA	1.12 (0.97 to 1.28)	1.1 (1 to 1.3)	2.2 (1.9 to 2.6)	Moderate

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Fibromyalgia	3	47,180	Yes [#]	No	No	No ^{**}	NA	1.12 (1 to 1.26)	1.1 (1 to 1.3)	2.2 (2 to 2.5)	Moderate
Neuropathic pain	7	455,798	No [†]	Yes [¶]	No	No ^{**}	NA	1.04 (0.82 to 1.31)	1 (0.8 to 1.3)	2.1 (1.6 to 2.6)	Moderate
Dementia	2	45,153	No	No	Yes [§]	No ^{**}	NA	0.96 (0.56 to 1.66)	1 (0.6 to 1.7)	1.9 (1.1 to 3.3)	Moderate
Sleep apnea	5	914,516	No [†]	Yes [¶]	No	No ^{**}	NA	1.09 (0.98 to 1.21)	1.1 (1 to 1.2)	2.2 (2 to 2.4)	Moderate
HIV/AIDS	5	726,080	Yes [#]	No	No	No ^{**}	NA	1.03 (0.91 to 1.15)	1 (0.9 to 1.2)	2.1 (1.8 to 2.3)	Moderate
Sexually transmitted disease	2	45,153	No	No	No	No ^{**}	NA	0.94 (0.78 to 1.12)	0.9 (0.8 to 1.1)	1.9 (1.6 to 2.2)	High
Herpes simplex infection	2	45,153	No	No	No	No ^{**}	NA	0.8 (0.54 to 1.19)	0.8 (0.5 to 1.2)	1.6 (1.1 to 2.4)	High
Burns	2	45,153	No	No	No	Yes [‡]	NA	0.77 (0.49 to 1.21)	0.8 (0.5 to 1.2)	1.5 (1 to 2.4)	Moderate
Number of drugs	3	132,801	Yes [#]	No	No	No ^{**}	NA	0.99 (0.94 to 1.04)	1 (0.9 to 1)	2 (1.9 to 2.1)	Moderate
Skin ulcers	3	672,544	No	No	Yes [§]	Yes [‡]	NA	1.45 (0.92 to 2.29)	1.5 (0.9 to 2.3)	2.9 (1.8 to 4.6)	Low
Chronic pain	3	355,431	No	No	Yes [§]	Yes [‡]	NA	1.29 (0.74 to 2.25)	1.3 (0.7 to 2.3)	2.6 (1.5 to 4.5)	Low
Peptic ulcer disease	3	672,544	No	Yes [¶]	Yes [§]	No ^{**}	NA	1.04 (0.73 to 1.48)	1 (0.7 to 1.5)	2.1 (1.5 to 3)	Low
Skin infections/abscesses	2	45,153	No	Very serious [¶]	No	No ^{**}	NA	1.08 (0.94 to 1.23)	1.1 (0.9 to 1.2)	2.2 (1.9 to 2.5)	Low

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of Patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Cardiovascular disease	2	45,153	No	Yes [¶]	Yes [§]	No [‡]	NA	0.9 (0.75 to 1.09)	0.9 (0.8 to 1.1)	1.8 (1.5 to 2.2)	Low
Peripheral vascular disease	3	672,544	No	Yes [¶]	Yes [§]	No [‡]	NA	0.99 (0.81 to 1.22)	1 (0.8 to 1.2)	2 (1.6 to 2.4)	Low
Myocardial infarction	3	672,544	No	Yes [¶]	Yes [§]	Yes [‡]	NA	1.3 (0.65 to 2.59)	1.3 (0.7 to 2.6)	2.6 (1.3 to 5.2)	Very Low
Cerebrovascular disease	3	672,544	No	Yes [¶]	Yes [§]	Yes [‡]	NA	1.35 (0.8 to 2.28)	1.4 (0.8 to 2.3)	2.7 (1.6 to 4.6)	Very Low
Serious autoimmune rheumatology disease	3	672,544	No	Very serious [¶]	Yes [§]	No [‡]	NA	1.02 (0.65 to 1.59)	1 (0.7 to 1.6)	2 (1.3 to 3.2)	Very Low
Days of hospitalization during the preceding 6 months (>=1 vs 0)	2	45,153	No	Very serious [¶]	Yes [§]	No [‡]	NA	1.04 (0.94 to 1.14)	1 (0.9 to 1.1)	2.1 (1.9 to 2.3)	Very Low

OR: odds ratio, 95%CI: 95% confidence interval, NA: not applicable; ED: emergency department; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

* We estimated the absolute risk of fatal or non-fatal overdose for each predictor using a baseline risk of 1% for fatal overdose or 2% for non-fatal overdose and the adjusted OR

‡ We rated down for imprecision because the lower and upper limits of 95%CI associated with the adjusted OR included both large and small associations with opioid overdose (95%CI[§] We rated down for indirectness as the evidence was drawn indirectly from high-risk population (e.g., veterans, ≥60% study population with mental disorders, or use of high dose opioids)

† We did not rate down for risk of bias as subgroup analysis showed no significant difference in studies at low vs. high risk of bias on a component-by-component basis.

We rated down for risk of bias because of at least 20% of the total weight from studies with high-risk of bias. of adjusted OR included the threshold of large association of OR=2 or OR=0.5).

¶ We rated down for inconsistency because of large heterogeneity across studies.

‡ Although the estimate of precision included no significant association, we did not rate down for imprecision because the 95%CI did not include important association.

¶ We rated down two levels for very serious inconsistency between studies.

eTable 10 GRADE evidence profile of socio-demographic factors associated with opioid overdose

Predictors		Study characteristics		Quality assessment				Summary of Findings			Overall quality of evidence	
		No. of Studies	No. of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000		Risk of non-fatal overdose (95%CI) *, per 1000
Age (every 10-year decrement from age 80)		18	2,305,963	No †	No	No	No	Undetected; Egger's p=0.55	1.22 (1.02 to 1.46)	1.2 (1 to 1.5)	2.4 (2 to 2.9)	High
Gender (male vs. female)		20	2,359,499	No †	No	No	No	Undetected; Egger's p=0.98	1.1 (1.01 to 1.19)	1.1 (1 to 1.2)	2.2 (2 to 2.4)	High
Non-married vs. Married		4	927,098	Yes #	No	No	No	NA	1.34 (1.27 to 1.41)	1.3 (1.3 to 1.4)	2.7 (2.5 to 2.8)	Moderate
White race vs others		14	1,964,160	No †	No	No	No	Undetected; Egger's p=0.12	1.5 (1.28 to 1.77)	1.5 (1.3 to 1.8)	3 (2.6 to 3.5)	High
Regions	West vs. Northeast	6	523,645	No †	No	No	No	NA	1.43 (1.16 to 1.76)	1.4 (1.2 to 1.8)	2.9 (2.3 to 3.5)	High
	Midwest vs. Northeast	5	394,971	No †	No	No	No	NA	1.21 (1.09 to 1.33)	1.2 (1.1 to 1.3)	2.4 (2.2 to 2.7)	High
	South vs. Northeast	6	846,894	No †	No	No	No	NA	1.09 (1.004 to 1.19)	1.1 (1 to 1.2)	2.2 (2 to 2.4)	High
Insurance (vs. private insurance)	Medicaid	2	276,493	No	No	No	Yes ‡	NA	1.73 (1.48 to 2.02)	1.7 (1.5 to 2)	3.5 (3 to 4)	Moderate
	Medicare	2	408,578	No	No	No	Yes ‡	NA	1.75 (1.51 to 2.03)	1.8 (1.5 to 2)	3.5 (3 to 4.1)	Moderate
	Uninsured	2	244,755	No	No	No	Yes ‡	NA	1.79 (1.51 to 2.12)	1.8 (1.5 to 2.1)	3.6 (3 to 4.2)	Moderate

Predictors	Study characteristics		Quality assessment					Summary of Findings			Overall quality of evidence
	No. of Studies	No. of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Small study effects	Adjusted OR (95% CI)	Risk of fatal overdose (95%CI) *, per 1000	Risk of non-fatal overdose (95%CI) *, per 1000	
Urban vs. rural areas	5	1,105,554	No †	No	No	No*	NA	1.07 (0.95 to 1.2)	1.1 (1 to 1.2)	2.1 (1.9 to 2.4)	High
Overweight & Obesity	5	196,829	Yes #	Yes ¶	No	No*	NA	0.96 (0.73 to 1.27)	1 (0.7 to 1.3)	1.9 (1.5 to 2.5)	Low

OR: odds ratio, 95%CI: 95% confidence interval, NA: not applicable

* We estimated the absolute risk of fatal or non-fatal overdose for each predictor using a baseline risk of 1% for fatal overdose or 2% for non-fatal overdose and the adjusted OR

† We did not rate down for risk of bias as subgroup analysis showed no significant difference in studies at low vs. high risk of bias on a component-by-component basis.

We rated down for risk of bias because of at least 20% of the total weight from studies with high-risk of bias.

‡ We rated down for imprecision because the lower and upper limits of 95%CI associated with the adjusted OR included the threshold of important association of OR=2 or OR=0.5.

§ Although the estimate of precision included no significant association, we did not rate down for imprecision because the 95%CI did not include important association.

¶ We rated down for inconsistency because of large heterogeneity across studies.

eTable 11 Consistency of results of predictors between pooled and unpooled studies

Predictors	Pooled results		Unpooled results		
	Significant factors	Non-significant factors	Predictor name measured	Significant factors	Non-significant factors
	No. of studies (n)	No. of studies (n)		No. of studies (n)	No. of studies (n)
Opioid dose-response relationship	14 (1,315,173)			3 (487,638) *	0
Long- vs short-acting opioid formulations	8 (925,558)		Opioid drug type with long- & short-acting formulation #	1 (150,821) #	0
Duration of opioid use	2 (153,033)		Periods on long-term opioids vs. Periods not on long-term opioids †	1 (98,140) †	0
Mental health diagnosis	17 (1,572,200)		Mental health care visit §	1 (151,313) §	0
Current substance use disorder	12 (1,143,838)		Opioid and non-opioid use disorder ‡	1 (405,631) ‡	0
Chronic pain		3 (355,431)	Pain clinic visit *	1 (151,313) *	2 (53,453) *
Age	15 (1,418,516)		Age ¶	1 (42,828) ¶	1 (10,708) ¶
Charlson comorbidity index	3 (22,987)		Rx-Risk Comorbidity Index	0	1 (9,940)
HIV/AIDS		4 (98,689)	Viral load or CD4 cell counts	0	1 (9,272)
Renal disease		4 (98,689)	Renal insufficiency	0	1 (266)
Chronic pain		2 (148,562)	Multiple chronic noncancer pain conditions	0	1 (266)

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

* Three studies showed significant association between higher opioid dose and overdose below

- Young 2019 reported dose-response relationship by comparing ≥ 90 mg vs. 20-50mg and ≥ 90 mg vs. 50-90mg among 4 categories of follow-up periods (ranging from 0 to 1 year)

	≥ 90 mg vs. 20-50mg		≥ 90 mg vs. 20-50mg	
	HR	95% CI	HR	95% CI
IPTW (0-7 days)	2.23	1.75-2.84	1.81	1.50-2.20
IPTW (8-30 days)	1.46	1.17-1.81	1.12	0.94-1.34
IPTW (31-90 days)	1.52	1.29-1.79	1.28	1.13-1.46
IPTW (91-365 days)	1.44	1.31-1.58	1.15	1.07-1.23

- Hayes 2020 reported the association of opioid dose escalators (at least a 20% increase) vs. maintainers with adjusted OR 1.39 (95%CI 1.02 to 1.9)
- Lo-Ciganic 2022 reported dose-response relationship for both opioid and benzodiazepine

Trajectory Groups	Adjusted HR (95%CI)
A. Very-low OPI (early discontinuation)-Very-low declining BZD	Ref
B. Very-low OPI (early discontinuation)-Very-low stable BZD	0.29 (0.06, 1.29)
C. Very-low OPI (early discontinuation)-Medium BZD	0.64 (0.22, 1.90)
D. Low OPI-Low BZD	1.17 (0.49, 2.79)
E. Low OPI-High BZD	3.27 (1.61, 6.63)
F. Medium OPI-Low BZD	4.04 (2.06, 7.95)
G. Very-high OPI-High BZD	6.98 (3.11, 15.64)

H. Very-high OPI-Very-high BZD	4.41 (1.51, 12.85)
I. Very-high OPI-Low BZD	6.50 (3.15, 13.42)

One study (Garg 2017) reported Schedule II vs non-schedule II only, but with different formulation for Schedule II opioids:

- short-acting only: HR 2.3 (1.6–3.3)
- long-acting only: HR 4.5 (3.1–6.4)
- both short- and long-acting: HR 4.7 (3.3–6.9)

† One study (Bedson 2019) reported the association of periods on long-term opioids vs. not on long-term opioids: HR 2.24 (95%CI 1.73, 2.89)

§ One study (Hayes 2020) reported a borderline significant association of mental health care visit OR & 95%CI: 1.012 (1.008 to 1.017)

‡ Hayes 2022a reported large association between opioid or non-opioid use disorder and opioid overdose with adjusted OR & 95%CI: 0.65 (0.34 to 0.96) and 0.31 (0.11 to 0.52) using accelerated failure time model.

* One study (Hayes 2020) reported a borderline significant association of pain clinic visit OR & 95%CI: 1.053 (1.017 to 1.092); but another two study (Hayes 2020, Salkar 2021) reported no significant difference with multiple chronic noncancer pain conditions.

‡ Age-squared was adjusted as well

eTable 12 Summary table of opioid tapering or discontinuation

Study	Overdose type	No. patients		Tapering/discontinuation definition	Reference	Results in adjusted analysis HR/RR/IRR/OR/0 (95%CI)	Conclusion
		tapering/discontinuation	Reference				
James, 2019	Fatal	344	228	Discontinued: Patients with chronic opioid therapy who were removed from the opioid registry at any point during the study period for any reason other than death	Chronic opioid therapy: regular opioid prescriptions for at least 3 months	HR 2.94 (1.01 to 8.61)	Opioid discontinuation was associated with increased risk of overdose death
Laroche, 2022 *	Fatal	42,246	332,121	Tapering: 2 consecutive months with a mean MME reduction of $\geq 15\%$ compared with the baseline month.	Stable dosage: MME ≥ 50 mg daily, no taper or abrupt discontinuation	RR 1.16 (1.01 to 1.30)	Opioid tapering was associated with increased risk of opioid-related suicide
		6,886		Abrupt discontinuation: the second qualifying month had an MME equal to 0 mg.		RR 1.55 (0.99 to 2.13)	No significant association between abrupt opioid discontinuation and opioid-related suicide
	Non-fatal	42,246	332,121	Tapering: 2 consecutive months with a mean MME reduction of $\geq 15\%$ compared with the baseline month.	Stable dosage: MME ≥ 50 mg daily, no taper or abrupt discontinuation	RR 1.16 (0.99 to 1.37)	No significant association between opioid tapering and non-fatal opioid overdose
		6,886		Abrupt discontinuation: the second qualifying month had an MME equal to 0 mg.		RR 1.26 (0.68 to 2.03)	No significant association between abrupt opioid discontinuation and non-fatal opioid overdose
	Mixed	42,246	332,121	Tapering: 2 consecutive months with a mean MME reduction of $\geq 15\%$ compared with the baseline month.	Stable dosage: MME ≥ 50 mg daily, no taper or abrupt discontinuation	RR 1.15 (1.04 to 1.27)	Opioid tapering was associated with increased risk of composite opioid overdose (mixed non-fatal overdose and suicide)
		6,886		Abrupt discontinuation: the second qualifying month had an MME equal to 0 mg.		RR 1.34 (0.97 to 1.79)	No significant association between abrupt opioid discontinuation and composite opioid overdose (mixed non-fatal overdose and suicide)

Study	Overdose type	No. patients		Tapering/discontinuation definition	Reference	Results in adjusted analysis HR/RR/IRR/OR/θ (95%CI)	Conclusion
		tapering/discontinuation	Reference				
Agnoli, 2021 *	Mixed	29,101	84,517	Tapering: for all months after the first of 6 overlapping 60-day period in which a person's mean daily opioid dose decreased by ≥15% from their baseline period	Stable dosage: MME ≥50 mg daily, no tapering	IRR 1.17 (0.98-1.40)	No significant association between opioid tapering and opioid overdose
DiPrete, 2022	Mixed	19,443		Gradual dose tapering or discontinuation: ≤10% dose reduction per week (≤34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 1.12 (0.65, 1.92) at 0-12m, HR 2.12 (1.00, 4.50) at 13-48m	No significant association between gradual opioid tapering or discontinuation and opioid overdose
				Rapid dose tapering or discontinuation: dose reduction >10% per week (>34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 1.45 (0.94, 2.25) at 0-12m, HR 3.05 (1.59, 5.85) at 13-48m	Rapid opioid tapering or discontinuation was associated with increased risk of opioid overdose at 13-48 months , but was not significant within 12 months
	Fatal	19,443		Gradual dose tapering or discontinuation: ≤10% dose reduction per week (≤34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 0.88 (0.26, 2.93) at 0-12m, HR 1.09 (0.27, 4.30) at 13-48m	No significant association between gradual opioid tapering or discontinuation and fatal opioid overdose
				Rapid dose tapering or discontinuation: dose reduction >10% per week (>34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 1.63 (0.56, 4.72) at 0-12m, HR 1.52 (0.50, 4.62) at 13-48 months	No significant association between rapid opioid tapering or discontinuation and fatal opioid overdose
	Non-fatal	19,443		Gradual dose tapering or discontinuation: ≤10% dose reduction per week (≤34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 1.24 (0.69, 2.21) at 0-12m, HR 2.24 (0.99, 5.05) at 13-48m	No significant association between gradual opioid tapering or discontinuation and non-fatal opioid overdose
				Rapid dose tapering or discontinuation: dose reduction >10% per week (>34% per month)	Dose maintained (MME ≥90 mg daily) or increased	HR 1.34 (0.84, 2.14) at 0-12m, HR 3.29 (1.64, 6.62) at 13-48m	Rapid opioid tapering or discontinuation was associated with increased risk of non-fatal overdose at 13-48 months , but was

Study	Overdose type	No. patients		Tapering/discontinuation definition	Reference	Results in adjusted analysis HR/RR/IRR/OR/θ (95%CI)	Conclusion
		tapering/discontinuation	Reference				
							not significant within 12 months
Hayes, 2022a ^{#,†}	Non-fatal	72,092	143,950	Persistent Moderate Days Covered	Persistent high days covered	θ 0.71 (0.60, 0.84)	Persistent moderate days covered trajectory was associated with decreased risk of non-fatal opioid overdose
		71,006		Persistent Modest Days Covered		θ 0.77 (0.65, 0.91)	Persistent modest days covered trajectory was associated with decreased risk of non-fatal opioid overdose
		23,927		Delayed Days Covered Reduction		θ 1.18 (0.97, 1.42)	No significant association between delayed days covered reduction trajectory and non-fatal opioid overdose
		51,181		Moderate Paced Discontinuation		θ 0.91 (0.77, 1.08)	No significant association between moderate paced discontinuation trajectory and non-fatal opioid overdose
		17,578		Delayed Discontinuation		θ 1.13 (0.90, 1.41)	No significant association between delayed discontinuation trajectory and non-fatal opioid overdose
		25,897		Rapid Discontinuation		θ 0.54 (0.41, 0.72)	Rapid discontinuation was associated with decreased risk of non-fatal opioid overdose
Hayes, 2021 [#]	Non-fatal	22,646	128,816	Discontinued: no any opioid prescription fills in the second 180-day period	COT: receiving ≥ 90-day supply of non-parenteral opioids within any 180-day period with no gaps >30 days	OR 0.638 (0.463, 0.879)	Discontinuation of chronic opioid therapy was associated with decreased risk of non-fatal opioid overdose

Study	Overdose type	No. patients		Tapering/discontinuation definition	Reference	Results in adjusted analysis HR/RR/IRR/OR/θ (95%CI)	Conclusion
		tapering/discontinuation	Reference				
Hayes, 2022b #	Non-fatal	40,184	58,927	Switching to intermittent opioid therapy: at least one opioid prescription within 180 days, but not meeting LTOT criteri	LTOT: >90 days' supply of opioids within 180 days with no gaps >30 days	OR 1.037 (0.820, 1.312)	No significant associations between transitioning patients from LTOT to intermittent opioid therapy and the risk of non-fatal opioid overdose

HR: hazard ratio, RR: risk ratio; IRR: incidence risk ratio, OR: odds ratio, MME: morphine milligram equivalents; COT: chronic opioid therapy; LTOT: long-term opioid therapy

Significant association was highlighted in **bold**

* Agnoli 2021 is overlapped with Larochelle 2022

Hayes 2021 and Hayes 2022b are overlapped with Hayes 2022a

† Hayes 2022a constructed 7 trajectories of opioid therapy based on the number of days opioids were supplied in 180-day time periods following initial LTOT and analyzed the association between trajectory group and opioid overdose using accelerated failure time model.

eTable 13 Significant associations of six unpooled predictors with opioid overdose

Predictor	Significant association with opioid overdose		Non-significant association	Total	Notes for significant results	
	No. studies (n)	OR/HR (95%CI) & p-value				No. studies (n)
Opioid-related factor						
Patients without prior established opioid tolerance to those with opioid tolerance	1 (372,038)	OR & 95%CI 0-7 days: 1.37 (1.07 to 1.76), p=0.01 8-30 days: 0.89 (0.67 to 1.19), p=0.43 31-90 days: 0.93 (0.77 to 1.14), p=0.48 91-365 days: 0.82 (0.72 to 0.92), p=0.002		0	1 (372,038)	Patients without established opioid tolerance prior to initiation were more likely to be diagnosed with opioid overdose in the first 7 days; but less likely after 7 days, particularly in 91 to 365 days after initiation (Young 2019)
Medical factors						
Traumatic brain injury (TBI)	1 (49,014)	HR & 95%CI: 2.18 (1.57 to 3.05), p<0.001		0	1 (49,014)	Veterans with TBI was associated with increased risk of opioid overdose (Fonda 2020)
Average pain score in 180 days before dose change index date	1(53,187)	OR & 95%CI: 1.17 (1.02 to 1.33), p=0.02		0	1(53,187)	Higher average pain score in 180 days before dose change index date was associated with increased risk of opioid overdose (Hayes 2020)
Social-demographic factors						
Regions in England	1 (10,801)	HR & 95%CI, p-value South vs. London, 3.28 (1.52 to 7.09), p=0.003 North vs. London, 3.27 (1.51 to 7.04), p=0.003 Midlands and East, 2.42 (1.10 to 5.32), p=0.03		0	1 (10,801)	Patients living in South, North, Midlands and East of England were associated with higher risk of opioid overdose (Bedson 2019)

Predictor	Significant association with opioid overdose		Non-significant association	Total	Notes for significant results
	No. studies (n)	OR/HR (95%CI) & p-value			
Social-economic status measured by Index of Multiple Deprivation	1 (98,140)	HR & 95%CI, p-value Level 2 vs 1, 1.34 (0.82 to 2.19), p=0.25 Level 3 vs 1, 1.24 (0.76 to 2.04), p=0.38 Level 4 vs 1, 1.19 (0.74 to 1.94), p=0.47 Level 5 vs 1, 1.7 (1.07 to 2.69), p=0.02	0	1 (98,140)	Patients living in higher neighbourhood deprivation level is associated with higher risk of intentional opioid overdose, particularly the highest level vs. the lowest level (Bedson 2019)
Year	3 (878,369)	Every-year increase from the year of 2009 to 2016 in USA, OR & 95%CI (Qeadan 2021): Chronic pain syndrome: 0.86 (0.82-0.90) Low back pain population: 0.85 (0.83-0.88) Antiretroviral therapy era for HIV patients In Canada, RR & 95%CI (El-Akkad 2020): 2000–2003 vs. 1996–1999: 0.82 (0.56 to 1.19), p=0.31 2004–2007 vs. 1996–1999: 0.61 (0.40 to 0.93), p=0.02 2008–2011 vs. 1996–1999: 0.53 (0.32 to 0.88), p=0.01 2012–2015 vs. 1996–1999: 1.53 (0.82 to 2.89), p=0.19	3 (932,400)	6 (1,810,769)	In USA, opioid overdose risk decreases overtime between 2009 to 2016 (Qeadan 2021); however, another two studies showed no significant association for every 6-month increase between 2008 to 2015 (Turner 2015) or 2008 to 2012 (Carey 2018). Also, no significant trend was found in UK between 2002 and 2012 (Bedson 2019); and in Canada among HIV patients, opioid related death decreased between 2004 to 2011 vs. 1996 to 1999, but no significant difference for other time periods (El-Akkad 2020).

OR: odds ratio, HR: hazard ratio, 95%CI: 95% confidence interval; TBI: traumatic brain injury.

eTable 14 Non-significant associations of 23 unpooled predictors with opioid overdose

Categories of predictors	Predictors	Non-significant association No. studies (n)
Social-demographic factors	Income or low-income status	2 (32,715)
	Non-English speaker	1 (2027)
	Long-term care residence	1 (2,027)
Opioid-related factors	Schedule II/III/IV opioids	1 (53,187)
	Number of opioid prescriptions dispensed	1 (8,987)
	Number of unique opioid NDCs	1 (8,987)
Medical factors	Motor vehicle accidents	1 (8,987)
	Osteoarthritis	2 (11,967)
	Temporomandibular pain	1 (9,940)
	Extremity pain	1 (9,940)
	Abdominal pain	1 (9,940)
	Menstrual pain	1 (9,940)
	All tracer pain conditions	1 (53,187)
	First pain score in 180 days before dose change index date	1(53,187)
	Last pain score in 180 days before dose change index date	1(53,187)
	Asthma	2 (98,406)
	Respiratory infection	1 (226)
	Endocarditis	1 (36,166)
	Parkinson	1 (226)
	Primary care visits in past year	4 (237,298)
	Physical therapy visit	1 (151,313)
	Chiropractic care visit	1 (151,313)
	Pharmacy visits in past year	2 (53,536)

NDCs: National Drug Codes

eTable 15 Subgroup analyses of pre-defined factors for opioid overdose #

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value		
Opioids related factors	Opioid dose (every 90-mg increase)	Overdose type	Fatal overdose	6	323639	2.58	1.63	4.09	0.99		
			Non-fatal overdose	5	977553	2.47	2.07	2.96			
			Mixed	3	13981	2.51	1.10	5.68			
		Intentional vs. unintentional	Intentional	2*	222086	3.13	0.88	11.12	0.18		
			Unintentional	7	361083	2.89	2.14	3.91			
			Mixed	6	855950	1.93	1.40	2.66			
		Type of chronic pain	Cancer	1	36803	6.49	3.47	12.14	0.68		
			CNCP	11	1233217	2.47	1.90	3.21			
			Mixed	2	45153	2.31	1.97	2.71			
		Representativeness	No	6	788981	2.91	2.14	3.97	0.37		
			Yes	8	526192	2.40	1.79	3.21			
		Validated measure	Yes	9	1076330	2.86	2.16	3.78	0.18		
			No	5	238843	2.14	1.56	2.93			
		Appropriate adjustment	Yes	7	414299	2.86	2.19	3.73	0.32		
			No	7	900874	2.29	1.62	3.23			
		Long- vs. short- acting opioids		Overdose type	Fatal overdose	1	2212	2.00	1.61	2.49	0.09
					Non-fatal overdose	4	918956	1.55	1.34	1.78	
					Mixed	4	57577	2.35	1.16	4.77	
Unintentional vs. mixed	Unintentional			5	922731	1.51	1.32	1.72	0.07		
	Mixed			4	56014	2.55	1.66	3.91			
Type of chronic pain	CNCP			7	933592	2.10	1.52	2.90	0.07		
	Mixed			2	45153	1.51	1.30	1.75			
Representativeness	No			5	886831	1.78	1.20	2.64	0.59		
	Yes			4	91914	2.05	1.46	2.88			
Validated measure	Yes			3	38644	1.79	1.26	2.53	0.64		
	No			6	940101	2.02	1.40	2.91			
Appropriate adjustment	Yes			6	923080	1.89	1.38	2.59	0.67		
	No			3	55665	2.11	1.26	3.52			
Use of benzodiazepine	Type			Current	7	289919	1.93	1.55	2.40	0.11	
				Prior	3	87848	2.13	1.31	3.46		

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value	
Co-prescription factors		Overdose type	Mixed	2	869097	1.21	1.10	1.32	0.41 [†]	
			Fatal overdose	3	43933	2.75	2.37	3.19		
			Non-fatal overdose	7	1198890	1.55	1.23	1.96		
		Intentional vs. unintentional	Mixed	2	4041	1.45	0.69	3.05	0.07 [†]	
			Unintentional	6	971212	1.45	1.20	1.77		
		Type of chronic pain	Mixed	6	275652	2.46	2.06	2.94	0.48	
			CNCP	10	1201711	1.84	1.38	2.44		
		Representativeness	Mixed	2	45153	1.61	1.29	2.02	0.09	
			No	4	66215	1.48	1.20	1.82		
		Validated measure	Yes	7	973780	1.97	1.53	2.54	0.38	
			No	4	71093	2.06	1.50	2.83		
		Appropriate adjustment	Yes	8	1175771	1.70	1.27	2.27	0.60	
			No	8	1181927	1.71	1.37	2.14		
		Sedatives and hypnotics	Intentional vs. unintentional	Unintentional	3	98340	1.32	1.21	1.44	0.39
	Mixed			3	239584	1.68	0.97	2.93		
	Type of chronic pain		CNCP	4	292771	1.51	1.20	1.897	0.26	
			Mixed	2	45153	1.29	1.10	1.504		
	Representativeness		No	3	62440	1.37	0.89	2.09	0.95	
			Yes	3	275484	1.38	1.26	1.52		
	Validated measure		Yes	3	68881	1.56	0.84	2.90	0.67	
			No	3	269043	1.36	1.10	1.68		
	Appropriate adjustment		Yes	4	284471	1.36	1.21	1.53	0.47	
			No	2	53453	2.05	0.68	6.23		
	Muscle relaxants		Type of chronic pain	CNCP	3	19731702	1.35	0.97	1.87	0.77
				Mixed	2	45153	1.27	1.01	1.60	
			Representativeness	No	3	62440	1.32	0.90	1.92	0.94
		Yes		2	19714416	1.34	1.17	1.53		
Validated measure		Yes	3	19740423	1.56	0.84	2.90	0.42		
		No	2	36432	1.19	0.93	1.52			
Appropriate adjustment	Yes	3	19723404	1.26	1.09	1.47	0.43			
	No	2	53453	1.99	0.65	6.09				

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value	
Psychological factors	Substance use disorder (SUD)	Timing	Curent SUD	12	1143838	2.62	2.09	3.27	0.01	
			Hx of SUD	4	46628	1.47	1.03	2.09		
		Overdose type	Fatal overdose	5	192495	2.22	1.85	2.65	0.84	
			Non-fatal overdose	6	930454	2.35	1.70	3.26		
			Mixed	5	67517	2.47	1.74	3.51		
			Intentional vs. unintentional	Intentional	1*	123946	2.00	1.44	2.78	0.75
		Intentional vs. unintentional	Unintentional	5	197490	2.47	1.54	3.97		
			Mixed	11	992976	2.23	1.72	2.90		
			Type of chronic pain	Cancer	1	36803	3.08	1.73	5.50	0.58
		Type of chronic pain	CNCP	12	1106483	2.38	1.92	2.97		
			Mixed	3	47180	1.87	0.85	4.10		
			Representativeness	No	7	837995	2.20	1.57	3.09	0.61
		Representativeness	Yes	9	352471	2.46	1.91	3.17		
			Validated measure	Yes	8	294406	2.47	1.96	3.11	0.54
		Validated measure	No	8	896060	2.12	1.39	3.24		
			Appropriate adjustment	Yes	11	1162512	2.16	1.59	2.94	0.22
		Appropriate adjustment	No	5	62791	1.68	1.30	2.18		
			Depression or Antidepressants	Depression or Antidepressants	Depression	6	413289	2.37	1.52	3.68
		Depression or Antidepressants	Timing	Antidepressants	7	340136	1.44	1.29	1.61	
				Current	4	252288	2.88	1.84	4.50	0.15
		Overdose type	Overdose type	Prior	5	195928	1.80	1.14	2.86	
				Fatal overdose	2	34661	1.44	1.27	1.64	0.31
				Non-fatal overdose	5	403349	2.57	1.74	3.80	
		Intentional vs. unintentional	Intentional vs. unintentional	Mixed	2	10206	2.41	1.51	3.86	
Intentional	1			98140	3.61	2.76	4.72	0.08		
Unintentional	3			98340	1.80	0.98	3.30	0.6		
Type of chronic pain	Type of chronic pain	Mixed	5	251736	2.29	1.19	4.41			
		CNCP	7	403063	2.20	1.32	3.67	0.96		
		Mixed	2	45153	2.25	1.17	4.33			
Representativeness	Representativeness	No	3	62440	1.56	1.03	2.34	0.10		
		Yes	6	385776	2.56	1.68	3.89			
Validated measure	Validated measure	Yes	5	169233	2.31	1.46	3.66	0.82		

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
			No	4	278983	2.09	1.00	4.35	
		Appropriate adjustment	Yes	5	294411	2.46	1.64	3.68	0.54
			No	4	153805	1.95	1.07	3.58	
			No	3	108346	3.17	2.39	4.21	
	Any mental health disorders	Timing	Current	10	507175	2.31	1.69	3.16	0.67
			Prior	5	195928	1.79	1.13	2.84	
			Mixed	2	869097	2.08	1.61	2.70	
		Overdose type	Fatal overdose	4	183223	1.84	1.48	2.29	0.18 [†]
			Non-fatal overdose	8	1321460	1.82	1.33	2.49	0.03
			Mixed	5	67517	2.29	1.89	2.78	<0.001
		Intentional vs. unintentional	Intentional	2	222086	2.96	1.98	4.41	0.19
			Unintentional	8	1119774	1.90	1.46	2.46	
			Mixed	8	354286	2.21	1.44	3.38	
		Type of chronic pain	Cancer	1	36803	1.68	0.95	2.99	0.70
			CNCP	14	1490244	2.18	1.75	2.72	0.82
			Mixed	2	45153	1.94	0.76	4.957	
		Representativeness	No	7	263791	1.60	1.26	2.03	0.06 [†]
			Yes	10	1308409	2.48	1.94	3.18	
	Validated measure	Yes	8	366809	2.01	1.45	2.79	0.68	
		No	9	1205391	2.21	1.62	3.02		
	Appropriate adjustment	Yes	12	1369381	2.27	1.81	2.85	0.33	
		No	5	202819	1.77	1.14	2.77		
	Psychotic disorders or use of antipsychotics	Type of mental disorders	Current	4	375968	1.73	1.11	2.68	0.39
			Prior	2	34661	1.22	1.00	1.49	
		Overdose type	Fatal overdose	3	158607	1.61	1.00	2.61	0.96
			Non-fatal overdose	3	252022	1.58	0.96	2.61	
		Type of chronic pain	CNCP	3	241530	1.71	0.94	3.103	0.61
			Mixed	3	169099	1.44	1.06	1.95	
		Representativeness	No	2	132933	1.71	0.94	3.13	0.78
			Yes	4	277696	1.55	1.01	2.36	
		Validated measure	Yes	4	194773	1.38	1.08	1.76	0.43
			No	2	215856	1.83	0.95	3.55	

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
	Tobacco use or use disorder	Type	Smoking status (current smoker vs not)	2	108080	1.75	1.34	2.287	0.66
			Tobacco use or use disorder	3	57311	1.67	1.33	2.09	
			Tobacco Use Disorder	2	45153	1.44	1.03	2.01	
		Overdose type	Non-fatal overdose	3	143293	1.55	1.21	1.98	0.75
			Mixed	4	67251	1.63	1.32	2.01	
		Intentional vs. unintentional	Intentional	1	98140	1.86	1.38	2.51	0.55
			Unintentional	3	48928	1.50	1.18	1.91	0.73
			Mixed	3	63476	1.60	1.23	2.09	
		Type of chronic pain	CNCP	5	165391	1.70	1.43	2.02	0.39
			Mixed	2	45153	1.44	1.03	2.01	
		Representativeness	No	2	12762	1.38	1.00	1.91	0.23
			Yes	5	197782	1.69	1.55	1.86	
		Validated measure	Yes	2	134306	1.71	1.55	1.88	0.08
			No	5	76238	1.43	1.20	1.70	
	Anxiety	Type of chronic pain	CNCP	2	102201	1.12	0.87	1.45	0.33
			Mixed	3	169099	1.36	1.03	1.79	
		Validated measure	Yes	3	209126	1.37	1.05	1.79	0.26
			No	2	62174	1.11	0.87	1.41	
		Appropriate adjustment	Yes	2	102201	1.12	0.87	1.45	0.33
			No	3	169099	1.36	1.03	1.79	
	PTSD	Type of chronic pain	CNCP	2	102201	1.31	0.48	3.551	0.55
			Mixed	3	169099	0.96	0.81	1.134	
		Validated measure	Yes	3	209126	1.18	0.69	2.01	0.52
			No	2	62174	0.98	0.77	1.23	
		Appropriate adjustment	Yes	3	169099	0.96	0.81	1.13	0.55
			No	2	102201	1.31	0.48	3.55	
Medical factors	History of non-fatal overdose	Validated measure	Yes	2	98406	6.76	0.78	58.94	0.79
			No	2	869097	4.98	3.42	7.27	
		Appropriate adjustment	Yes	2	869097	4.98	3.42	7.27	0.79

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
			No	2	98406	6.76	0.78	58.94	
	Injury & acute pain	Overdose type	Fatal overdose	2	148562	1.28	0.96	1.70	0.31
			Non-fatal overdose	2	45153	1.44	1.26	1.63	0.47
			Mixed	1	9940	2.52	1.09	5.84	
		Type of chronic pain	Cancer	1	36803	0.94	0.50	1.77	0.39
			CNCP	2	121699	1.62	0.95	2.76	0.67
			Mixed	2	45153	1.44	1.26	1.63	
		Representativeness	No	3	157549	1.43	1.17	1.74	0.68
			Yes	2	46106	1.61	0.96	2.68	
		Validated measure	Yes	3	184728	1.37	1.27	1.48	0.15
			No	2	18927	1.66	1.30	2.14	
	Renal disease	Overdose type	Non-fatal overdose	3	672544	1.64	1.30	2.08	0.14 [†]
			Mixed	2	53536	1.00	0.88	1.14	
		Intentional vs. unintentional	Unintentional	2	45153	1.14	1.01	1.30	0.13 [†]
			Mixed	3	680927	1.11	0.90	1.36	
		Type of chronic pain	CNCP	3	680927	1.11	0.90	1.36	0.13 [†]
			Mixed	2	45153	1.14	1.01	1.30	
		Representativeness	No	2	636378	1.47	1.18	1.84	0.54
			Yes	3	89702	1.25	0.79	1.99	
		Validated measure	Yes	2	663557	1.62	1.14	2.30	0.18
			No	3	62523	1.18	0.86	1.61	
	COPD	Overdose type	Non-fatal overdose	5	1541641	1.44	1.33	1.56	0.16 [†]
			Mixed	3	53802	0.97	0.79	1.20	
		Intentional vs. unintentional	Unintentional	4	914250	1.50	1.41	1.59	0.07 [†]
			Mixed	4	681193	1.10	0.94	1.29	
		Type of chronic pain	CNCP	6	1550290	1.24	1.05	1.47	0.08
			Mixed	2	45153	1.48	1.34	1.62	
		Representativeness	No	3	636644	1.27	0.99	1.62	0.61
			Yes	5	958799	1.36	1.20	1.55	
		Validated measure	Yes	3	663823	1.29	1.04	1.61	0.79
			No	5	931620	1.34	1.14	1.57	

Categories	Predictor	Subgroup factor	No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value	
Liver diseases	Appropriate adjustment	Yes	6	967786	1.39	1.24	1.55	0.29	
		No	2	627657	1.03	0.60	1.77		
	Overdose type	Non-fatal overdose	3	672544	1.26	1.15	1.39	0.20	
		Mixed	3	53802	0.98	0.68	1.43		
	Intentional vs. unintentional	Unintentional	2	45153	1.39	1.09	1.78	0.32	
		Mixed	4	681193	1.22	1.10	1.35		
	Type of chronic pain	CNCP	4	681193	1.22	1.10	1.35	0.32	
		Mixed	2	45153	1.39	1.09	1.78		
	Representativeness	No	3	636644	1.34	0.91	1.96	0.70	
		Yes	3	89702	1.22	0.96	1.56		
	Validated measure	Yes	3	663823	1.25	1.13	1.38	0.69	
		No	3	62523	1.18	0.89	1.56		
	Appropriate adjustment	Yes	4	98689	1.27	1.03	1.56	0.82	
		No	2	627657	1.24	1.11	1.37		
	Cancer	Intentional vs. unintentional	Intentional	1*	123946	0.94	0.64	1.39	0.52
			Unintentional	3	156912	1.13	0.99	1.28	0.52
Mixed			2	629418	1.26	0.91	1.75		
Type of chronic pain		CNCP	2	739150	1.23	0.86	1.74	0.70	
		Mixed	3	47180	1.14	0.99	1.30		
Representativeness		No	3	748137	1.28	1.05	1.55	0.20	
		Yes	2	38193	1.09	0.93	1.27		
Validated measure		Yes	3	775316	1.19	0.95	1.49	0.98	
		No	2	11014	1.20	0.94	1.52		
Appropriate adjustment		Yes	3	156912	1.13	0.99	1.28	0.52	
	No	2	629418	1.26	0.91	1.75			
Headache	Overdose type	Fatal overdose	2	148562	0.98	0.72	1.33	0.29	
		Non-fatal overdose	4	305209	1.23	0.95	1.60	0.27	
		Mixed	1	9940	2.18	0.68	7.02		
	Intentional vs. unintentional	Intentional	1*	123946	1.08	0.73	1.60	0.88	
		Unintentional	5	246902	1.22	0.96	1.55	0.61	
		Mixed	2	216809	1.19	0.67	2.09		
	Representativeness	No	4	210736	1.06	0.84	1.34	0.32	

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
			Yes	3	252975	1.30	0.93	1.80	
		Validated measure	Yes	3	203655	1.18	0.83	1.69	0.65
			No	4	206869	1.08	0.92	1.27	
		Type of chronic pain	Cancer	1	36803	0.72	0.29	1.79	0.07
			CNCP	4	121699	1.04	0.89	1.22	
			Mixed	2	45153	1.45	1.27	1.65	
	Neuropathic pain	Overdose type	Fatal overdose	2	148562	0.56	0.28	1.14	0.15 [†]
			Non-fatal overdose	5	307236	1.21	1.09	1.35	
		Intentional vs. unintentional	Intentional	1	123946	1.20	0.77	1.87	0.61
			Unintentional	5	246902	0.96	0.70	1.32	0.42
			Mixed	2	208896	1.19	0.82	1.72	
		Type of chronic pain	Cancer	1	36803	0.21	0.03	1.51	0.18
			CNCP	3	371815	0.90	0.52	1.54	0.39
			Mixed	3	47180	1.16	0.95	1.40	
		Representativeness	No	4	210736	0.80	0.54	1.19	0.14 [†]
			Yes	3	245062	1.27	1.15	1.41	
	Validated measure	Yes	3	184728	0.81	0.40	1.65	0.49	
		No	4	271070	1.05	0.86	1.28		
	Appropriate adjustment	Yes	5	400584	1.04	0.79	1.36	0.80	
		No	2	55214	0.95	0.52	1.75		
	Sleep apnea	Type of chronic pain	CNCP	3	869363	1.04	0.88	1.23	0.36
			Mixed	2	45153	1.14	1.01	1.30	
		Representativeness	No	2	9253	0.77	0.22	2.64	0.59
			Yes	3	905263	1.08	0.99	1.17	
		Validated measure	Yes	2	36432	0.73	0.25	2.11	0.47
			No	3	878084	1.08	0.99	1.19	
	HIV/AIDS	Overdose type	Non-fatal overdose	3	672544	1.06	0.86	1.31	0.84
			Mixed	2	53536	1.00	0.59	1.69	
		Intentional vs. unintentional	Unintentional	2	45153	1.39	0.80	2.42	0.26
			Mixed	3	680927	1.01	0.90	1.14	
		Type of chronic pain	CNCP	3	680927	1.01	0.90	1.14	0.26
			Mixed	2	45153	1.39	0.80	2.42	

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value	
		Representativeness	No	2	636378	1.22	0.67	2.23	0.67	
			Yes	3	89702	1.04	0.69	1.58		
		Validated measure	Yes	2	663557	1.01	0.90	1.14	0.50	
			No	3	62523	1.19	0.76	1.87		
Demographic factors	Age: every 10-year decrement	Overdose type	Fatal overdose	5	341104	1.36	0.86	2.14	0.42	
			Non-fatal overdose	10	1950878	1.24	0.99	1.54		
			Mixed	3	13981	1.05	0.86	1.28		
		Intentional vs. unintentional	Intentional	2*	222086	1.50	0.92	2.46	0.08	
			Unintentional	9	1270595	1.08	1.02	1.15		
			Mixed	8	937228	1.31	1.08	1.58		
	Type of chronic pain	Cancer-related chronic pain	1	36803	1.78	0.47	6.66	0.13		
		CNCP	14	2221980	1.26	1.04	1.53			
		Mixed	3	47180	1.04	0.97	1.11			
	Representativeness	No	8	891182	1.27	1.07	1.50	0.60		
		Yes	10	1414781	1.17	0.93	1.48			
	Validated measure	Yes	9	1142809	1.38	1.04	1.84	0.16		
		No	9	1163154	1.13	1.08	1.18			
		Appropriate adjustment	Yes	10	1315845	1.13	1.06		1.20	0.36
			No	8	990118	1.33	0.95		1.86	
	Sex: Male vs. Female	Overdose type	Fatal overdose	5	341104	1.38	0.91	2.09	0.48	
Non-fatal overdose			10	1950878	1.07	1.00	1.15			
Mixed			5	67517	1.11	0.91	1.37			
Intentional vs. unintentional		Intentional	2*	222086	0.86	0.69	1.07	0.07		
		Unintentional	9	1270595	1.14	1.03	1.26			
		Mixed	10	990764	1.07	0.93	1.23			
Type of chronic pain		Cancer	1	36803	1.58	0.44	5.65	0.83		
		CNCP	16	2275516	1.10	1.00	1.22			
		Mixed	3	47180	1.09	1.00	1.18			
Representativeness		No	8	891182	1.08	0.92	1.27	0.84		
		Yes	12	1468317	1.10	0.99	1.22			
Validated measure		Yes	9	1142809	1.17	1.00	1.37	0.35		

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
			No	11	1216690	1.08	1.02	1.15	
		Appropriate adjustment	Yes	12	1369381	1.11	1.05	1.17	0.44
			No	8	990118	1.01	0.81	1.26	
	Non-married vs. Married	Representativeness	No	2	58001	1.28	1.11	1.48	0.52
			Yes	2	869097	1.35	1.27	1.42	
	White Race vs. others	Type of race	White	10	937758	1.36	1.04	1.77	0.19
			Hispanic whaite	4	1026402	1.70	1.39	2.07	
		Overdose type	Fatal overdose	3	299383	1.75	1.24	2.46	0.07 [†]
			Non-fatal overdose	7	1607200	1.70	1.42	2.03	
			Mixed	4	57577	0.88	0.69	1.14	
		Intentional vs. unintentional	Intentional	1	123946	1.99	1.31	3.01	0.27
			Unintentional	8	1231926	1.61	1.29	2.01	
			Mixed	6	732234	1.30	0.95	1.78	
		Type of chronic pain	Cancer	1	36803	1.34	0.66	2.71	0.91
			CNCP	11	1918846	1.52	1.27	1.83	0.76
			Mixed	2	8511	1.39	0.78	2.46	
		Representativeness	No	8	888679	1.59	1.24	2.05	0.47
			Yes	6	1075481	1.41	1.13	1.75	
		Validated measure	Yes	6	976054	1.80	1.57	2.08	0.88 [†]
			No	8	988106	1.36	1.07	1.73	
		Appropriate adjustment	Yes	8	1081454	1.32	1.11	1.57	0.09 [†]
			No	6	882706	1.86	1.46	2.39	
	West vs. Northeast	Type of chronic pain	CNCP	4	508574	1.33	0.97	1.84	0.43
			Mixed	2	15071	1.54	1.32	1.79	
		Intentional vs. unintentional	Unintentional	4	425806	1.54	1.38	1.71	0.05
			Mixed	2	97839	1.00	0.84	1.19	
		Representativeness	No	2	3068	1.79	1.30	2.46	0.19
			Yes	4	520577	1.36	1.08	1.73	
		Validated measure	Yes	2	12143	1.48	1.29	1.693	0.82
			No	4	511502	1.43	1.05	1.933	
	Midwest vs. Northeast	Intentional vs. unintentional	Unintentional	3	322289	1.21	1.09	1.34	0.97
			Mixed	2	72682	1.20	0.87	1.65	

Categories	Predictor	Subgroup factor		No. of studies	Sample size	Adjusted OR & 95% CI			Test of interaction p-value
		Validated measure	Yes	2	17410	1.22	1.09	1.362	0.66
			No	3	377561	1.15	0.93	1.435	
	South vs. Northeast	Intentional vs. unintentional	Unintentional	4	689096	1.12	1.01	1.23	0.35
			Mixed	2	157798	1.00	0.81	1.23	
		Type of chronic pain	CNCP	4	820049	1.06	0.90	1.24	0.63
			Mixed	2	26845	1.11	1.00	1.23	
		Representativeness	No	2	4586	1.19	0.88	1.62	0.57
			Yes	4	842308	1.09	0.99	1.19	
		Validated measure	Yes	2	22577	1.19	0.88	1.619	0.89
			No	4	824317	1.09	0.99	1.189	
	Urban vs. rural areas	Overdose type	Fatal overdose	2	183270	1.03	0.85	1.26	0.67
				Non-fatal overdose	3	922284	1.09	0.94	1.27
		Validated measure	Yes	2	183270	1.03	0.85	1.26	0.67
			No	3	922284	1.09	0.94	1.266	
		Appropriate adjustment	Yes	3	901546	1.07	0.92	1.24	0.99
			No	2	204008	1.07	0.89	1.29	
	Overweight	Overdose type	Non-fatal overdose	3	143293	0.95	0.62	1.47	0.83
				Mixed	2	53536	1.00	0.89	1.13
		Intentional vs. unintentional	Intentional	1*	111312	0.61	0.46	0.79	0.35
			Unintentional	2	45153	1.23	1.08	1.39	
		Type of chronic pain	Mixed	2	53536	1.00	0.89	1.13	
			CNCP	3	151676	0.86	0.63	1.16	0.15
		Validated measure	Mixed	2	45153	1.23	1.08	1.39	
			Yes	2	134306	0.88	0.43	1.81	0.70
			No	3	62523	1.02	0.91	1.14	

OR: odds ratio, 95%CI: 95% confidence interval; CNCP: chronic noncancer pain, SUD: substance use disorder; PTSD: Post-traumatic stress disorder

No subgroup analysis for those predictors or subgroup factors when there are less than 2 studies in a given subgroup.

* One study (Ilgen 2016) that reported intentional overdose had overlapped study population with study Bohnert 2011 for unintentional overdose subgroup.

† p-values from multivariable meta-regression.

eTable 16 Sensitivity analyses to test robustness of results ^{*,#}

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
Opioid dose (every 90-mg increment)	Primary analysis	14	1315173	2.57	2.08	3.18
	Dose reported as continuous data	1	627391	2.41	2.23	2.60
	One-stage dose response analysis	13	687782	2.61	2.03	3.36
	Adjusted OR	6	689357	2.57	2.06	3.20
	Adjusted HR	7	616544	2.99	2.09	4.27
	Adjusted RR	1	9272	1.26	0.89	1.80
	100% Chronic pain	10	640417	2.90	2.07	4.07
	Chronic pain<100%	4	674756	2.08	1.53	2.82
Long- vs short-acting opioids	Primary analysis	9	978745	1.92	1.51	2.45
	Adjusted data reported (without imputation)	9	978745	1.92	1.51	2.45
	Adjusted OR	6	104593	1.66	1.32	2.07
	Adjusted HR	3	874152	2.74	1.92	3.91
	100% Chronic pain	5	880056	1.83	1.29	2.59
	Chronic pain<100%	4	98689	2.07	1.32	3.23
Duration of opioid use	Primary analysis	2	153033	1.01	1.003	1.03
	Adjusted data reported (without imputation)	2	153033	1.01	1.003	1.03
	Adjusted OR	1	2212	1.01	1.00	1.03
	Adjusted HR	1	150821	1.26	1.06	1.51
	100% Chronic pain	2	153033	1.01	1.003	1.03
Number of pharmacies	Primary analysis	2	639823	4.92	4.35	5.57
	Adjusted data reported (without imputation)	2	639823	4.92	4.35	5.57
	Adjusted OR	2	639823	4.92	4.35	5.57
	100% Chronic pain	1	12432	6.00	4.37	8.24
	Chronic pain<100%	1	627391	4.75	4.15	5.44
Number of prescribers	Primary analysis	3	790644	4.68	3.57	6.12
	Adjusted data reported (without imputation)	3	790644	4.68	3.57	6.12
	Adjusted OR	2	639823	4.98	3.04	8.16
	Adjusted HR	1	150821	4.26	3.46	5.25
	100% Chronic pain	2	163253	5.228	3.459	7.903
	Chronic pain<100%	1	627391	3.923	3.581	4.298
Use of benzodiazepines	Primary analysis	12	1246864	1.79	1.46	2.19
	Adjusted data reported (without imputation)	12	1246864	1.79	1.46	2.19

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
	Adjusted OR	8	973690	1.53	1.26	1.87
	Adjusted HR	3	263902	2.39	1.84	3.11
	Adjusted RR	1	9272	2.97	2.41	3.66
	100% Chronic pain	10	1201711	1.84	1.38	2.44
	Chronic pain<100%	2	45153	1.61	1.29	2.02
Sedatives and hypnotics	Primary analysis	6	337924	1.37	1.2	1.56
	Adjusted data reported (without imputation)	6	337924	1.37	1.20	1.56
	Adjusted OR	4	98606	1.31	1.08	1.59
	Adjusted HR	2	239318	1.53	1.28	1.83
	100% Chronic pain	4	292771	1.51	1.20	1.90
	Chronic pain<100%	2	45153	1.29	1.10	1.50
Muscle relaxants	Primary analysis	5	19776855	1.28	1.10	1.50
	Adjusted data reported (without imputation)	5	19776855	1.28	1.10	1.50
	Adjusted OR	4	98606	1.31	1.06	1.63
	Adjusted HR	1	19678250	1.21	1.00	1.47
	100% Chronic pain	3	19731702	1.35	0.97	1.87
	Chronic pain<100%	2	45153	1.27	1.01	1.60
Use of non-opioid analgesics	Primary analysis	3	98340	0.79	0.58	1.09
	Adjusted data reported (without imputation)	3	98340	0.79	0.58	1.09
	Adjusted OR	1	266	0.97	0.41	2.29
	100% Chronic pain	1	53187	0.977	0.688	1.388
	Chronic pain<100%	2	45153	0.73	0.51	1.06
NSAIDs	Primary analysis	3	104920	0.94	0.78	1.14
	Adjusted data reported (without imputation)	3	104920	0.94	0.78	1.14
	Adjusted OR	2	6780	1.04	0.90	1.19
	Adjusted HR	1	98140	0.81	0.64	1.02
	100% Chronic pain	2	98406	0.82	0.66	1.02
	Chronic pain<100%	1	6514	1.04	0.90	1.20
Substance use disorders	Primary analysis	16	1190466	2.32	1.88	2.85
	Excluding tobacco use disorders	16	1190466	2.48	1.76	3.48
	Adjusted data reported (without imputation)	15	1188439	2.41	1.95	2.97
	Adjusted OR	6	678797	2.44	1.76	3.39
	Adjusted HR	9	502397	2.20	1.53	3.16
	Adjusted RR	1	9272	2.03	1.47	2.81
	100% Chronic pain	11	464386	2.04	1.47	2.83
	Chronic pain<100%	5	726080	2.77	2.00	3.85

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
Any mental health disorders	Primary analysis	17	1572200	2.12	1.73	2.61
	Adjusted data reported (without imputation)	17	1572200	2.12	1.73	2.61
	Adjusted OR	8	973690	1.82	1.36	2.43
	Adjusted HR	9	598510	2.43	1.78	3.32
	100% Chronic pain	13	1473511	2.07	1.64	2.62
	Chronic pain<100%	4	98689	2.29	1.32	3.99
Depression or antidepressants	Primary analysis	9	448216	2.22	1.57	3.14
	Adjusted data reported (without imputation)	9	448216	2.22	1.57	3.14
	Adjusted OR	5	100818	1.82	1.14	2.90
	Adjusted HR	4	347398	2.85	1.75	4.66
	100% Chronic pain	7	403063	2.20	1.32	3.67
	Chronic pain<100%	2	45153	2.25	1.17	4.33
Bipolar disorder	Primary analysis	3	98340	2.07	1.77	2.41
	Adjusted data reported (without imputation)	3	98340	2.07	1.77	2.41
	Adjusted OR	3	98340	2.07	1.77	2.41
	100% Chronic pain	1	53187	1.76	0.54	5.77
	Chronic pain<100%	2	45153	2.02	1.61	2.53
Psychotic disorders or use of antipsychotics	Primary analysis	6	410629	1.59	1.16	2.19
	Adjusted data reported (without imputation)	6	410629	1.59	1.16	2.19
	Adjusted OR	3	47365	1.21	1.09	1.34
	Adjusted HR	3	363264	2.45	2.06	2.92
	100% Chronic pain	3	241530	1.71	0.94	3.10
	Chronic pain<100%	3	169099	1.44	1.06	1.95
Tobacco use or use disorder	Primary analysis	7	210544	1.57	1.37	1.81
	Adjusted data reported (without imputation)	7	210544	1.57	1.37	1.81
	Adjusted OR	3	48928	1.50	1.18	1.91
	Adjusted HR	4	161616	1.71	1.40	2.09
	100% Chronic pain	4	98689	1.72	1.39	2.13
	Chronic pain<100%	3	111855	1.52	1.23	1.88
Anxiety	Primary analysis	5	271300	1.28	1.02	1.61
	Adjusted data reported (without imputation)	5	271300	1.28	1.02	1.61
	Adjusted OR	3	98340	1.34	0.96	1.86
	Adjusted HR	2	172960	1.18	0.95	1.46
	100% Chronic pain	2	102201	1.12	0.87	1.45
	Chronic pain<100%	3	169099	1.36	1.03	1.79

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
PTSD	Primary analysis	5	271300	1.08	0.78	1.5
	Adjusted data reported (without imputation)	5	271300	1.08	0.78	1.5
	Adjusted OR	3	98340	1.00	0.83	1.19
	Adjusted HR	2	172960	1.26	0.49	3.24
	100% Chronic pain	1	49014	1.31	0.48	3.55
	Chronic pain<100%	3	169099	0.96	0.81	1.13
Schizophrenia	Primary analysis	3	98340	1.78	1.20	2.65
	Adjusted data reported (without imputation)	3	98340	1.78	1.20	2.65
	Adjusted OR	3	98340	1.78	1.20	2.65
	100% Chronic pain	1	53187	1.20	0.16	9.00
	Chronic pain<100%	2	45153	1.81	1.21	2.71
History of overdose	Primary analysis	4	967503	4.83	3.34	6.99
	Adjusted data reported (without imputation)	4	967503	4.83	3.34	6.99
	Adjusted OR	4	967503	4.83	3.34	6.99
	100% Chronic pain	4	967503	4.83	3.34	6.99
Injury & acute pain	Primary analysis	5	203655	1.42	1.27	1.59
	Adjusted data reported (without imputation)	5	203655	1.42	1.27	1.59
	Adjusted OR	2	45153	1.44	1.26	1.63
	Adjusted HR	3	158502	1.38	0.93	2.04
	Chronic pain<100%	5	203655	1.42	1.27	1.59
Renal disease	Primary analysis	5	726080	1.35	1.01	1.79
	Adjusted data reported (without imputation)	3	672544	1.64	1.30	2.08
	Adjusted OR	3	672544	1.64	1.30	2.08
	Adjusted HR	2	53536	1.00	0.88	1.14
	Chronic pain<100%	5	726080	1.35	1.01	1.79
COPD	Primary analysis	8	1595443	1.34	1.19	1.49
	Adjusted data reported (without imputation)	6	1541907	1.42	1.30	1.56
	Adjusted OR	6	1541907	1.422	1.295	1.56
	Adjusted HR	2	53536	1.00	0.80	1.25
	100% Chronic pain	3	869363	1.44	1.22	1.71
Liver diseases	Chronic pain<100%	5	726080	1.27	1.08	1.49
	Primary analysis	6	726346	1.24	1.13	1.36

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
	Adjusted data reported (without imputation)	4	672810	1.26	1.14	1.39
	Adjusted OR	4	672810	1.26	1.14	1.39
	Adjusted HR	2	53536	1.00	0.68	1.47
	100% Chronic pain	1	266	0.79	0.20	3.07
	Chronic pain<100%	5	726080	1.25	1.13	1.37
Neck/Back pain	Primary analysis	6	317176	1.12	0.97	1.28
	Adjusted data reported (without imputation)	5	315149	1.12	0.97	1.29
	Adjusted OR	3	98340	1.17	0.99	1.39
	Adjusted HR	3	218836	1.03	0.91	1.17
	100% Chronic pain	4	272023	1.02	0.90	1.15
	Chronic pain<100%	2	45153	1.21	1.04	1.40
Charlson comorbidity index	Primary analysis	4	76174	1.14	1.02	1.27
	Adjusted data reported (without imputation)	4	76174	1.14	1.02	1.27
	Adjusted OR	2	56962	1.25	1.16	1.35
	Adjusted HR	1	9940	0.93	0.75	1.14
	Adjusted RR	1	9272	1.13	1.08	1.19
	100% Chronic pain	4	76174	1.14	1.02	1.27
Headache	Primary analysis	7	463711	1.18	0.95	1.47
	Adjusted data reported (without imputation)	7	463711	1.18	0.95	1.47
	Adjusted OR	3	98340	1.46	1.32	1.61
	Adjusted HR	4	365371	1.03	0.89	1.21
	100% Chronic pain	5	418558	1.03	0.88	1.21
	Chronic pain<100%	2	45153	1.45	1.27	1.65
Fibromyalgia	Primary analysis	3	47180	1.12	1.00	1.26
	Adjusted data reported (without imputation)	2	45153	1.12	1.00	1.26
	Adjusted OR	2	45153	1.12	1.00	1.26
	Adjusted HR	1	2027	1.00	0.53	1.87
	100% Chronic pain	1	2027	1.00	0.53	1.87
	Chronic pain<100%	2	45153	1.12	1.00	1.26
Cancer	Primary analysis	5	786330	1.20	1.02	1.40
	Adjusted data reported (without imputation)	4	784303	1.22	1.03	1.45
	Adjusted OR	3	672544	1.28	1.07	1.52
	Adjusted HR	2	113786	0.99	0.77	1.28

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
Neuropathic pain	100% Chronic pain	2	113786	0.99	0.77	1.28
	Chronic pain<100%	3	672544	1.276	1.07	1.52
	Primary analysis	7	455798	1.04	0.82	1.31
	Adjusted data reported (without imputation)	6	453771	1.03	0.80	1.33
	Adjusted OR	3	98340	1.16	0.94	1.43
	Adjusted HR	3	150589	0.87	0.54	1.41
Sleep apnea	100% Chronic pain	5	410645	0.87	0.58	1.32
	Chronic pain<100%	2	45153	1.16	0.92	1.47
	Primary analysis	5	914516	1.09	0.98	1.21
	Adjusted data reported (without imputation)	5	914516	1.09	0.98	1.21
	Adjusted OR	5	914516	1.09	0.98	1.21
	100% Chronic pain	2	45153	1.14	1.01	1.30
HIV/AIDS	Chronic pain<100%	3	869363	1.04	0.88	1.23
	Primary analysis	5	726080	1.03	0.91	1.15
	Adjusted data reported (without imputation)	3	672544	1.06	0.86	1.31
	Adjusted OR	3	672544	1.06	0.86	1.31
	Adjusted HR	2	53536	1.00	0.59	1.69
	Chronic pain<100%	5	726080	1.03	0.91	1.15
Number of drugs	Primary analysis	3	132801	0.99	0.94	1.04
	Adjusted data reported (without imputation)	3	132801	0.99	0.94	1.04
	Adjusted OR	1	2212	0.98	0.97	1.00
	Adjusted HR	2	130589	0.98	0.87	1.11
	100% Chronic pain	3	132801	0.99	0.94	1.04
	Age (every 10-year decrement)	Primary analysis	18	2305963	1.22	1.02
Adjusted data reported (without imputation)		16	2303670	1.23	1.03	1.47
Age reported as continuous data only (without categorical data)		10	1277074	1.31	1.04	1.66
Adjusted OR		8	1598869	1.10	1.07	1.14
Adjusted HR		9	697822	1.32	1.04	1.67
Adjusted RR		1	9272	2.57	0.58	11.35
100% Chronic pain		15	1633419	1.25	1.03	1.52
Chronic pain<100%		3	672544	1.07	0.90	1.26
Primary analysis		20	2359499	1.1	1.01	1.19

Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
Sex (male vs. female)	Adjusted data reported (without imputation)	17	2303936	1.10	1.01	1.20
	Adjusted OR	8	1598869	1.11	1.07	1.16
	Adjusted HR	11	751358	1.15	0.95	1.39
	Adjusted RR	1	9272	0.75	0.54	1.04
	100% Chronic pain	15	1633419	1.12	0.97	1.29
Non-married vs Married	Chronic pain<100%	5	726080	1.10	1.01	1.19
	Primary analysis	4	927098	1.34	1.27	1.41
	Adjusted data reported (without imputation)	4	927098	1.34	1.27	1.41
	Adjusted OR	3	878084	1.34	1.27	1.42
	Adjusted HR	1	49014	1.15	0.83	1.59
White race vs others	100% Chronic pain	3	918111	1.34	1.27	1.42
	Chronic pain<100%	1	8987	1.31	1.12	1.54
	Primary analysis	14	1964160	1.50	1.28	1.77
	Adjusted data reported (without imputation)	11	1908597	1.64	1.39	1.94
	Adjusted OR	7	1560200	1.60	1.28	2.00
West vs Northeast	Adjusted HR	7	403960	1.39	1.08	1.79
	100% Chronic pain	10	1276749	1.51	1.23	1.86
	Chronic pain<100%	4	687411	1.45	1.06	2.00
	Primary analysis	6	523645	1.43	1.16	1.76
	Adjusted data reported (without imputation)	6	523645	1.43	1.16	1.76
Midwest vs Northeast	Adjusted OR	5	425876	1.54	1.38	1.71
	100% Chronic pain	4	508574	1.33	0.97	1.84
	Chronic pain<100%	2	15071	1.54	1.32	1.79
	Primary analysis	5	394971	1.21	1.09	1.33
	Adjusted data reported (without imputation)	5	394971	1.21	1.09	1.33
South vs Northeast	Adjusted OR	4	322376	1.206	1.088	1.337
	100% Chronic pain	4	377648	1.15	0.93	1.43
	Chronic pain<100%	1	17323	1.22	1.09	1.36
	Primary analysis	6	846894	1.09	1.004	1.19
	Adjusted data reported (without imputation)	6	846894	1.09	1.004	1.19
	Adjusted OR	5	689255	1.115	1.014	1.226
	100% Chronic pain	2	26845	1.11	1.00	1.23

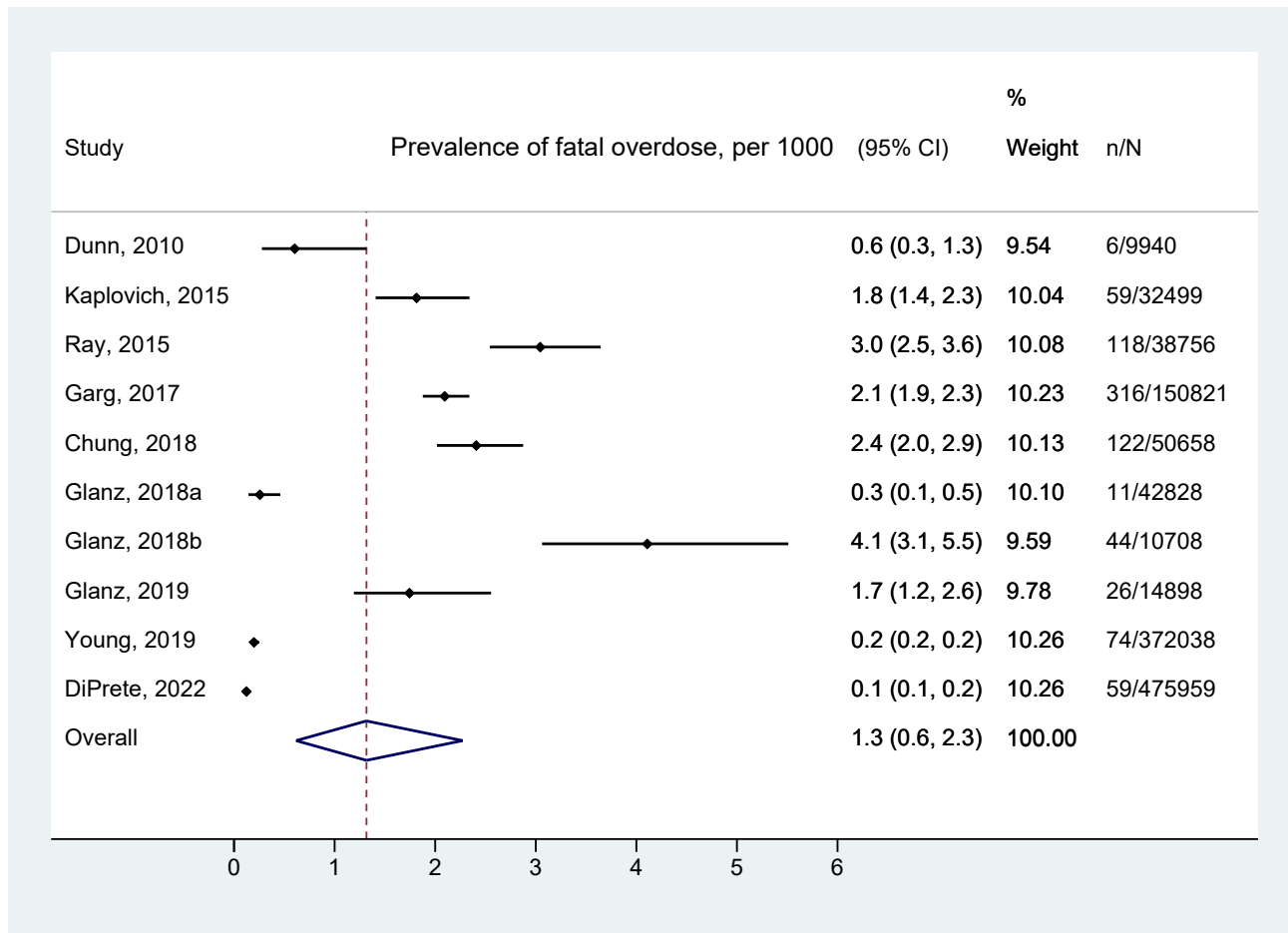
Predictor name	Approaches	No. of studies	Sample size	Adjusted OR & 95%CI		
Urban vs rural areas	Chronic pain<100%	4	820049	1.06	0.90	1.24
	Primary analysis	5	1105554	1.07	0.95	1.20
	Adjusted data reported (without imputation)	4	1073105	1.08	0.95	1.22
	Adjusted OR	3	922284	1.09	0.94	1.27
	Adjusted HR	2	183270	1.03	0.85	1.26
Overweight/obesity	Primary analysis	5	196829	0.98	0.79	1.22
	Adjusted data reported (without imputation)	3	143293	0.95	0.62	1.47
	Adjusted OR	2	45153	1.23	1.08	1.39
	Adjusted HR	3	151676	0.86	0.63	1.16
	100% Chronic pain	1	98140	0.61	0.46	0.79
	Chronic pain<100%	4	98689	1.10	0.96	1.26

OR: odds ratio, 95%CI: 95% confidence interval, HR: hazards ratio, RR: relative risk, PTSD: Post-traumatic stress disorder, COPD: Chronic obstructive pulmonary disease, NSAIDs: Non-steroidal anti-inflammatory drugs, HIV: human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome

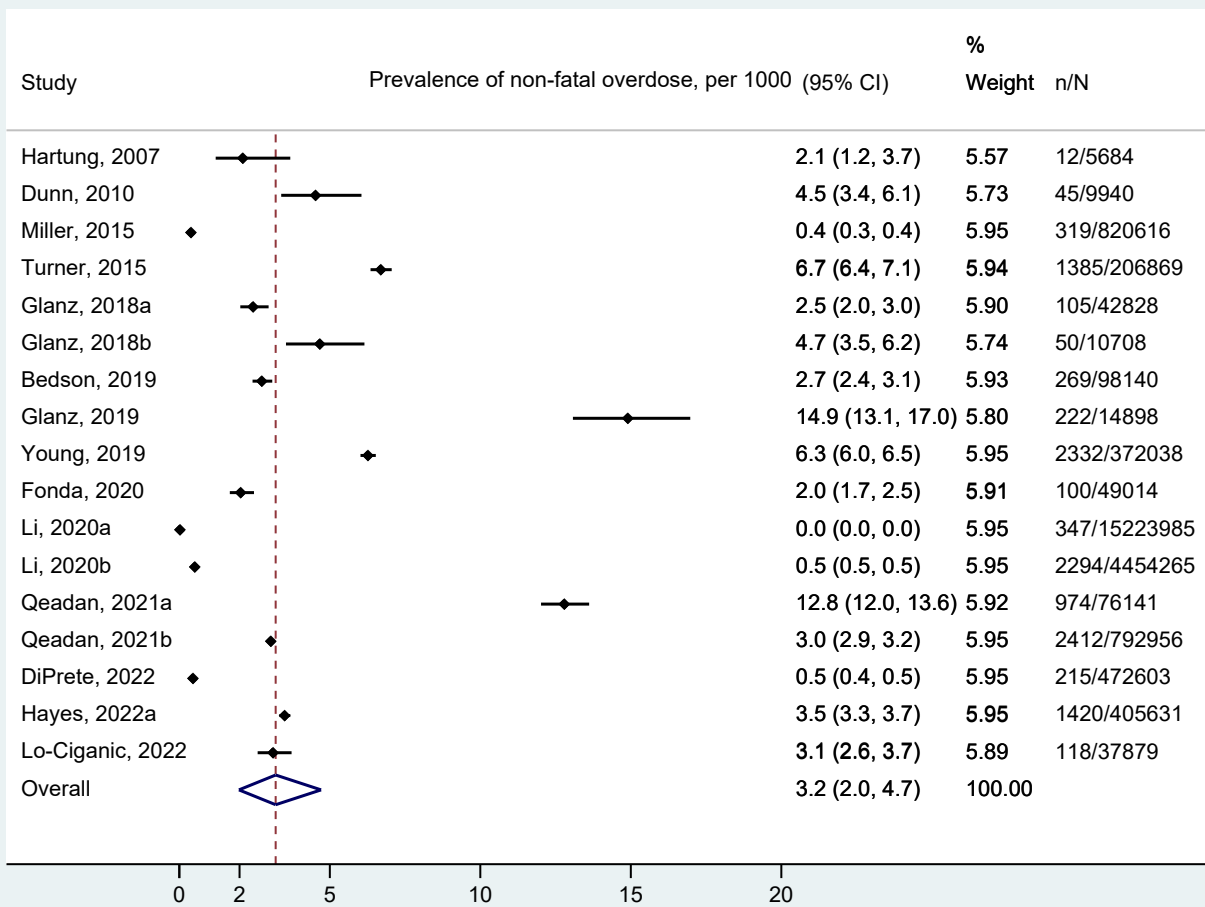
* Factors were reported by two studies with HR/OR among 100% patients with chronic pain: opioid schedule, number of naloxone prescriptions, or medical insurance.

Factors were reported by two or three studies with OR among patients mixed with acute pain (<20%): route of administration, myocardial infarction, cerebrovascular diseases, pancreatitis, heart failure, cardiovascular disease, diabetes, hypertension, hemiplegia or paraplegia, peripheral vascular disease, skin ulcers, peptic ulcer disease, skin infections/abscesses, burns, herpes simplex infection, dementia, sexually transmitted disease, warfarin, stimulants, serious autoimmune rheumatology disease, or days of hospitalization during the preceding 6 months.

eFigure 1 Meta-analysis of the prevalence of opioid overdose

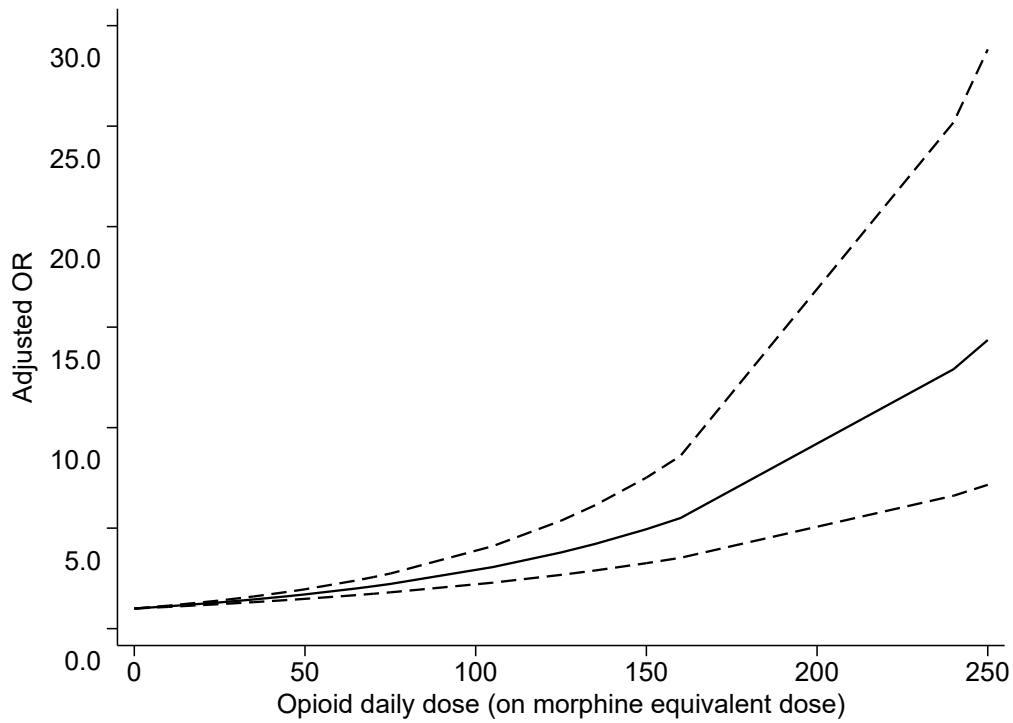


eFigure 1A Pooled prevalence of fatal overdose



eFigure 1B Pooled prevalence of non-fatal overdose

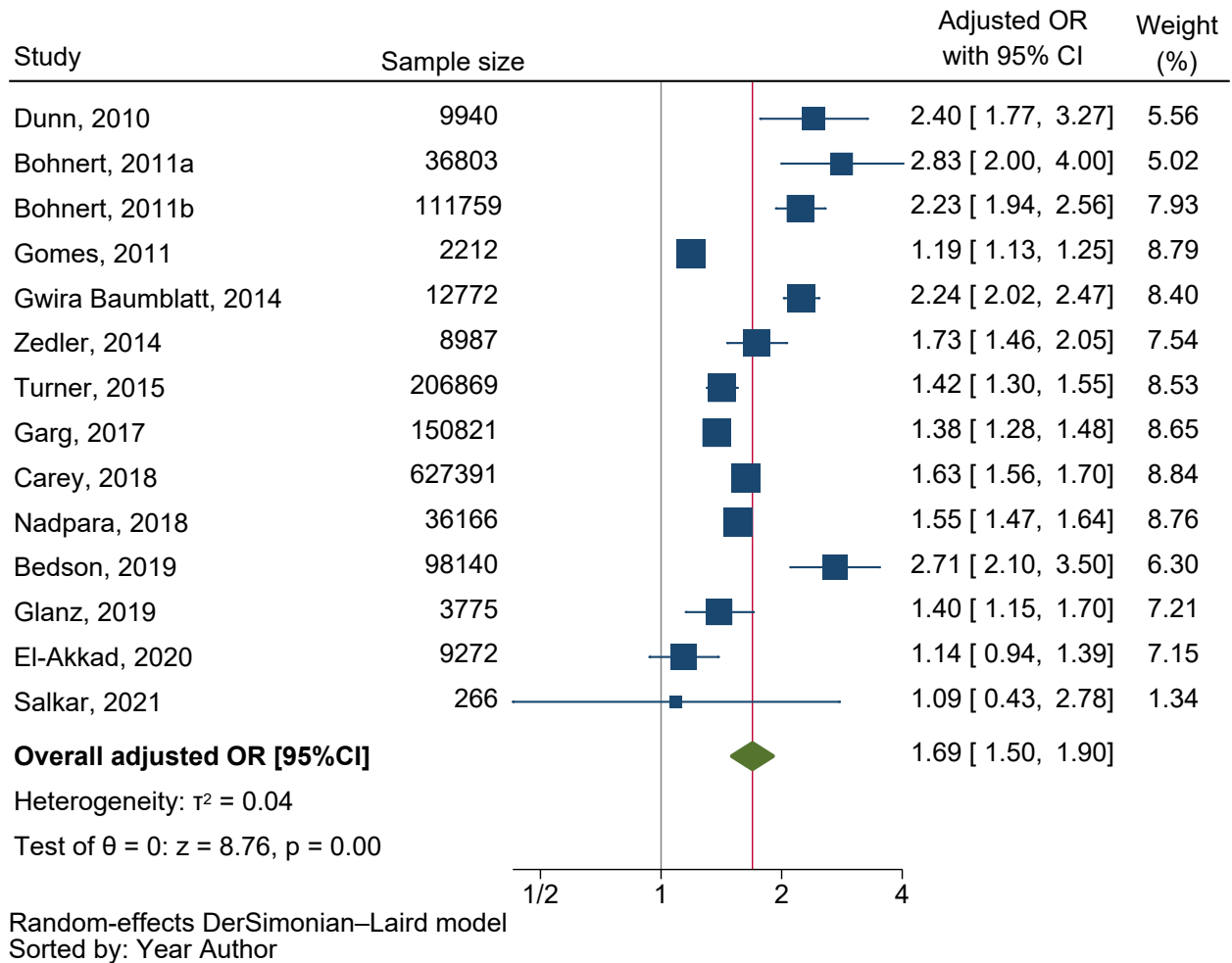
eFigure 2 Meta-analysis of the association of opioid prescribing factors



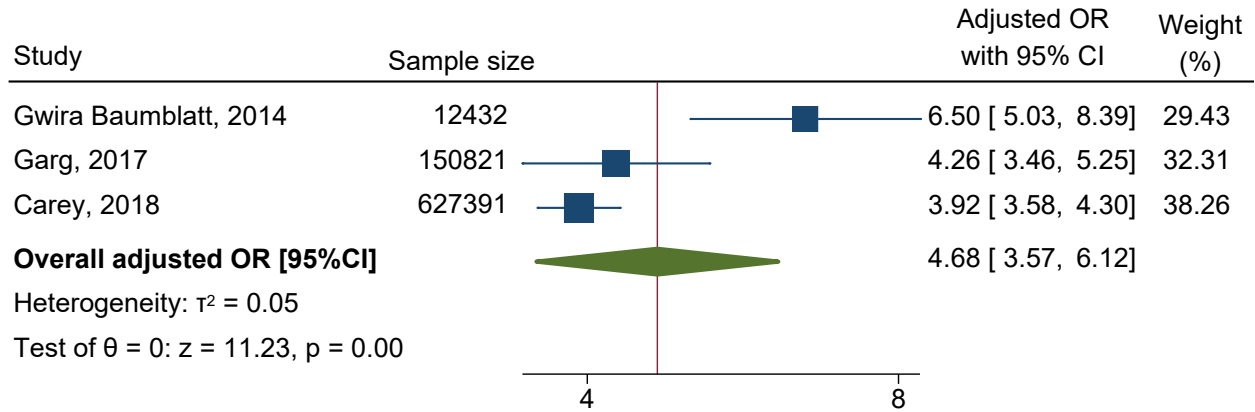
eFigure 2A Dose-response relationship between opioid dose and fatal/nonfatal overdose
OR: odds ratio

P=0.006 for linear dose-response trend

P=0.45 for restricted cubic splines trend analysis (non-linear relationship)

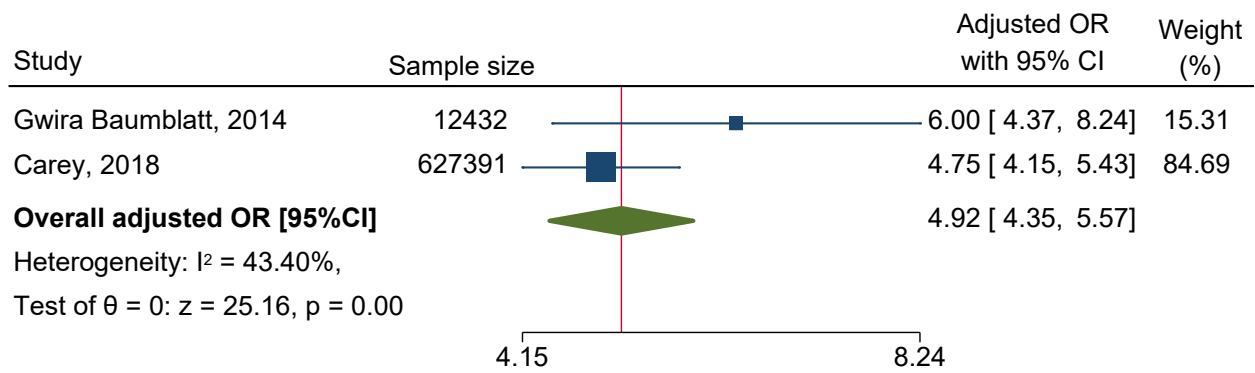


eFigure 2B Predictor of opioid dose (every 50mg increment on a morphine equivalent dose)



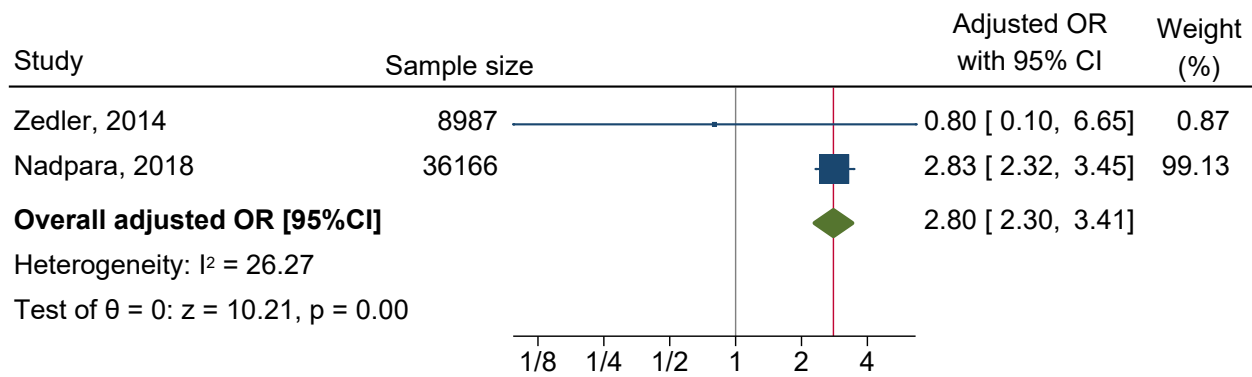
Random-effects DerSimonian–Laird model
 Sorted by: Year Author

eFigure 2C Predictor of multiple opioid prescribers: ≥ 3 vs. less



Fixed-effects inverse-variance model
 Sorted by: Year Author

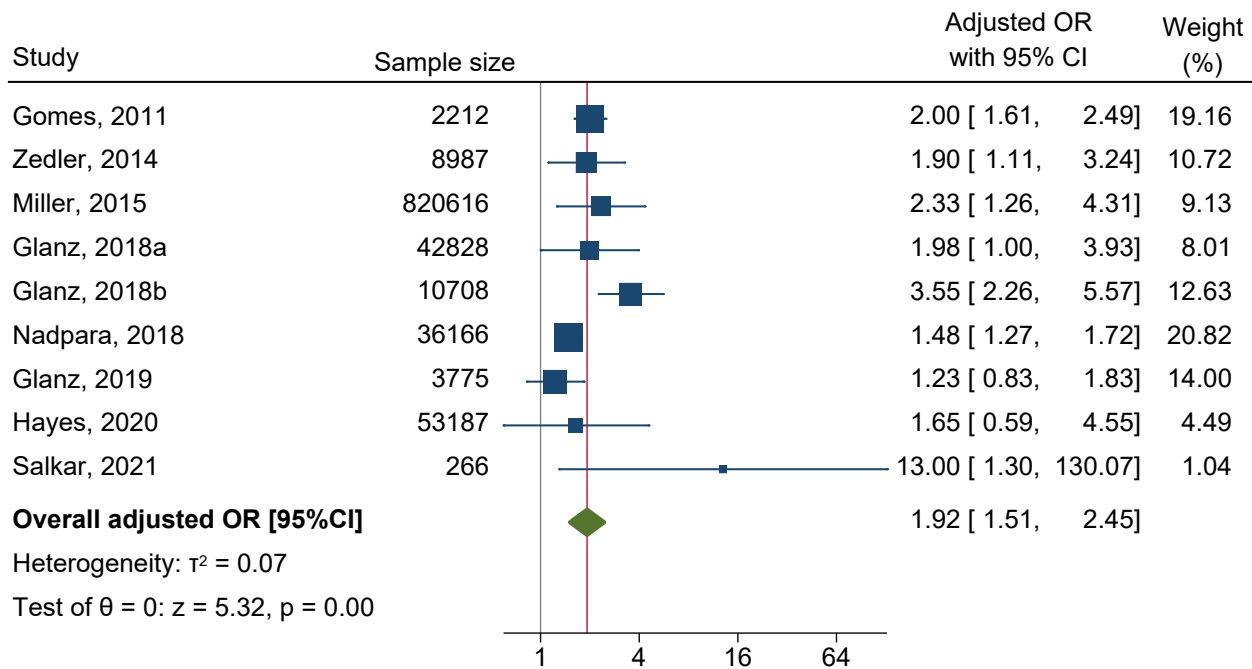
eFigure 2D Predictor of opioid dispensing at multiple pharmacies: ≥ 4 vs. less
 *Fixed-effects model was used for pooling two studies



Fixed-effects inverse-variance model
Sorted by: Year Author

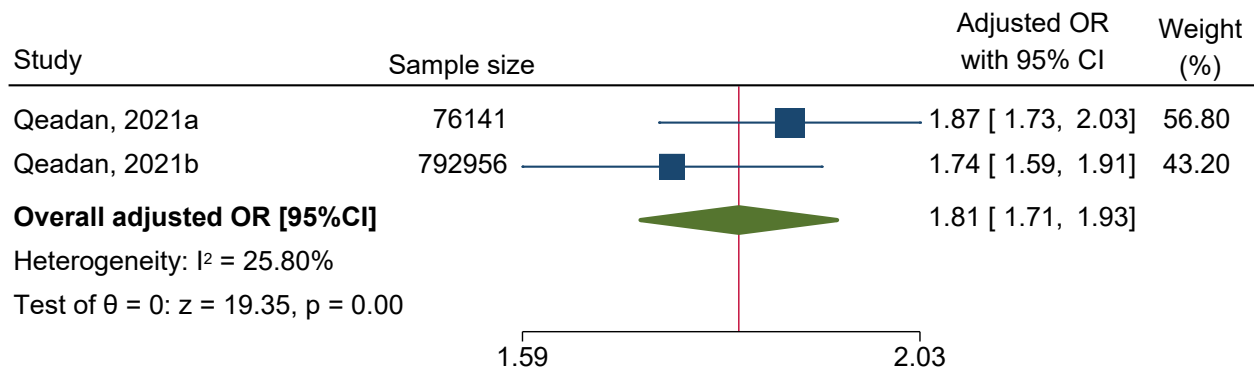
eFigure 2E Predictor of fentanyl (including both transmucosal and transdermal fentanyl)

*Fixed-effects model was used for pooling two studies



Random-effects DerSimonian–Laird model
Sorted by: Year Author

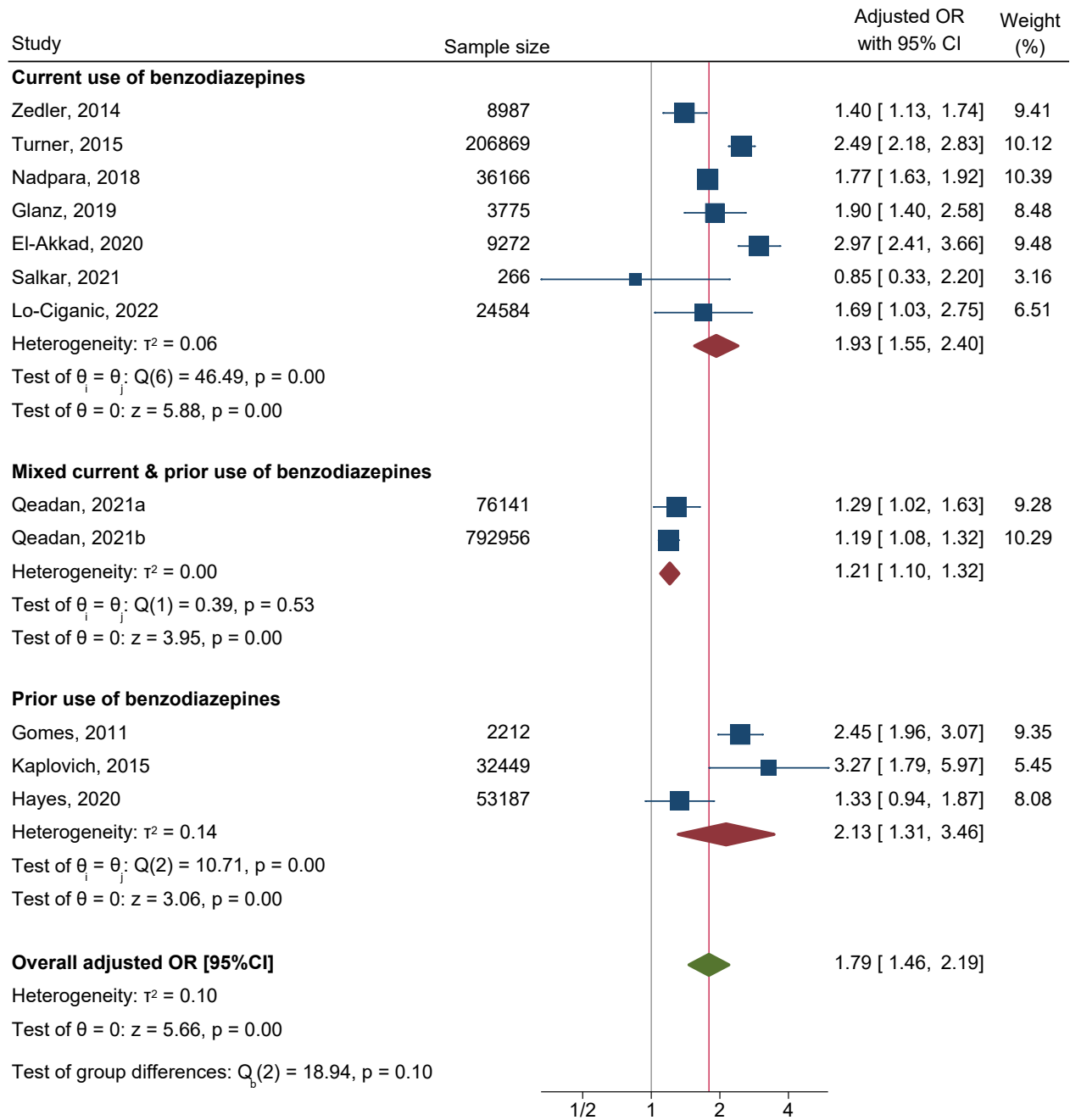
eFigure 2F Predictor of long- vs. short-acting opioids



Fixed-effects inverse-variance model
 Sorted by: Year Author

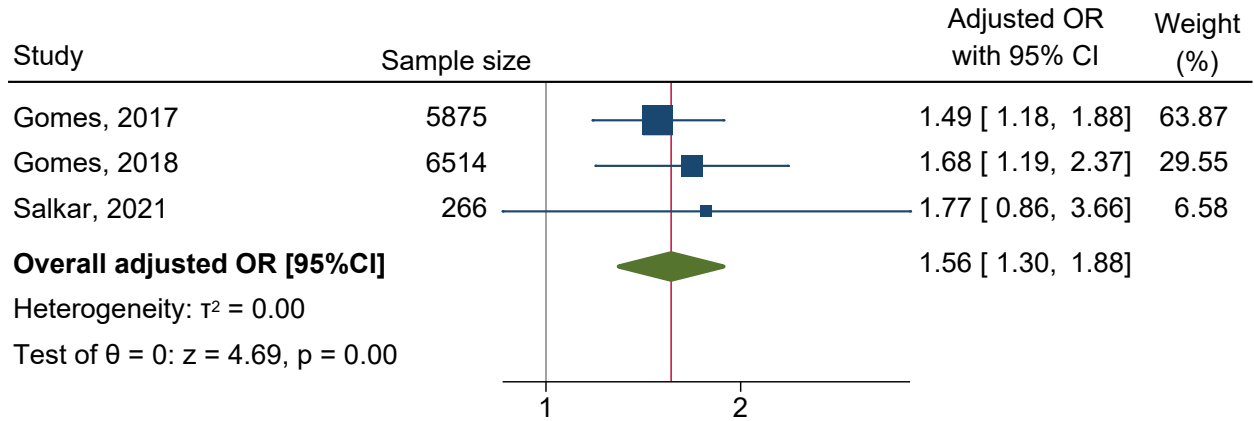
eFigure 2G Predictor of number of naloxone prescriptions
 *Fixed-effects model was used for pooling two studies

eFigure 3 Meta-analysis of the association of co-medication factors



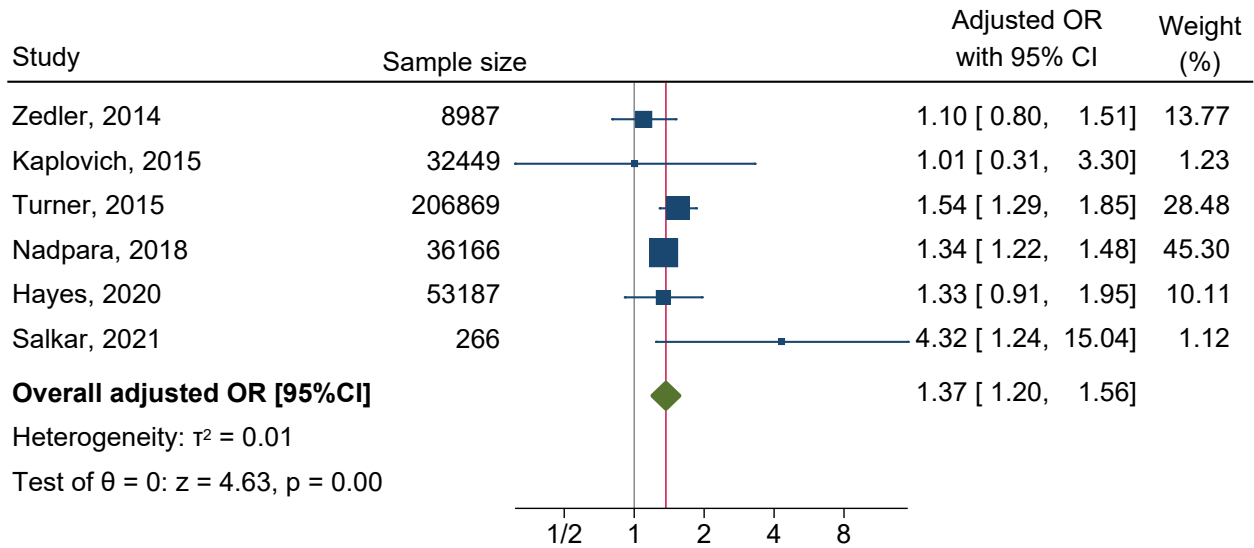
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 3A Predictor of use of benzodiazepines: current vs history
*test of interaction=0.10



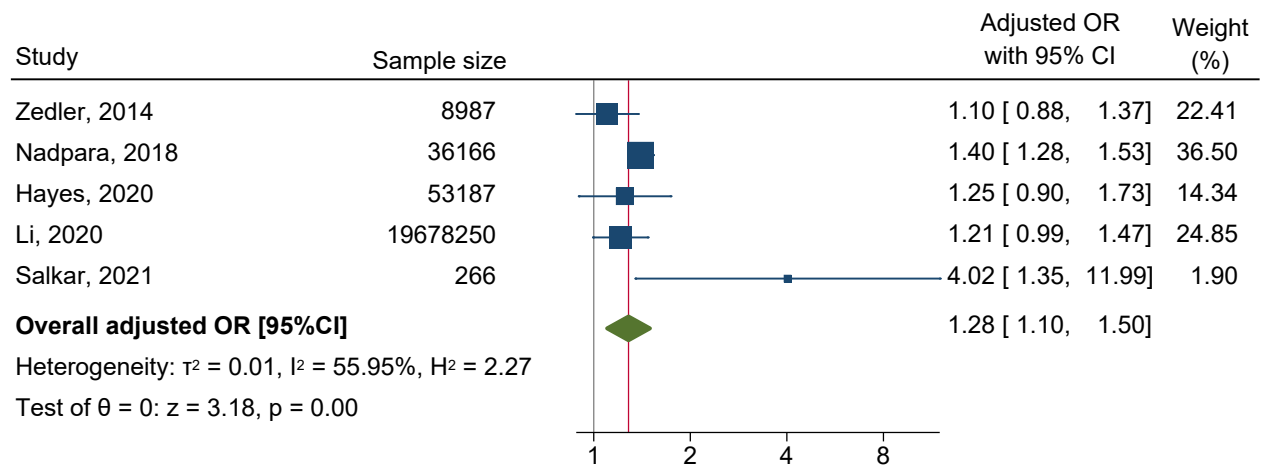
Random-effects DerSimonian–Laird model
 Sorted by: Year Author

eFigure 3B Predictor of anticonvulsants



Random-effects DerSimonian–Laird model
 Sorted by: Year Author

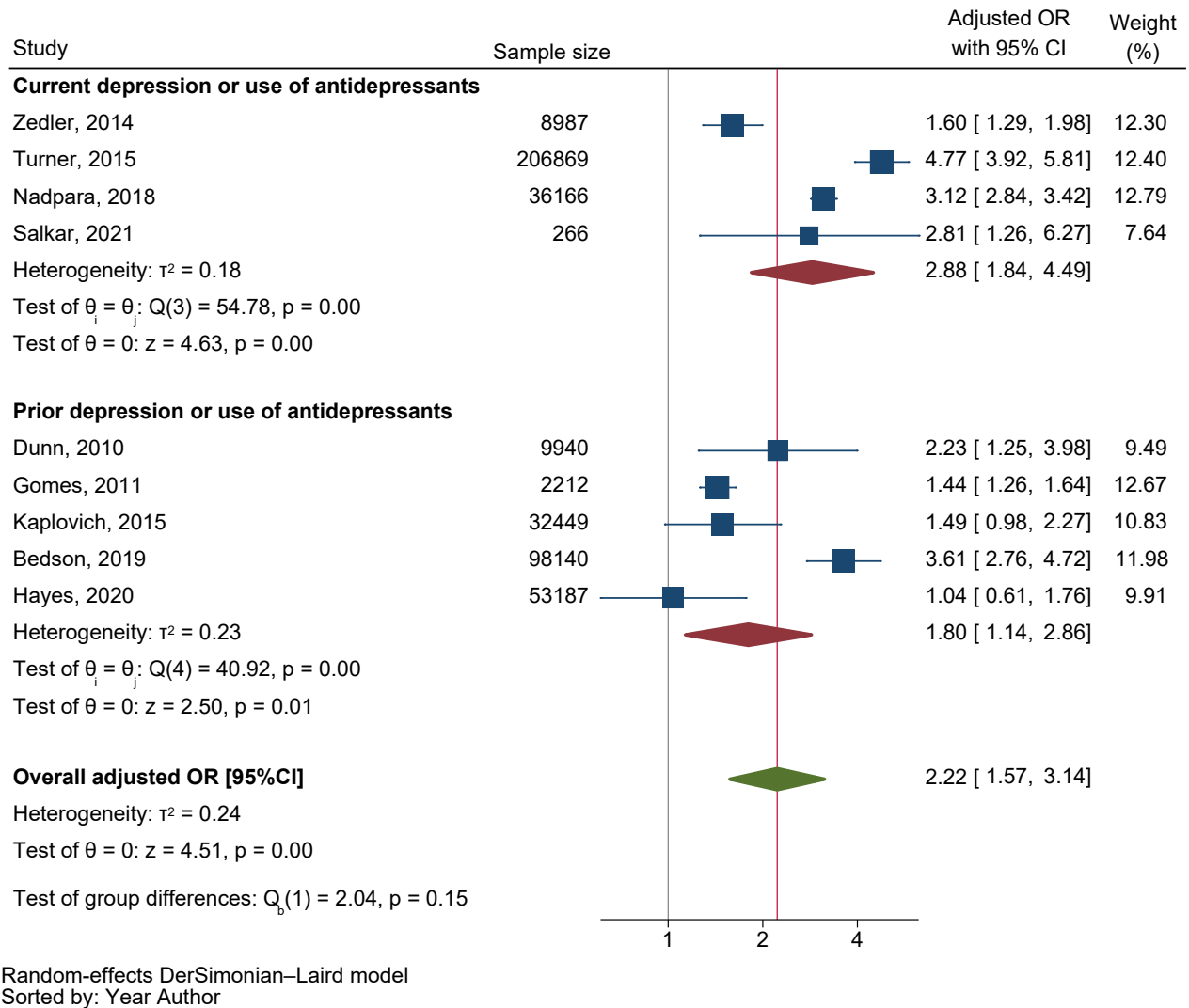
eFigure 3C Predictor of sedatives and hypnotics



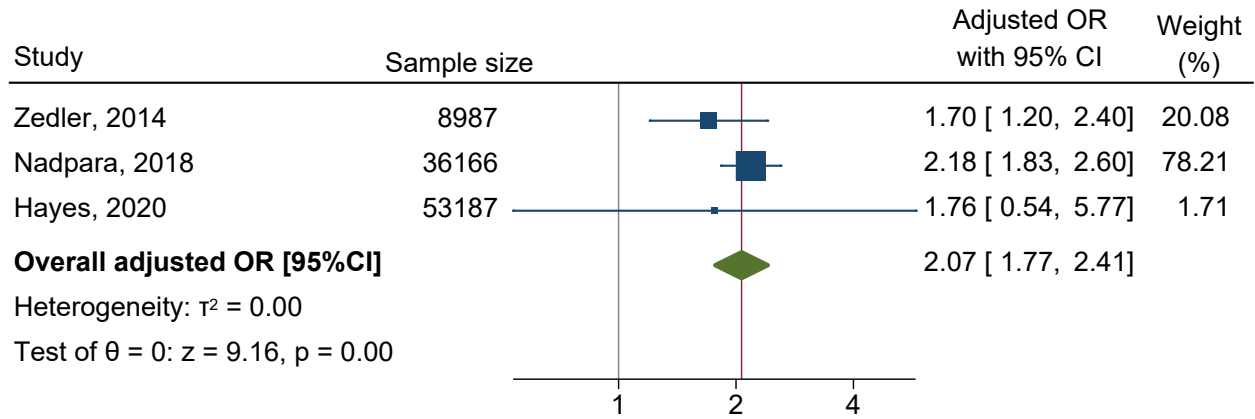
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 3D Predictor of muscle relaxants

eFigure 4 Meta-analysis of the association of psychological factors

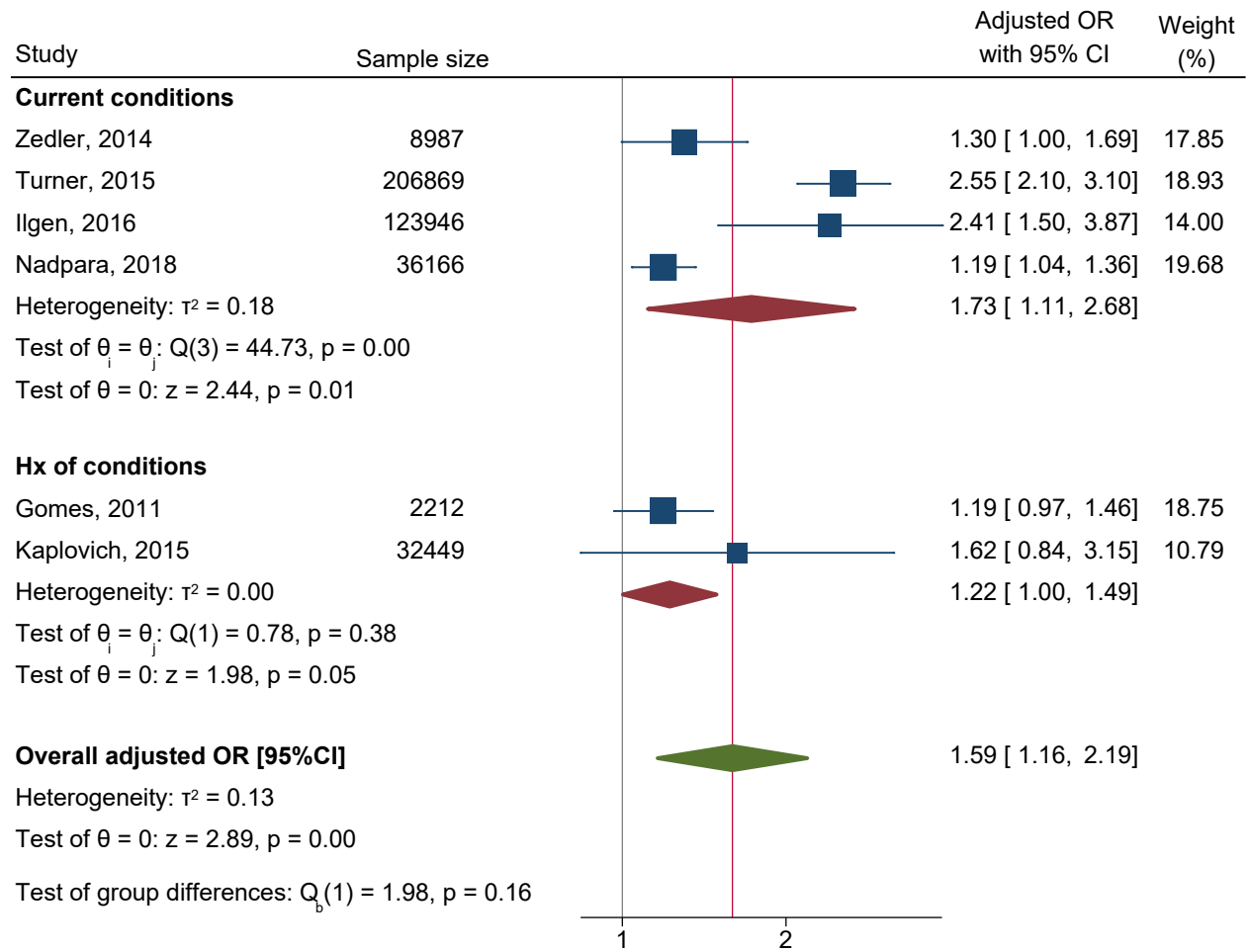


eFigure 4A Predictor of depression or use of antidepressants: current vs history
*test of interaction=0.15



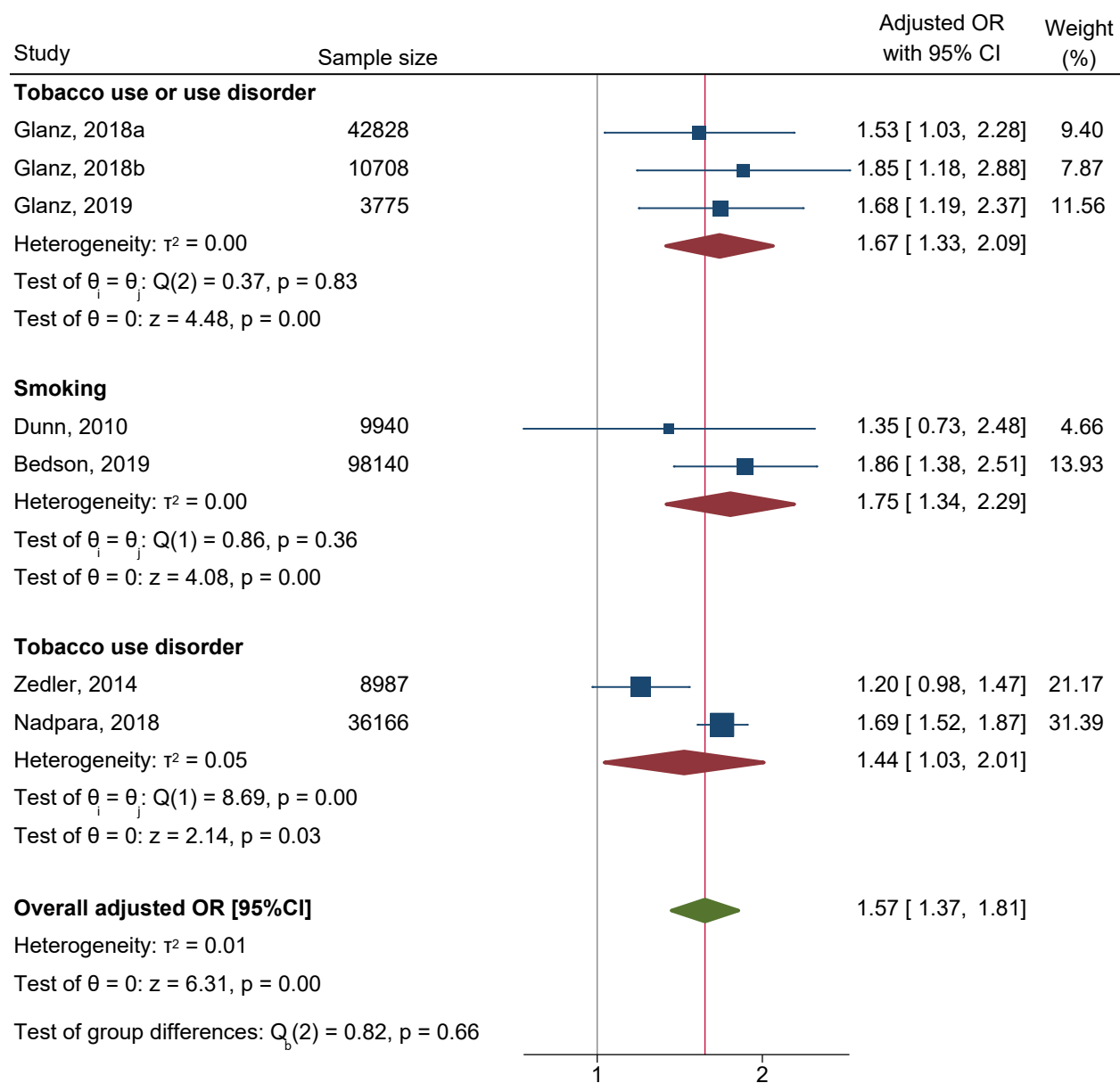
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 4B Predictor of bipolar disorder



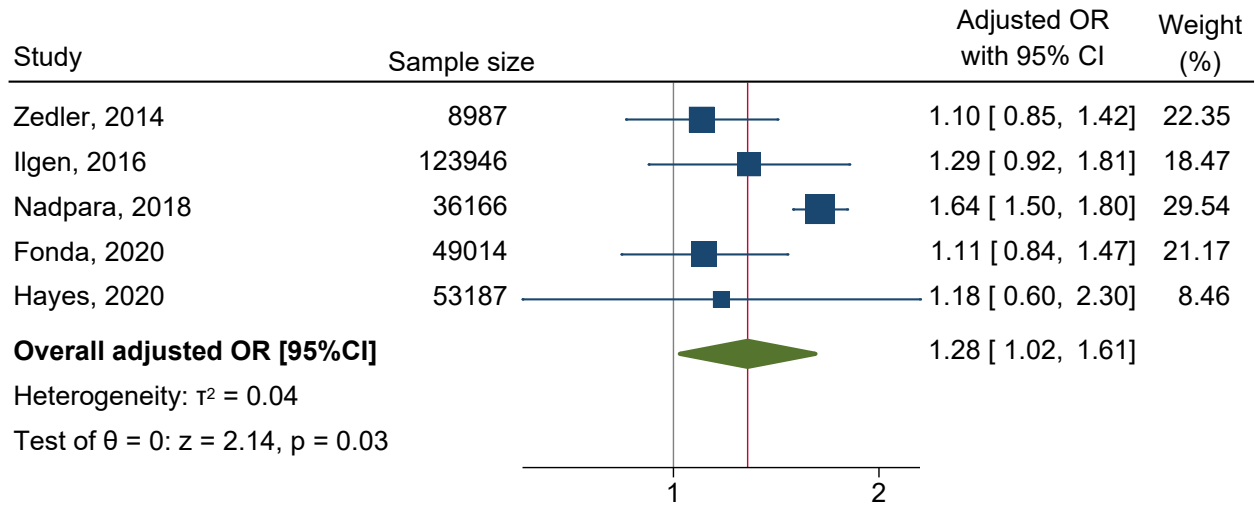
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 4C Predictor of psychotic disorders or use of antipsychotics: current vs history
*test of interaction=0.16



Random-effects DerSimonian–Laird model
Sorted by: Year Author

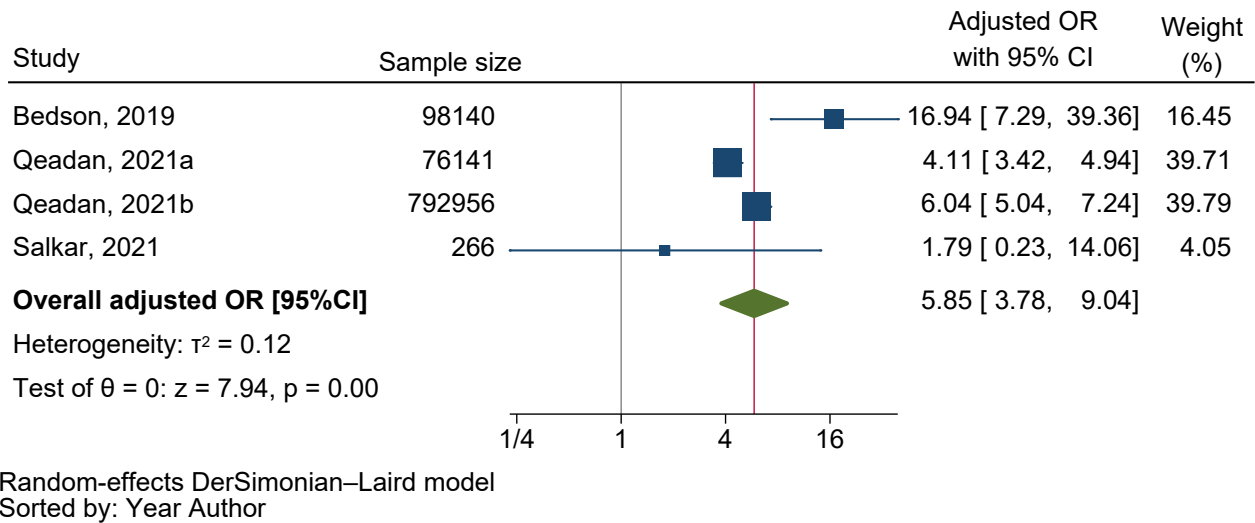
eFigure 4D Predictor of tobacco use or use disorder: tobacco use vs. tobacco use disorder
* test of interaction $p=0.66$



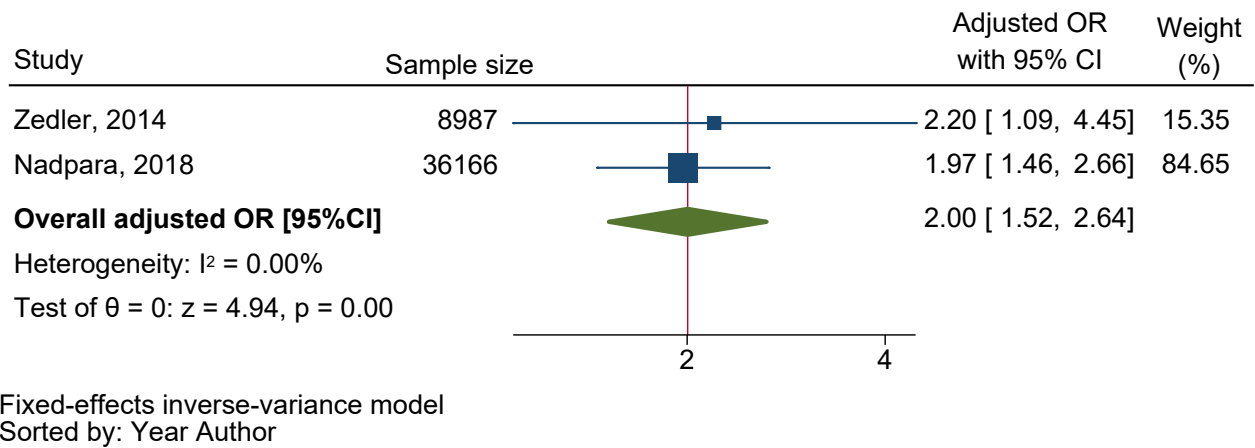
Random-effects DerSimonian–Laird model
 Sorted by: Year Author

eFigure 4E Predictor of anxiety

eFigure 5 Meta-analysis of the association of medical factors



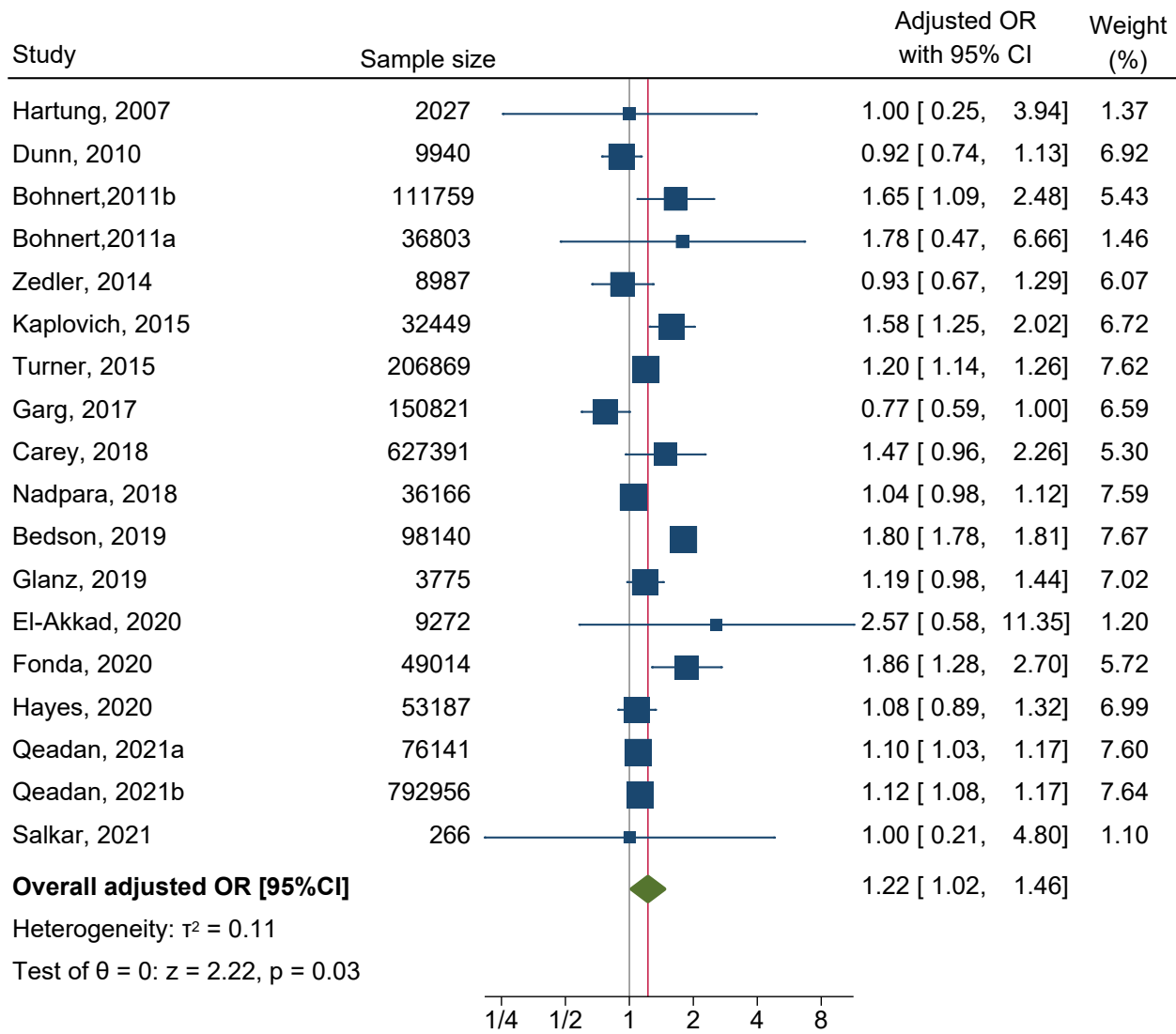
eFigure 5A Predictor of previous overdose



eFigure 5B Predictor of pancreatitis

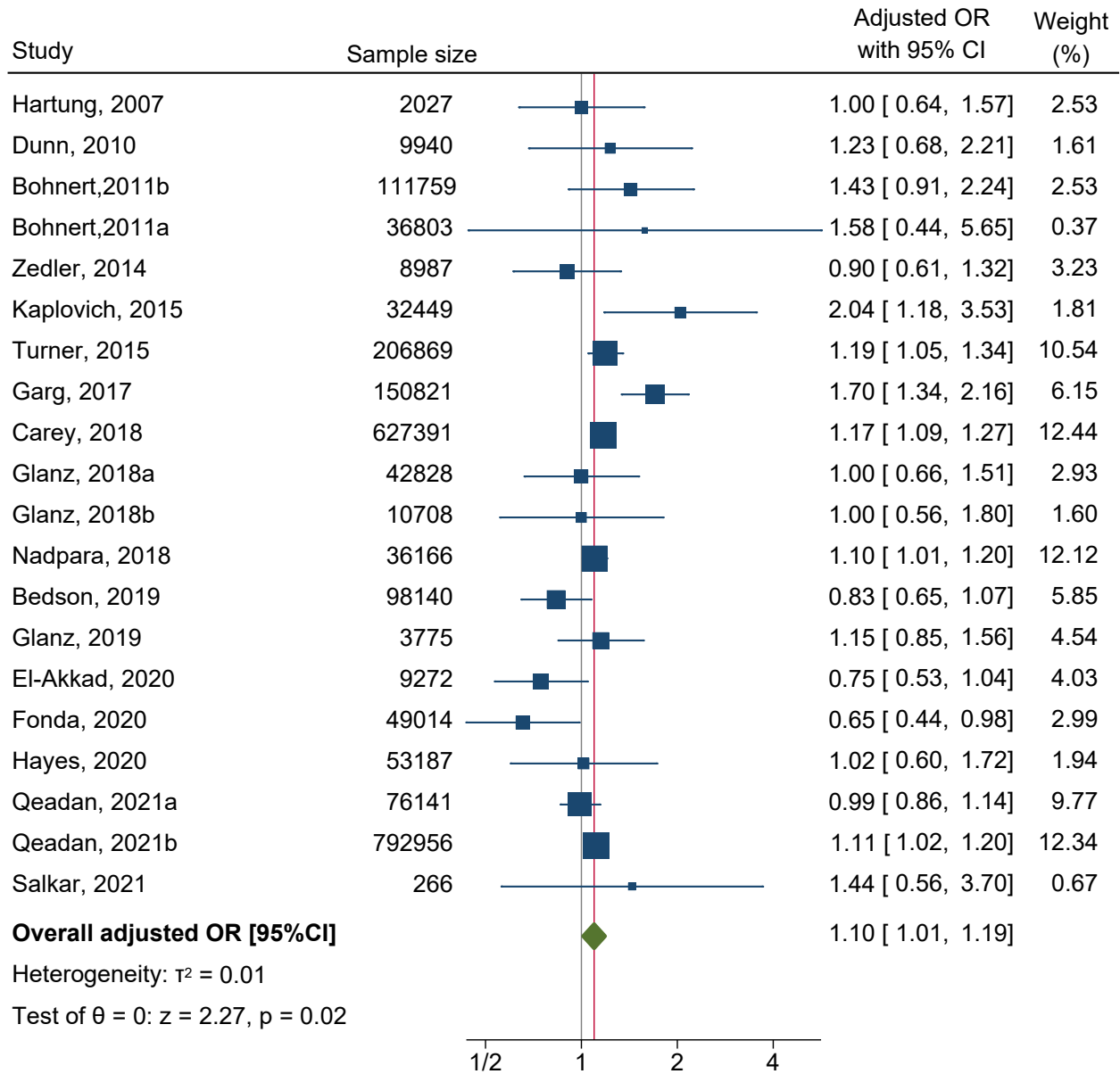
*Fixed-effects model was used for pooling two studies

eFigure 6 Meta-analysis of the association of socio-demographic factors



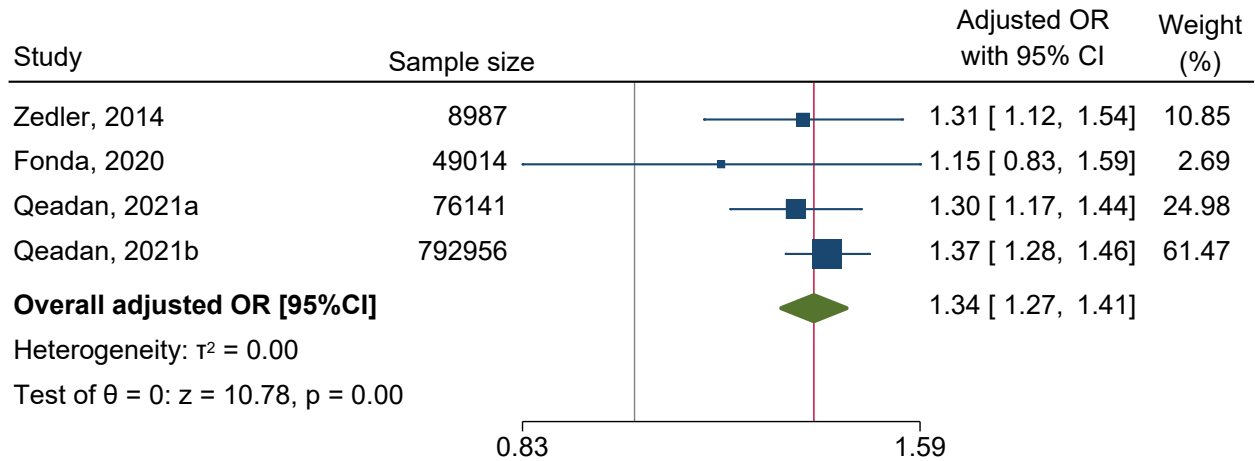
Random-effects DerSimonian–Laird model
 Sorted by: Year Author

eFigure 6A Predictor of age (every 10-year decrement)



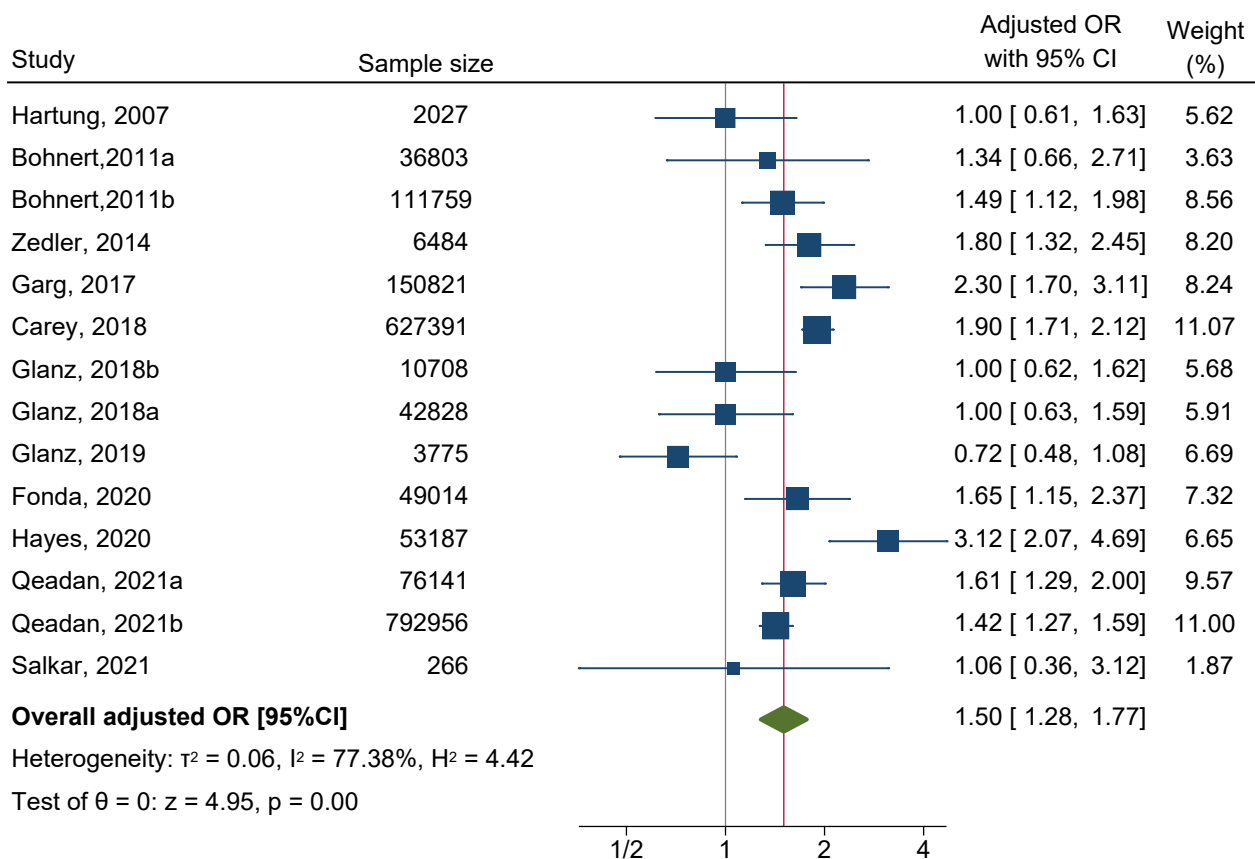
Random-effects DerSimonian–Laird model
 Sorted by: Year Author

eFigure 6B Predictor of sex (Male vs. Female)



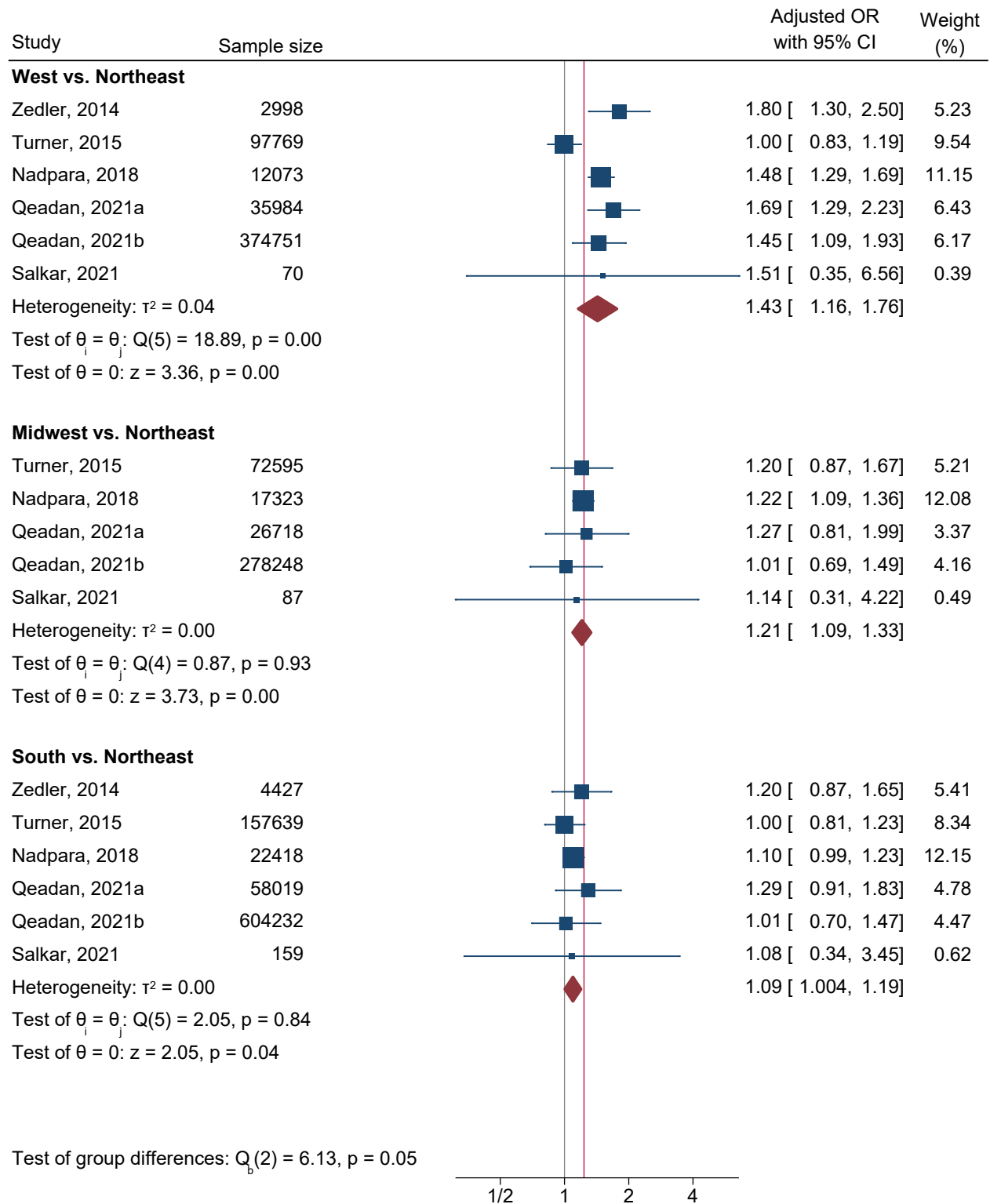
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 6C Predictor of marital status: non-married vs. married



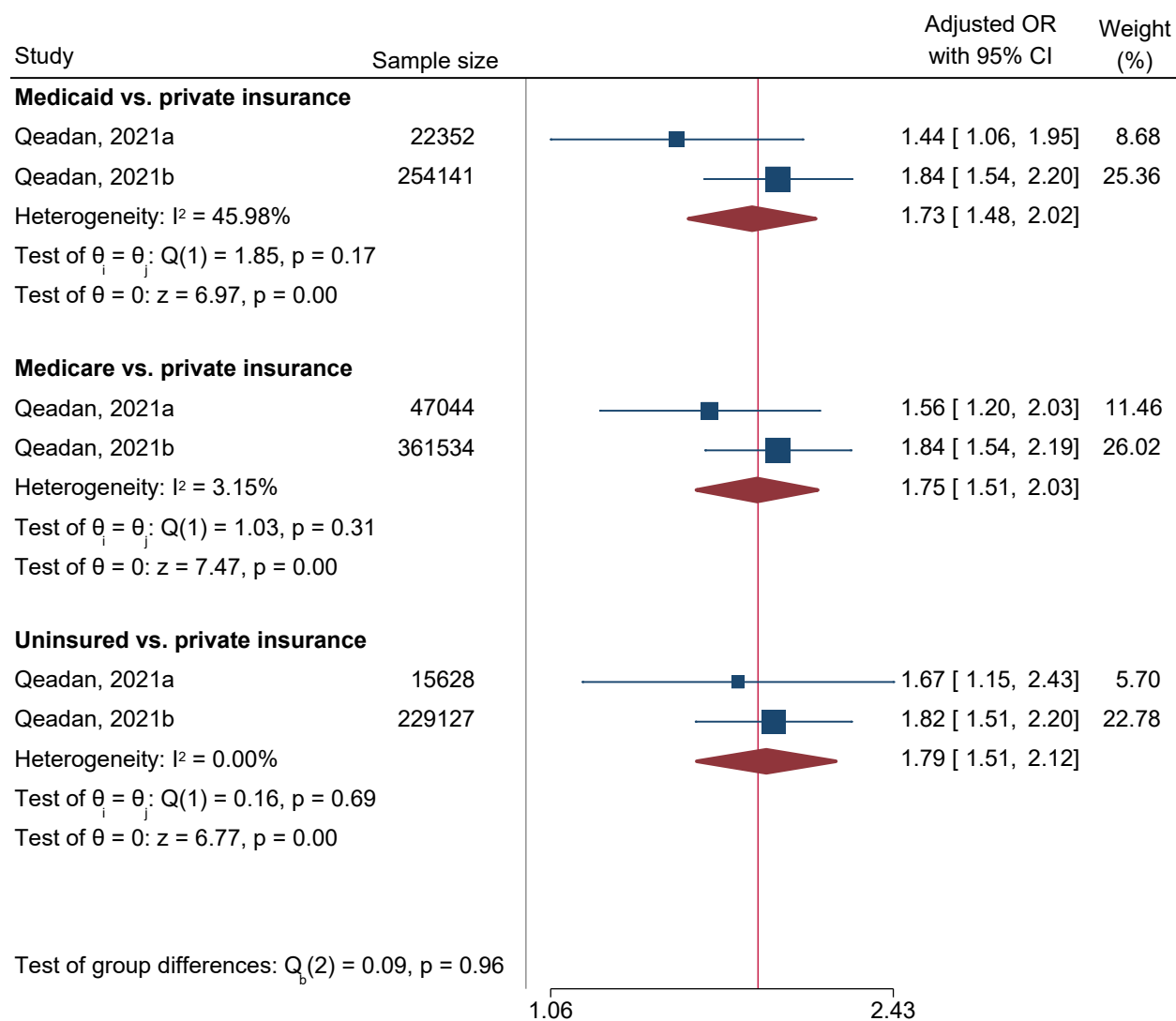
Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 6D Predictor of White race vs others



Random-effects DerSimonian–Laird model
Sorted by: Year Author

eFigure 6E Predictor of geographic region in United States

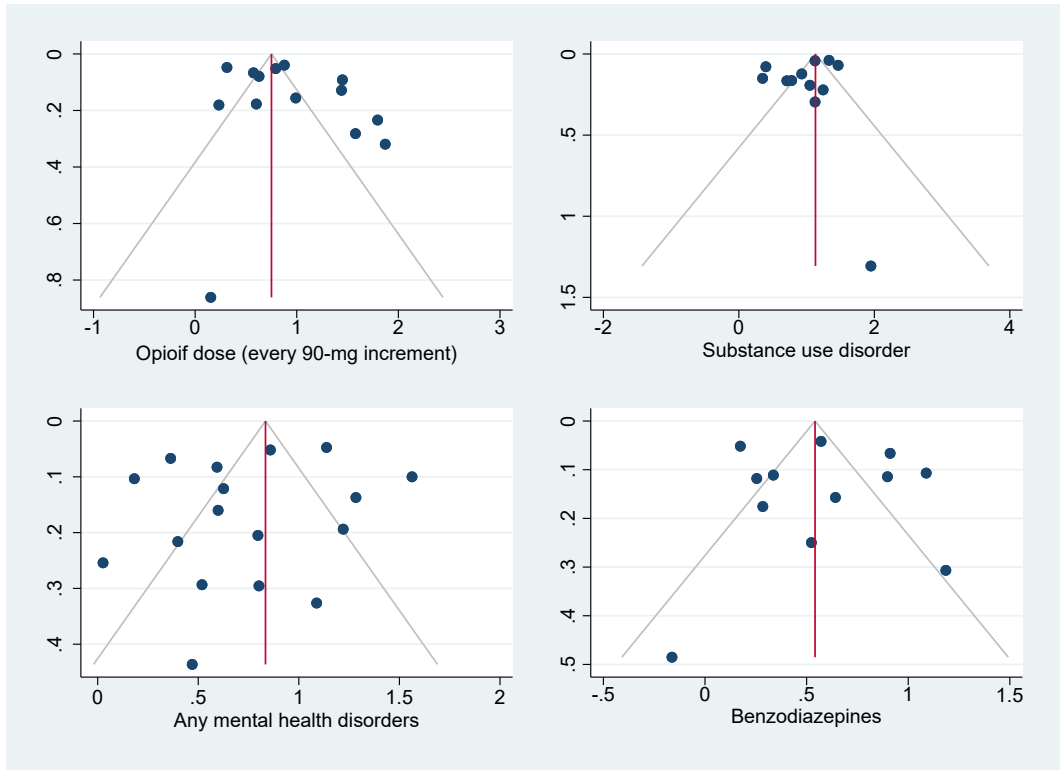


Fixed-effects inverse-variance model
Sorted by: Year Author

eFigure 6F Predictor of insurance

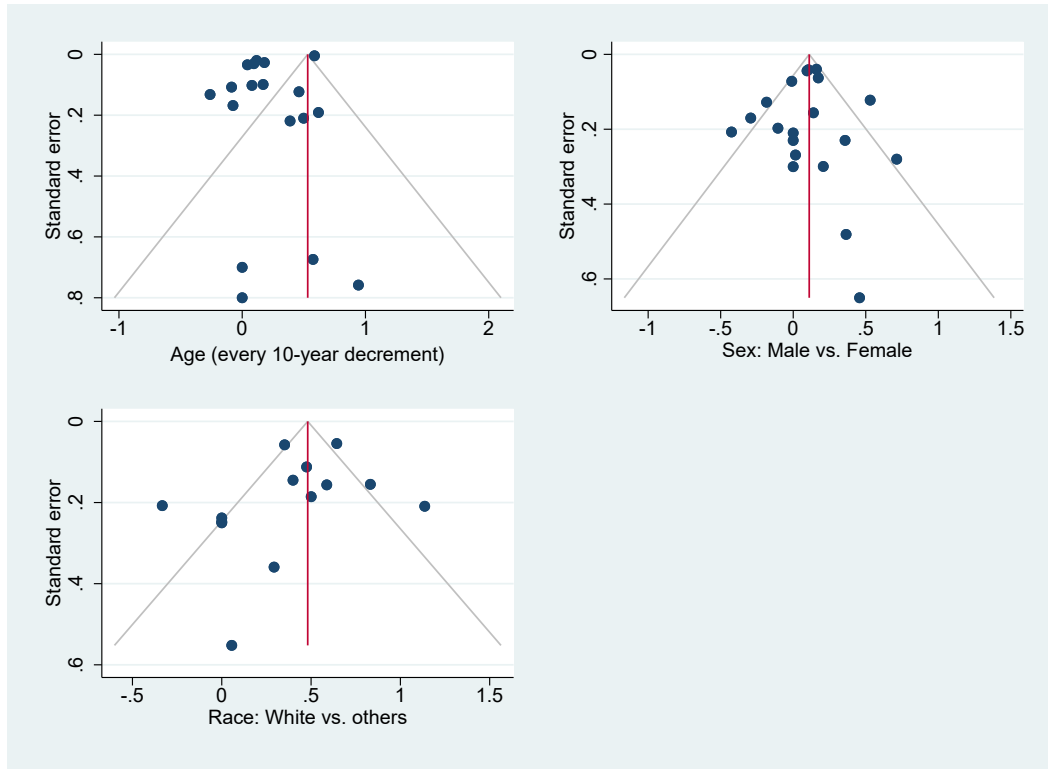
*Fixed-effects model was used for pooling two studies

eFigure 7 Funnel plots with pseudo 95% confidence limits for opioid dose, current substance use disorder, age and sex



eFigure 7A Funnel plots for opioid dose, current substance use disorder, any mental health disorders and use of benzodiazepines

* X-axis: adjusted odds ratio (on log scale); Y-axis: standard error of adjusted odds ratio.



eFigure 7B Funnel plots for age, sex and race

* X-axis: adjusted odds ratio (on log scale); Y-axis: standard error of adjusted odds ratio.

Section 1 Search strategies

MEDLINE

1 exp Analgesics, Opioid/ (131570)

2 (opioid* or opiate*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (154252)

3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (167325)

4 exp Narcotics/ (139764)

5 (narcotic* or adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodone or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphanol or levo-dromoran or levodromoran or lexicr or lidol or lydol or morfín or morfíne or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodone or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (75782)

6 or/1-5 (279610)

7 ((chronic* or recur* or persist* or non-malign* or malign* or noncancer* or non-cancer* or cancer*) adj3 pain).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (111121)

8 Chronic Pain/ or Cancer Pain/ or exp Osteoarthritis/ or exp Arthritis, Rheumatoid/ or exp Neuralgia/ or Diabetic Neuropathies/ or Irritable Bowel Syndrome/ or Migraine Disorders/ or Fibromyalgia/ or complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ or Pain, Intractable/ or Phantom Limb/ or Hyperalgesia/ or exp back pain/ or Radiculopathy/ or musculoskeletal pain/ or headache/ or exp Arthralgia/ or exp Headache Disorders/ or Temporomandibular Joint Disorders/ or exp whiplash injury/ or exp Cumulative Trauma Disorders/ or exp Peripheral Nervous System Diseases/dt or Pain Measurement/de (444350)

9 (osteoarthritis* or osteo-arthritis or degenerative arthritis* or neuralgia* or zoster or IBS or migraine* or complex regional pain syndromes or causalgia or radiculopathy* or headache* or whiplash* or TMD or backache* or backpain* or dorsalgia* or arthralgia* or polyarthralgia* or arthrodynia* or myalgia* or fibromyalgia* or myodynin* or neuralgia* or ischialgia* or crps or rachialgia*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (360852)

10 ((back or discogen* or bone or musculoskeletal* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachial* or orofacial or somatic or shoulder* or knee* or hip or hips or TMJ or TMJD) adj3 pain).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (198852)

11 (irritable adj3 (colon or bowel)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17371)
12 or/7-11 (743895)
13 6 and 12 (36876)
14 Drug Overdose/ (13738)
15 exp Drug Misuse/ (16666)
16 (overdos* or poison*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (187834)
17 mortality/ or death/ (68260)
18 (mortality or death).ti,ab. (1577261)
19 or/14-18 (1768050)
20 13 and 19 (2363)
21 Epidemiologic Studies/ (9187)
22 exp Case-Control Studies/ (1358034)
23 exp Cohort Studies/ (2400853)
24 Case control.tw. (146885)
25 (cohort adj (study or studies)).tw. (286892)
26 Cohort analy\$.tw. (10787)
27 (Follow up adj (study or studies)).tw. (54492)
28 (observational adj (study or studies)).tw. (146787)
29 Longitudinal.tw. (301979)
30 Retrospective.tw. (688718)
31 Cross sectional.tw. (470226)
32 Cross-sectional studies/ (441886)
33 or/21-32 (3614350)
34 exp animals/ not humans.sh. (5052213)
35 33 not 34 (3541325)
36 20 and 35 (647)

EMBASE

1 chronic pain/ or cancer pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or fibromyalgia/ or intractable pain/ or agnosia/ or phantom pain/ or amputation stump/ or hyperalgesia/ or exp backache/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (1052612)
2 ((chronic* or recur* or persist* or non-malign* or malign* or noncancer* or non-cancer* or cancer*) adj3 pain).mp. (186805)
3 (osteoarthrit* or osteo-arthritis or degenerative arthrit* or neuralg* or zoster or IBS or migraine* or complex regional pain syndromes or causalgia or radiculopath* or headache* or whiplash* or TMD or backache* or backpain* or dorsalg* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).mp. (790387)
4 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips or TMJ or TMJD) adj3 pain).mp. (343192)
5 (irritable adj3 (colon or bowel)).mp. (33903)
6 or/1-5 (1406078)
7 exp narcotic analgesic agent/ (379013)
8 (opioid* or opiate*).mp. (232259)
9 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, heading word, drug trade

name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (321772)

10 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodone or dihydronone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogenic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodone or isocodeine or isonipeccain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodone or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontosfort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramador or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (59179)

11 or/7-10 (478289)

12 6 and 11 (86545)

13 drug overdose/ or intoxication/ (209934)

14 exp drug misuse/ (10788)

15 (overdos* or poison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (174162)

16 mortality/ or death/ (1073718)

17 (mortality or death).ti,ab. (2273353)

18 or/13-17 (2845489)

19 12 and 18 (8107)

20 clinical study/ (160539)

21 case control study/ (193429)

22 family study/ (25694)

23 longitudinal study/ (179050)

24 retrospective study/ (1315395)

25 prospective study/ (798586)

26 randomized controlled trials/ (235679)

27 25 not 26 (789160)

28 cohort analysis/ (901841)

29 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (422852)

30 (Case control adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (255086)

31 (follow up adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (74294)

32 (observational adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (354731)

33 (epidemiologic\$ adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (123487)

34 (cross sectional adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (557146)

35 or/20-24,27-34 (3798235)

36 19 and 35 (1571)

PsycInfo

- 1 exp opiates/ (28821)
- 2 (opioid* or opiate*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (39529)
- 3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (34521)
- 4 (narcotic* or adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodone or dihydronone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolconal or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodone or isocodeine or isonipecaïn or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodone or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (15146)
- 5 or/1-4 (59819)
- 6 chronic pain/ or back pain/ or myofascial pain/ or somatoform pain disorder/ (19047)
- 7 ((chronic* or recur* or persist* or non-malign* or malign* or noncancer* or non-cancer* or cancer*) adj3 pain).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (29560)
- 8 (osteoarthritis* or osteo-arthritis or degenerative arthritis* or neuralgia* or zoster or IBS or migraine* or complex regional pain syndromes or causalgia or radiculopathy* or headache* or whiplash* or TMD or backache* or backpain* or dorsalgia* or arthralgia* or polyarthralgia* or arthrodynia* or myalgia* or fibromyalgia* or myodynin* or neuralgia* or ischialgia* or crps or rachialgia*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (38999)
- 9 ((back or discogen* or bone or musculoskeletal* or muscle* or skeletal* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachial* or orofacial or somatic or shoulder* or knee* or hip or hips or TMJ or TMJD) adj3 pain).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (23406)
- 10 (irritable adj3 (colon or bowel)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (2014)
- 11 or/6-10 (73816)
- 12 5 and 11 (6679)
- 13 drug overdoses/ (2501)
- 14 drug abuse/ (49049)
- 15 (overdos* or poison*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (13196)
- 16 exp "death and dying"/ (45080)
- 17 (mortality or death).ti,ab. (124001)
- 18 or/13-17 (189905)
- 19 12 and 18 (870)
- 20 epidemiology/ (54215)
- 21 Case control.tw. (12411)
- 22 (cohort adj (study or studies)).tw. (27110)
- 23 Cohort analy\$.tw. (1061)

- 24 (Follow up adj (study or studies)).tw. (13933)
- 25 (observational adj (study or studies)).tw. (12905)
- 26 Longitudinal.tw. (136933)
- 27 Retrospective.tw. (41484)
- 28 Cross sectional.tw. (98685)
- 29 or/20-28 (349650)
- 30 19 and 29 (175)

CINAHL

- S1 (MH "Analgesics, Opioid+")
- S10 (MH "Arthritis, Rheumatoid+")
- S11 (MH "Neuralgia+")
- S12 (MH "Diabetic Neuropathies+")
- S13 (MH "Irritable Bowel Syndrome")
- S14 (MH "Migraine")
- S15 (MH "Fibromyalgia")
- S16 (MH "Complex Regional Pain Syndromes") OR (MH "Reflex Sympathetic Dystrophy") OR (MH "Causalgia")
- S17 (MH "Phantom Limb")
- S18 (MH "Hyperalgesia")
- S19 (MH "Back Pain+")
- S2 TX opioid* or opiate*
- S20 (MH "Radiculopathy")
- S21 (MH "Headache+")
- S22 (MH "Arthralgia")
- S23 (MH "Temporomandibular Joint Diseases+")
- S24 (MH "Whiplash Injuries")
- S25 (MH "Cumulative Trauma Disorders")
- S26 (MH "Peripheral Nervous System Diseases/DT")
- S27 TX osteoarthritis* or osteo-arthritis or degenerative arthrit* or neuralg* or zoster or IBS or migraine* or complex regional pain syndromes or causalgia or radiculopath* or headache* or whiplash* or TMD or backache* or backpain* or dorsalg* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*
- S28 TX ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips or TMJ or TMJD) N3 pain)
- S29 TX (irritable N3 (colon or bowel))
- S3 TX alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piritramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol
- S30 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
- S31 S5 AND S30
- S32 (MH "Overdose")
- S33 (MH "Substance Abuse+")
- S34 TX overdos* or poison*
- S35 (MH "Mortality")
- S36 (MH "Death")
- S37 TI mortality or death
- S38 AB mortality or death
- S39 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
- S4 TX narcotic* or adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgi or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or

dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipeccain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexis or lidol or lydol or morfín or morfíne or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram

S40 S31 AND S39
S41 (MH "Epidemiological Research")
S42 (MH "Case Control Studies+")
S43 (MH "Prospective Studies+")
S44 TX Case control
S45 TX (cohort N1 (study or studies))
S46 TX Cohort analy*
S47 TX (Follow up N1 (study or studies))
S48 TX (observational N1(study or studies))
S49 "Longitudinal"
S5 S1 OR S2 OR S3 OR S4
S50 (MH "Retrospective Design") OR "Retrospective"
S51 (MH "Cross Sectional Studies") OR "Cross sectional"
S52 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51
S53 S40 AND S52
S6 TX ((chronic* or recur* or persist* or non-malign* or malign* or noncancer* or non-cancer* or cancer*) N3 pain)
S7 (MH "Chronic Pain")
S8 (MH "Cancer Pain")
S9 (MH "Osteoarthritis+")

Web of Science

15 #14 AND #11 888
14 #12 OR #13 2,611,196
13 TS=(Longitudinal or Retrospective or Cross sectional or epidemiol*) 2,191,919
12 TS=((cohort or observational or case-control or cohort) NEAR/3 (study or studies or analy*)) 687,720
11 #9 AND #10 3,046
10 TS=(overdos* or poison* or mortality or death) 2,202,776
9 #8 AND #3 33,358
8 #4 OR #5 OR #6 OR #7 587,963
7 TS=(irritable NEAR/3 (colon or bowel)) 26,118
6 TS=((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips or TMJ or TMJD) NEAR/3 pain) 210,437
5 TS=(osteoarthrit* or osteo-arthritis or degenerative arthrit* or neuralg* or zoster or IBS or migraine* or complex regional pain syndromes or causalgia or radiculopath* or headache* or whiplash* or TMD or backache* or backpain* or dorsalg* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*) 346,218
4 TS(((chronic* or recur* or persist* or non-malign* or malign* or noncancer* or non-cancer* or cancer*) NEAR/3 pain)) 122,948
3 #1 OR #2 254,991
2 TS=(opioid* or opiate*) 144,712

1 TS=(alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or narcotic* or adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicotid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontosfort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram) 175,652

Section 2 Risk of bias assessment criteria

1. Is the source population (sampling frame) representative of the general population? Yes (low risk of bias); no (high risk of bias)

Examples of low risk of bias:

- Selection of target population from a representative population roster such as national population registry, or selection from a random sample of a representative study population

Examples of high risk of bias:

- Studies where the source population cannot be defined or from unrepresentative populations, e.g., very young or old population, veterans, large proportion of patients disabled or comorbid with substance user disorders, or other mental illness.

2. Is the assessment of the outcome accurate both at baseline and at follow-up? Yes (low risk of bias); no (high risk of bias)

Examples of low risk of bias:

- Repeated interview or other ascertainment asking about state with validated instrument or method (with demonstrated validity).

Examples of high risk of bias:

- Unvalidated instrument or method with concern of accuracy of responses
- Uncertain how information was obtained
- Using ICD 9 or 10 codes of opioid overdose, which included codes for illicit opioid or non-opioid overdose

3. Is there little missing data? Yes (low risk of bias); no (high risk of bias)

Examples of low risk of bias:

- High response proportion (rate) with little missing data (<20%)

Examples of high risk of bias:

- Response proportion (rate) or missing data $\geq 20\%$

4. Whether predictive models were adjusted, at minimum, for age, sex, substance user disorder and any other comorbid mental illness? Yes (low risk of bias); no (high risk of bias)

Examples of low risk of bias:

- The regression models adjusted for at least four factors, including age, sex, substance user disorder, and any other comorbid mental illness (e.g., anxiety, depression, bipolar disorder, etc.)

Examples of high risk of bias:

- The regression models adjusted a part of four factors, e.g., only age, sex, and other comorbidities but without either substance user disorder, or other mental illness.

Section 3 Excluded studies

Excluded studies for conference abstracts: n=29

1. Passik SD, Narayana AK, Janka L. Aberrant drug-related behavior observed during a long-term clinical study involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *Pain Medicine*. 2010;11 (2):320.
2. Barrantes F, Luan FL, Kommareddi M, et al. Painful consequences: Chronic use of prescription opioids is associated with adverse kidney transplant outcomes. *American Journal of Transplantation*. 2011;11:83.
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4. Kaplovitch E, Gomes T, Camacho X, Dhalla I, Mamdani MM, Juurlink DN. Gender, dose escalation and mortality during opioid therapy. *Clinical Toxicology*. 2013;51 (4):334.
5. Turner BJ, Liang Y, Louden CL, Ehler BR, Aung K. Intensity of opioid analgesic prescribing and urgent care services: A national cohort study. *Journal of General Internal Medicine*. 2013;28:S109.
6. Allen C, Meeraus W, Donegan K. The comparative risk of all-cause mortality in older patients prescribed opioids for non-malignant pain: A retrospective observational cohort study. *Drug Safety*. 2015;38 (10):962-963.
7. Gaither JR, Goulet J, Becker W, et al. Mortality and guideline-concordant long-term opioid therapy for pain. *Drug and Alcohol Dependence*. 2015;156:e77.
8. Holbrook A. 2015 - Use of long-acting, vs short-acting, opioids for chronic pain was linked to unintentional overdose. *ACP Journal Club*. 2015;163(2):10-10.
9. Klemisch R. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose among Patients Receiving Opioid Therapy Miller M, Barber CW, Leatherman S, et al. *JAMA Intern Med* 2015;17:608-15. *Journal of Emergency Medicine*. 2015;49(4):593.
10. Laroche M, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid prescribing after nonfatal overdose and association with repeat overdose. *Journal of General Internal Medicine*. 2015;30:S216.
11. Makris UE, Pugh M, Alvarez CA, Mortensen EM. Exposure to high risk medications is associated with worse outcomes in older veterans with chronic pain. *Journal of the American Geriatrics Society*. 2015;63:S71.
12. Allen C, Meeraus W, Donegan K. Comparative risk of all-cause mortality in older patients prescribed codeine or tramadol for non-malignant pain: Retrospective cohort study. *Pharmacoepidemiology and Drug Safety*. 2016;25 (Supplement 3):368.
13. Anderson JT, Tye E, Haas A, Ahn NU. Predictors of chronic opioid therapy after lumbar fusion surgery for degenerative disc disease in a workers' compensation setting. *Spine Journal*. 2016;16 (10 Supplement 1):S343.
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16. Chung CP, Dupont W, Murray K, Hall K, Stein CM, Ray W. Comparative safety of long-acting opioids for non-cancer pain. *Arthritis and Rheumatology*. 2016;68 (Supplement 10):2523-2524.
17. Khodneva Y, Muntner P, Kertesz S, Kissela B, Safford MM. Prescription Opioid Use and Risk of Coronary Heart Disease, Stroke, and Cardiovascular Death Among Adults from a Prospective Cohort (REGARDS Study). *Pain Medicine*. 2016;17(3):444-455.
18. Laroche M, Liebschutz JM, Wharam JF, Zhang F, Ross-Degnan D. Association of urine drug test screening during initiation of chronic opioid therapy with risk of opioid overdose. *Journal of General Internal Medicine*. 2016;31(2):S131.
19. Dave C, Alrwisan A, Zhu Y, Winterstein A, Hartzema A. Concomitant use of opioid and benzodiazepines and the risk of opioid overdose requiring hospitalizations: A retrospective cohort study. *Value in Health*. 2017;20 (5):A212.
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22. Lee YH, Huang YN, Chen HY. The mortality and medical service utilization by long-term opioids patients for chronic non-cancer pain. *Pharmacotherapy*. 2017;37 (12):e196.

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25. Luu H, Slavova S. Long-term use of high-dose opioid analgesics in Kentucky from 2012 to 2016. *Pharmacoepidemiology and Drug Safety*. 2018;27 (Supplement 2):330.
26. Hill MV, O'Halloran EA, Reddy SS, Sigurdson ER, Farma J. Preoperative Opioid Use in Patients Undergoing Surgical Resection for Treatment of Rectal Cancer. *Journal of the American College of Surgeons*. 2019;229 (4 Supplement 2):e99.
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29. Merlin J, Black A, Becker W, Lorenz K. Long-term opioid therapy and opioid overdose in patients with and without cancer. *Journal of General Internal Medicine*. 2021;36(SUPPL 1):S121.

Excluded studies for non-observational studies: n=4

1. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Medicine*. 2011;12(SUPPL. 2):S26-S35.
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4. Chou R. Long-acting opioids for chronic noncancer pain were linked to mortality. *Annals of Internal Medicine*. 2016;165(6):JC34.

Excluded studies for unclear or non-chronic pain conditions: n=58

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4. Maloney E, Degenhardt L, Darke S, Nelson EC. Are non-fatal opioid overdoses misclassified suicide attempts? Comparing the associated correlates. *Addictive Behaviors*. 2009;34(9):723-729.
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19. Kelty E, Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *International Journal of Drug Policy*. 2017;46:54-60.
20. Oliva EM, Bowe T, Tavakoli S, et al. Development and applications of the veterans health administration's stratification tool for opioid risk mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychological Services*. 2017;14(1):34-49.
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24. Nadpara PA, Joyce AR, Murrelle EL, et al. Risk factors for serious prescription opioid-induced respiratory depression or overdose: Comparison of commercially insured and veterans health affairs populations. *Pain Medicine (United States)*. 2018;19(1):79-96.
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32. Mudumbai SC, Lewis ET, Oliva EM, et al. Overdose Risk Associated with Opioid Use upon Hospital Discharge in Veterans Health Administration Surgical Patients. *Pain Medicine*. 2019;20(5):1020-1031.
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55. Kim KW, Brodeur PG, Mullen MA, et al. Postoperative Pain Management Following Orthopedic Spine Procedures and Consequent Acute Opioid Poisoning: An Analysis of New York State From 2009 to 2018. *Spine (03622436)* 2022;47(18):1270-78.
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Excluded studies for unclear or non-prescriptions of opioids: n=38

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Excluded studies without outcome of interest (fatal or non-fatal overdose): n=35

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Excluded studies without adjusted analysis: n=18

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Excluded studies with significant postbaseline factors: n=2

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Excluded studies with patients exclusively having prior opioid overdose: n=2:

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Section 4 Credibility assessment of subgroup effects for substance use disorder

ICEMEN Criteria	Current vs. prior
1: Is the analysis of effect modification based on comparison within rather than between trials?	Between-study
2: For within-trial comparisons, is the effect modification similar from trial to trial?	NA
3: For between-trial comparisons, is the number of trials large?	Rather small (4 studies exploring prior SUD)
4: Was the direction of effect modification correctly hypothesized a priori?	Definitely yes
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance may not explanation (p=0.01)
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Probably no (7 factors)
7: Did the authors use a random effects model?	Definitely yes
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?	NA
9 Optional: Are there any additional considerations that may increase or decrease credibility?	
The effect modification persisted after adjustment for other potential effect modifiers	Yes
The effect modification is consistent across related outcomes:	Probably yes
A sensitivity analysis suggested robustness to relevant assumptions	NA
Effect modification supported by external evidence	Yes, from observational studies
“Dose-response effect” across levels of the effect modifier	Yes
Risk of bias of the main effects of the individual RCTs or the meta-analysis	NA
The meta-analysis had had exceptionally high power to detect the effect modification	Yes
Overall credibility	Moderate

*ICEMAN: Instrument for assessing the Credibility of Effect Modification Analyses

*NA: not applicable