Additional File 1: Supplementary Materials

Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.

Item No	Recommendation	Line numbers	Text
Reporting of background should include			
1	Problem definition	105-107	"understanding who is taking high doses and what may be driving high-dose prescribing would help reduce such uncertainties. However, evidence has not been synthesized to understand this uncertainty."
2	Hypothesis statement	-	-
3	Description of study outcome(s)	108	"factors"
4	Type of exposure or intervention used	108	"high-dose opioids"
5	Type of study designs used	108	"observational evidence"
6	Study population	109	"primary care"
Reporting of search strategy should include			
7	Qualifications of searchers (eg, librarians and investigators)	Table S2	"We developed the search strategy in consultation with an information specialist."
8	Search strategy, including time period included in the synthesis and key words	146 Table S2	"The search terms and search strategy are available in S2 Table and S3 Table." "Search terms included "opioid*", "prescri*", "factor*", "primary healthcare" and variations of these, including specific drug and brand names of opioids (see Table S2). The search strategy was initially developed for Medline as presented in S3 Table, then adapted for Embase and Web of Science databases."
9	Effort to include all available studies, including contact with authors	128 153-154	"We included all languages." "we contacted authors of studies by electronic mail"
10	Databases and registries searched	142	"Medline (Ovid), Embase (Ovid), and Web of Science Core Collection"
11	Search software used, name and version, including special features used	150 194-195	"Endnote X8" "Stata software version 16.0"
12	Use of hand searching	143-144	"We hand searched forward citations and reference lists of eligible studies"
13	List of citations located and those excluded, including justification	119-139 Figure 1	"We included …" "We excluded studies if…"
14	Method of addressing articles published in languages other than English	128	"We included all languages."
15	Method of handling abstracts and unpublished studies	144-147	"Conference proceedings were also used to identify potentially eligible studies but were not included unless a complete manuscript was published."
16	Description of any contact with authors	153-154	"we contacted authors of studies by electronic mail for clarification of inclusion status."

Reporting of methods should include			
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	119-139	"We included …" "We excluded studies if…"
18	Rationale for the selection and coding of data	158-165	"extracted data using a predeveloped data extraction spreadsheet…"
19	Documentation of how data were classified and coded	Not applicable	Not applicable
20	Assessment of confounding appropriate	175	"adjustment for confounding"
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	168-180	"Quality and risk of bias assessment…"
22	Assessment of heterogeneity	191-193	"When considerable heterogeneity, defined as $I^2 \geq 75\%$..."
23	Description of statistical methods in sufficient detail to be replicated	182-195	"Data synthesis and analysis…"
24	Provision of appropriate tables and graphics	Table 1-2 Figures 1-2	
Reporting of results should include			
25	Graphic summarizing individual study estimates and overall estimate	Figure 2, Figures S1-S3	-
26	Table giving descriptive information for each study included	Table 1	-
27	Results of sensitivity testing (eg, subgroup analysis)	Figure S1 & S2	-
28	Indication of statistical uncertainty of findings	219-224	Quality and risk of bias & the reporting of CIs
Reporting of discussion should include			
29	Quantitative assessment of bias (e.g. publication bias)	363-406	"…inherent limitations and complexities of using observational evidence impacts the quality and availability of data." "…two large studies did not report data on the co-morbidities or the indication for high doses…"
30	Justification for exclusions	380-381	"few studies were included in our review because most observational studies on the prescribing of high-dose opioids use population-level prescribing data"
31	Assessment of quality of included studies	-	In results, lines 219-224
Reporting of conclusions should include			
32	Consideration of alternative explanations for observed results	-	-
33	Generalization of the conclusions	420	"high-income primary care settings"
34	Guidelines for future research	424-426	"Standardizing the reporting of all outcomes and promoting the sharing of data from observational studies"
35	Disclosure of funding source	532-537	"Funding: …"

Search strategy

We developed the search strategy in consultation with an information specialist. Search terms included "opioid*", "prescri*", "factor*", "primary healthcare" and variations of these, including specific drug and brand names of opioids (see Table S2). The search strategy was initially developed for Medline as presented in Table S3, then adapted for Embase and Web of Science databases. The first search was run on 12 February 2018. We updated this search in all three databases on 5 April 2019.

Table S2. International brand names for opioids collated using the UpToDate database

Drug name	Brand names	Countries	# of countries	Included or excluded
Codeine	N/A	N/A	N/A	Included
Morphine	MS Contin	AU, BE, CN, IT, LU, NL, VE, KR	8	Included
	MST Continus	AE, AR, BF, BG, BH, BJ, CI, CY, CZ, EE, EG, ES, ET, GB, GH, GM, GN, HK, HR, ID, IE, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MT, MU, MW, MY, NE, NG, OM, PH, PK, PL, QA, RO, SA, SC, SD, SG, SK, SL, SN, SY, TH, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW	61	Included
	Oramorph	BE, ES, FR, GB, IE, LU, PT, SE	8	Included
	Sevredol	AU, CH, CZ, HR, IE, NZ, RO, SI, SK, TR	10	Included
Hydro-morphone	Himop	CR, DO, GT, HN, NI, PA, SV	7	Included
	Jurnista	AT, AU, CR, CZ, DE, DK, DO, EE, ES, GT, HN, HU, ID, IT, MX, NI, NZ, PA, PH, PT, SA, SG, SI, SV, ZW	25	Included
	Palladon*	CH, DK, FI, IS, NL, NO, SE, SI, SE, BE, CZ, EE, ES, GB, GR, HN, IE, IL, LU, PT	20	Included

	Liberaxim	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
Nicomorphine	N/A	N/A	N/A	Included
Oxycodone	Oxycontin	AR, AT, BR, CH, CL, CN, CO, CR, CY, CZ, DK, DO, EC, EE, ES, FI, GB, GT, HK, HN, IE, IL, IT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, SE, SG, SV, VE, HR, HU, IS, LU, RO, SI, SK, TR, VN	45	Included
	Oxynorm	AT, AU, BE, CH, CY, DK, ES, FI, FR, GB, HK, IE, IS, MY, NO, NZ, PH, SE, SG, TR, JP, SG,	22	Included
Dihydro-codeine	N/A	N/A	N/A	Included
Papaveretum	N/A	N/A	N/A	Included
Ketobemidone	N/A	N/A	N/A	Included
Pethidine	Meperidine	N/A	N/A	Included
	Dolosal	BR, CR, DO, GT, HN, NI, PA, SV	8	Included
Fentanyl	Abstral	BM, ES, GB, HR, IE, PH, QA, TR	8	Included
	Actiq	AU, CH, DE, DK, ES, FI, FR, GB, IE, IL, KR, PT, SE	13	Included
	Durogesic	AE, AU, BH, CN, CO, CY, EG, ES, ID, IN, JO, KW, LB, LK, MX, NZ, PH, PK, PY, QA, SA, SG, TH, VN	24	Included
	Instanyl	AT, BE, CZ, DE, DK, EE, ES, FR, HR, IS, LT, LU, MT, NL, PL, SE, SI, SK	18	Included
	Ionsys	AT, BE, BG, CH, CZ, DE, DK, EE, FI, FR, GB, GR, HN, IE, IT, MT, NL, NO, PT, RU, SE, SK, TR	23	Included

	Sublimaze	AR, AU, GB, IE, NZ, PH, ZA	7	Included
Dextro-moramide	N/A	N/A	N/A	Included
Piritramide	N/A	N/A	N/A	Included
Dextro-propoxyphene	N/A	N/A	N/A	Included
Bezitramide	N/A	N/A	N/A	Included
Pentazocine	Fortral	AT, AU, BG, DE, DK, GB, HR, IE, NZ, PL	10	Included
	Fortwin	BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW	29	Included
	Sosegon	AE, BF, BH, BJ, CI, CY, EC, EG, ET, GH, GM, GN, IL, IQ, IR, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PK, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW	42	Included
Phenazocine	N/A	N/A	N/A	Included
Bupren-orphine	Norspan patch	AU, DE, DK, EE, FI, HK, KR, NO, NZ, PH	10	Included
	Subutex	AE, AT, AU, BE, BG, CH, CZ, DE, DK, FR, GR, HR, ID, IE, IL, IS, LU, LV, MT, NO, PT, QA, SE, TW	23	Included
	Temgesic	AE, AT, BE, BF, BH, BJ, BR, CH, CI, CY, DE, DK, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, HK, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PK, QA, RU, SA, SC, SD, SE, SG, SK, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW	66	Included

	Transtec	BE, CH, CL, CO, DE, DK, EC, ES, GB, HN, HR, HU, IE, IT, MX, NL, NO, PE, PL, PT, SK	21	Included
Butorphanol	N/A	N/A	N/A	Included
Nalbuphine	Bufigen	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
	Nalcryn	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
	Nubain	AE, AT, BF, BH, BJ, BR, CI, CY, CZ, DE, EE, EG, ET, GB, GH, GM, GN, GR, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PL, QA, SA, SC, SD, SI, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW	57	Included
Methadone	Amidone	CR, DO, GT, HN, NI, PA, SV	7	Included
	Rubidexol	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
Tramadol	Adamon	AR, CR, DO, GT, HN, NI, PA, PY, SV	9	Included
	Bongesic	CR, DO, GT, HN, NI, PA, SV	7	Excluded
	Mabron	AE, BH, CY, EG, ET, IQ, IR, JO, KW, LB, LV, LY, MY, OM, QA, SA, SG, SY, YE	20	Excluded
	Trabilin	BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, NI, PA, SR, SV, TT	15	Excluded
	Tradolan	AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE	16	Excluded

	Tramal	AE, AT, AU, BF, BH, BJ, CH, CI, CN, CO, CR, CU, CY, CZ, DE, DO, EC, EE, EG, ET, FI, GH, GM, GN, GR, GT, HN, HR, IQ, IR, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MT, MU, MW, NE, NG, NI, NL, NZ, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SK, SL, SN, SV, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW	72	Included
	Tramazac	BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZM, ZW	27	Included
Tilidine	N/A	N/A	N/A	Included
Dezocine	N/A	N/A	N/A	Included
Meptazinol	N/A	N/A	N/A	Included
Tapentadol	Palexia*	AT, BG, CH, CR, CZ, DK, DO, EE, ES, FI, FR, GB, GT, HN, HR, IE, IL, LT, LU, LV, MT, NI, NL, NO, PA, PL, PT, SI, SK, SV, TR, AT, BG, CR, DE, DO, EE, ES, GT, HN, HR, LT, LV, MT, NI, NL, PA, PL, PT, RO, SK, SV	52	Included

Table S3. MEDLINE strategy and results.

Search #	Search terms	# of results
1	exp Analgesics, Opioid/	109489
2	exp Narcotics/	117473
3	1 or 2	117473
4	opioid*.ti,ab.	79690
5	narcotic*.ti,ab.	14579
6	"opioid analgesic*".ti,ab.	4475
7	opiate*.ti,ab.	24064
8	opium.ti,ab.	2439
9	4 or 5 or 6 or 7 or 8	112098
10	codeine*.ti,ab.	4774
11	morphine*.ti,ab.	48019
12	("MS Contin" or "MST Continus" or Oramorph or Sevredol).ti,ab.	118
13	Papaveretum.ti,ab.	138
14	Ketobemidone.ti,ab.	134
15	Dextromoramide.ti,ab.	177
16	Hydromorphone.ti,ab.	1466
17	(Himop or Jurnista or Palladon*).ti,ab.	14
18	Piritramide.ti,ab.	353
19	Dextropropoxyphene*.ti,ab.	530
20	Oxycodone.ti,ab.	2989
21	(Oxycontin or Oxynorm).ti,ab.	240
22	Dihydrocodeine.ti,ab.	433
23	(Meperidine or Pethidine*).ti,ab.	4850
24	Nicomorphine.ti,ab.	43
25	Dolosal.ti,ab.	20
26	Fentanyl.ti,ab.	17437

27	Abstral.ti,ab.	7
28	Actiq.ti,ab.	26
29	Durogesic.ti,ab.	44
30	(Instanyl or Ionsys or Sublimaze).ti,ab.	43
31	Methadone.ti,ab.	12800
32	Amidone.ti,ab.	44
33	Pentazocine.ti,ab.	2333
34	(Fortral or Fortwin or Sosegon).ti,ab.	52
35	Bezitramide.ti,ab.	20
36	Phenazocine.ti,ab.	70
37	Buprenorphine.ti,ab.	6016
38	Norspan*.ti,ab.	4
39	Subutex.ti,ab.	94
40	(Temgesic or Transtec).ti,ab.	70
41	Butorphanol.ti,ab.	1434
42	Nalbuphine.ti,ab.	885
43	Nubain.ti,ab.	44
44	Tramadol.ti,ab.	4608
45	Adamon.ti,ab.	9
46	(Tramal or Tramazac).ti,ab.	98
47	Tilidine.ti,ab.	133
48	Tapentadol.ti,ab.	418
49	Palexia*.ti,ab.	10
50	Dezocine.ti,ab.	142
51	meptazinol.ti,ab.	219
52	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	92514
53	3 or 9 or 52	196757

54	exp INAPPROPRIATE PRESCRIBING/ or exp Drug Prescriptions/ or exp Drug Utilization/ or exp Practice Patterns, Physicians'/	98731
55	exp Potentially Inappropriate Medication List/	279
56	exp Prescription Drugs/	5235
57	exp Prescription Drug Misuse/	11706
58	exp Medical Overuse/ or exp Deprescriptions/ or exp Prescriptions/	39044
59	exp Prescription Drug Overuse/ or exp Drug Misuse/ or exp Self Medication/	16227
60	exp Behind-the-Counter Drugs/ or exp Nonprescription Drugs/	5885
61	prescri*.ti,ab.	195505
62	Utiliz*.ti,ab.	514119
63	utilis*.ti,ab.	44114
64	dispens*.ti,ab.	35225
65	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64	852797
66	53 and 65	19678
67	exp Primary Health Care/	145132
68	exp Ambulatory Care Facilities/	52697
69	exp Physicians, Primary Care/	2888
70	exp Outpatient Clinics, Hospital/	16767
71	exp Ambulatory Care/	51044
72	exp Emergency Service, Hospital/ or exp Family Practice/ or exp General Practice/	142600
73	exp General Practice, Dental/	4727
74	exp Office Visits/	6681
75	exp Physicians, Family/ or exp General Practitioners/	22706
76	exp Emergency Medical Services/	128929
77	exp Pharmacies/ or exp Community Pharmacy Services/	11288
78	exp Community Health Services/ or exp Community Medicine/ or exp Community Health Nursing/ or exp Community Health Centers/	299456

79	exp Community Dentistry/	1213
80	exp Home Nursing/ or exp Residential Facilities/	58938
81	(ambulatory adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab.	17870
82	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	112376
83	((primary* adj3 (care or health*)) or community or communities or population).ti,ab.	1775651
84	(clinic? or office or visit? or "health centre" or "health center" or "medical centre" or "medical center").ti,ab.	560228
85	("out of hours" or ooh or "after hours").ti,ab.	4235
86	(emergency adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab.	127109
87	exp Housing for the Elderly/ or exp Assisted Living Facilities/ or exp Home Care Services/ or exp Homes for the Aged/	60450
88	exp INSTITUTIONALIZATION/ or exp Long-Term Care/	32735
89	((nursing or residential or longterm or long-term or institutional) adj2 home).ti,ab.	23609
90	(((residential or longterm or long-term) adj2 care) or facilit*).ti,ab.	624294
91	exp Home Care Services/	45434
92	((home or domiciliary) adj (visit* or call*)).ti,ab.	8212
93	((refill or repeat) adj prescri*).ti,ab.	461
94	67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93	3285822
95	66 and 94	7761
96	predict*.ti,ab.	1419106
97	characteristic*.ti,ab.	1259013
98	varian*.ti,ab.	480043
99	variat*.ti,ab.	649635
100	factor*.ti,ab.	3073031
101	96 or 97 or 98 or 99 or 100	5779446
102	95 and 101	2612

Table S4. Quality assessment of included studies, using the National Institute of Health, National Heart, Lung & Blood Institute Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies with additional data to assess risk of bias.

	NIH NHLBI Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies																Additional data					
Study ID	**1**	**2**	**3**	**4**	**5a**	**5b**	**5c**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Quality rating**	**Ethical approval**	**Enrolment incentives**	**Study sponsor**	**Pharmaceutical sponsorship**	**COI declared**	**Pharmaceutical COI**
Morasco, 2019	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Fair**	NR	NR	✓	✗	✓	✗
Chang, 2018a	✓	✓	NA	✓	NA	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	NR	NA	NR	✗	✓	✗
Chang, 2018b	✓	✓	NA	✓	NA	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	Deemed not required	NA	NR	✗	✓	✗
Campbell, 2015	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✗	NR	✗	**Fair**	✓	$20 AUD to Pharmacists for referrals	✓	✗	✓	Reckitt Benckiser & Mundipharma
Chapman, 2013	✓	✓	NA	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	NA	✓	**Good**	✓	NA	✓	✗	None to report	✗
Kobus, 2012	✓	✓	NA	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	✓	NA	✓	✗	None to report	✗

✓: yes; ✗: no; COI: conflict of interest; NA: not applicable; NR: not reported; 5a refers to sample size justification, 5b power description and 5c a measure of variance and effect estimates.

Figure S1. Forest plot of the sensitivity analysis conducted for benzodiazepine co-prescriptions

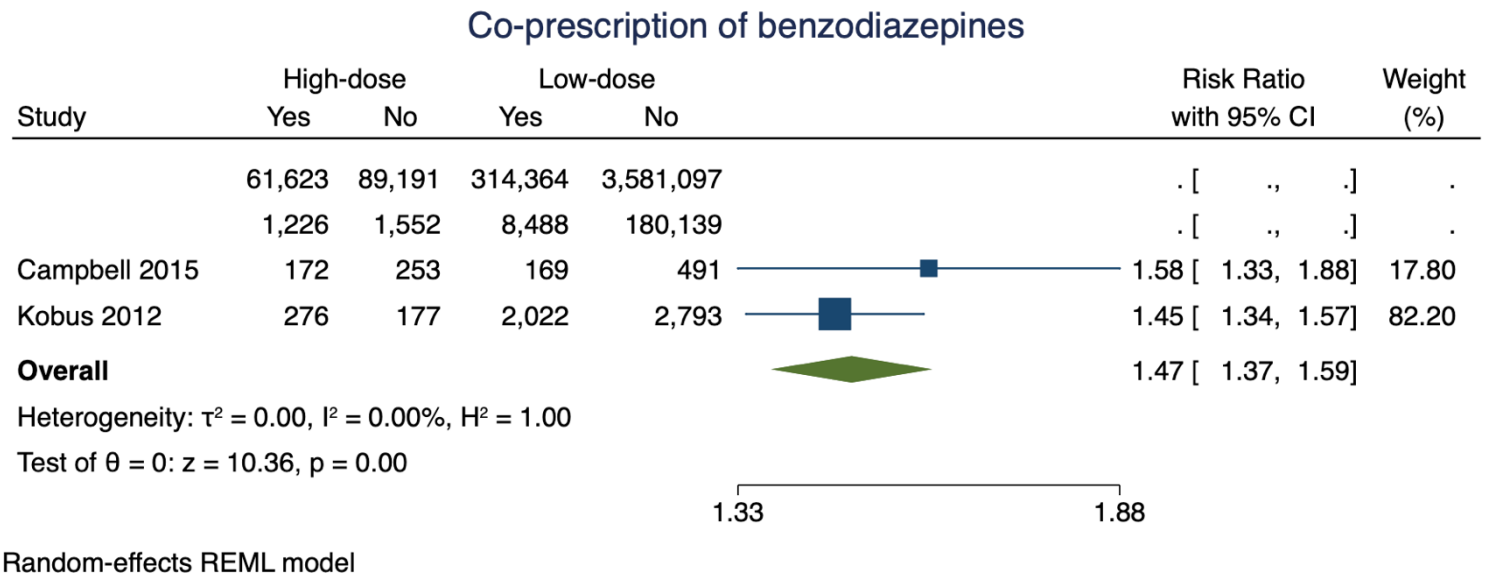

Figure S2. Forest plot of the sensitivity analysis conducted for gender

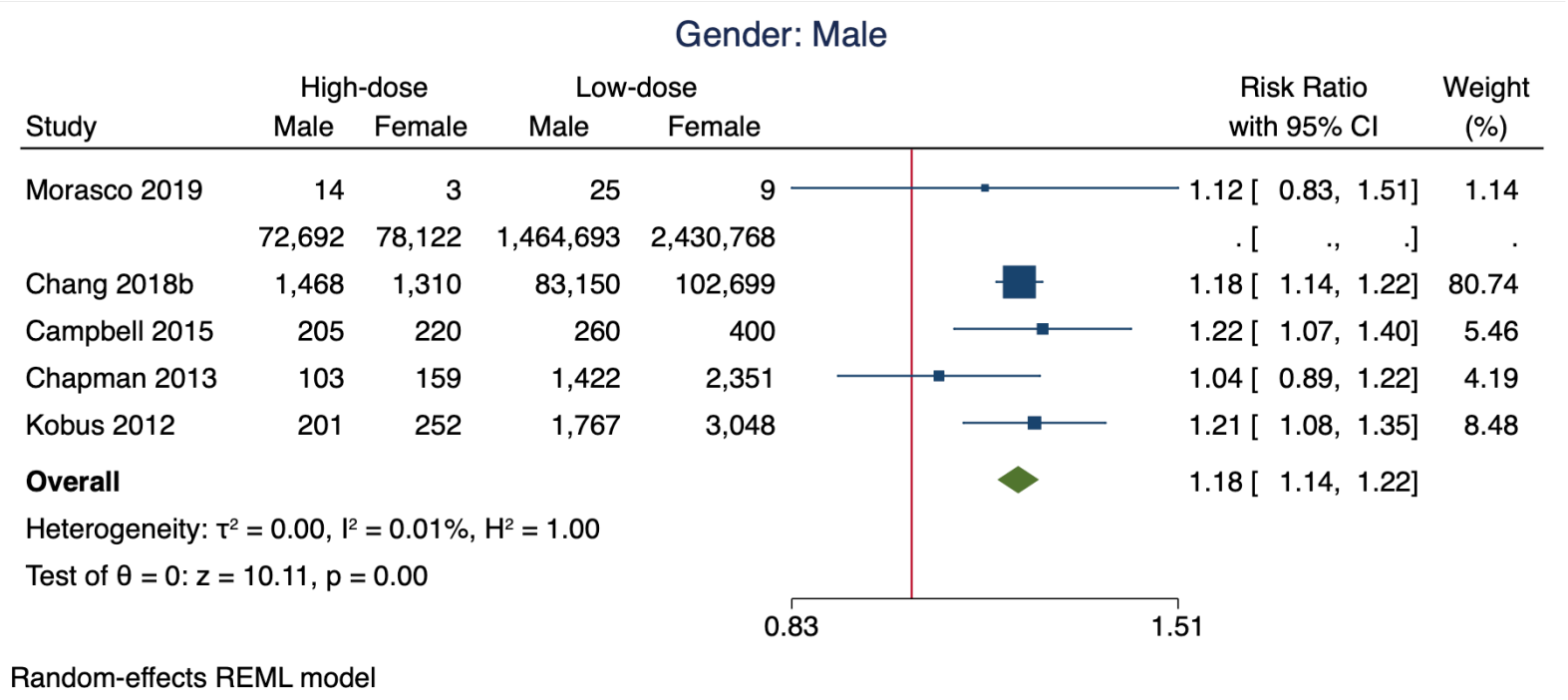

Figure S3. Forest plot of factors not associated with the prescribing of high-dose opioids in primary care

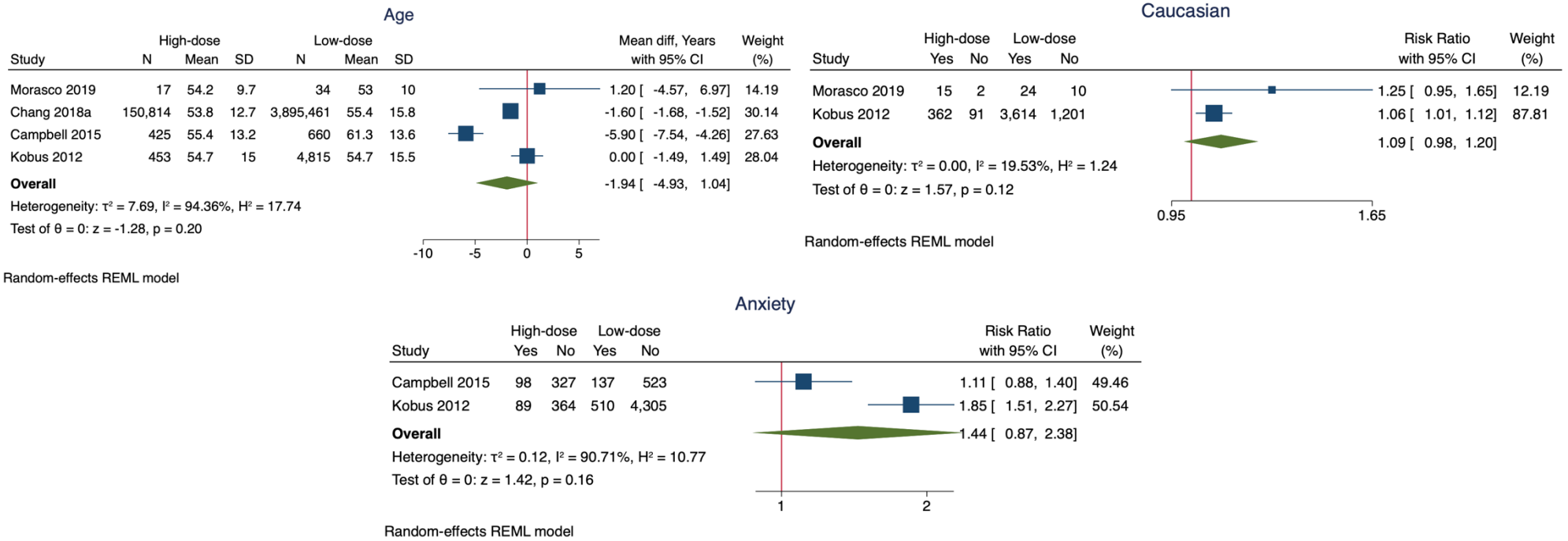

Table S5. Factors not associated with the prescribing of high-dose opioids reported by individual studies.

Study ID	Variable	High-dose	Low-dose	RR (95% CI)
		Count (%)	Count (%)	
Sociodemographic characteristics				
Kobus, 2012	Ethnicity			
	Black	7 (2%)	134 (3%)	0.56 (0.26, 1.18)
	Native American/ Alaskan	9 (2%)	49 (1%)	1.95 (0.97, 3.95)
	Asian Pacific Islander	4 (1%)	40 (1%)	1.06 (0.38, 2.96)
	Hispanic	5 (2%)	93 (3%)	0.57 (0.23, 1.40)
	Other	7 (2%)	99 (2%)	0.75 (0.35, 1.61)
Morasco, 2019	Employment status			
	Employed	1 (6%)	3 (9%)	0.67 (0.07, 5.94)
	Receiving disability	12 (71%)	20 (60%)	1.20 (0.79, 1.82)
	Other	1 (6%)	4 (12%)	0.50 (0.06, 4.13)
	Marriage status			
	Married	7 (41%)	11 (32%)	1.27 (0.60, 2.69)
	Separated/divorced	8 (41%)	16 (47%)	1.00 (0.54, 1.85)
	Single	2 (12%)	5 (15%)	0.80 (0.17, 3.71)
	Widowed	0 (0%)	2 (6%)	0.39 (0.02, 7.68)
Kobus, 2012	Insurance coverage			
	Medicaid	1 (0.2%)	3 (0.06%)	3.54 (0.37, 33.99)
Treatment-related characteristics				
Campbell, 2015	Australian Schedule 4 drug	146 (34%)	197 (30%)	1.15 (0.97, 1.37)
	Over-the-counter analgesic use	259 (61%)	424 (64%)	0.95 (0.86, 1.04)
	Past week oxycodone	251 (59%)	400 (61%)	0.91 (0.82, 1.01)
	Past week buprenorphine	36 (8%)	209 (32%)	0.25 (0.18, 0.35)
	Past 3-month doctor shopping	6 (1%)	5 (1%)	1.86 (0.57, 6.07)
	Used other person's opioid medication past 3-months	12 (3%)	12 (2%)	1.55 (0.70, 3.42)
Substance use				
Campbell, 2015	Lifetime overdose on any substance	79 (19%)	103 (16%)	1.19 (0.91, 1.55)
	Past 12 months risky drinking (>5 standard drinks)	96 (23%)	165 (25%)	0.90 (0.73, 1.13)
Physical health and patient behaviours				
		Median (IQR)	**Median (IQR)**	**Mean difference**

Kobus, 2012	Comorbidity (RxRisk) score	895.9 (653–2,115)	895.9 (653–1,432)	0
		Count (%)	**Count (%)**	**RR (95% CI)**
	Smoking	256 (57%)	2,489 (52%)	1.09 (1.00, 1.19)
	BMI ≥ 30	235 (52%)	2,388 (50%)	1.05 (0.95, 1.15
Clinical factors				
Campbell, 2015	Type of pain Arthritis or rheumatism Visceral pain	 256 (60%) 96 (23%)	 424 (64%) 141 (21%)	 0.94 (0.85, 1.03) 1.06 (0.84, 1.33)
Healthcare utilisation				
Kobus, 2012	ED visit with back pain diagnosis	131 (29%)	1,348 (28%)	1.03 (0.89, 1.20)

Table S6. All factors reported by included studies

1. Sociodemographic characteristics

1.1 Age					
Study ID	**High-dose**		**Low-dose**		**Mean difference, years (95% CI)**
	Mean age (years)	**SD**	**Mean age (years)**	**SD**	
Morasco, 2019	54.2	9.7	53.0	10.0	1.20 (-4.6, 6.9)
Chang, 2018a	53.8	12.7	55.4	15.8	-1.6 (-1.7, -1.5)
Chang, 2018b	47.22	10.6	-	-	-
Campbell, 2015	55.4	13.2	61.3	13.6	-5.9 (-7.5, -4.3)
Kobus, 2012	54.7	15.0	54.7	15.5	0 (-1.5, 1.5)
Chapman, 2013	Age was reported for all participants on opioids, split by women and men. Women had a mean age of 67 years (SD: 17, range: 24 to 104 years) and men were 62 years (SD: 16, range: 19 to 97 years).				

1.2 Gender (male)			
	High-dose	**Low-dose**	**RR (95% CI)**
	Count (%)	**Count (%)**	
Morasco, 2019	14 (82%)	25 (74%)	1.12 (0.83, 1.51)
Chang, 2018a	72,692 (48%)	1,464,693 (38%)	1.28 (1.28, 1.29)
Chang, 2018b	1,468 (53%)	83,150 (44%)	1.18 (1.14, 1.22)
Campbell, 2015	205 (48%)	260 (39%)	1.22 (1.07, 1.40)
Chapman, 2013	103 (39%)	1,422 (38%)	1.04 (0.89, 1.22)
Kobus, 2012	201 (44%)	1,767 (37%)	1.21 (1.08, 1.35)

1.3 Ethnicity				
	Variable	**High-dose**	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Morasco, 2019	Caucasian	15 (88%)	24 (71%)	1.25 (0.95, 1.65)
Kobus, 2012	Caucasian	362 (80%)	3,614 (75%)	1.06 (1.01, 1.12)
Kobus, 2012	Black	7 (2%)	134 (3%)	0.56 (0.26, 1.18)
	Native American/ Alaskan	9 (2%)	49 (1%)	1.95 (0.97, 3.95)

	Asian Pacific Islander	4 (1%)	40 (1%)	1.06 (0.38, 2.96)
	Other	7 (2%)	99 (2%)	0.75 (0.35, 1.61)
	Unknown/declined to answer	64 (14%)	879 (18%)	0.77 (0.61, 0.98)
	Hispanic	5 (2%)	93 (3%)	0.57 (0.23, 1.40)
1.4 Employment status				
Morasco, 2019	Unemployed	3 (18%)	7 (21%)	0.86 (0.25, 2.91)
Campbell, 2015	Unemployed	245 (58%)	263 (40%)	1.45 (1.28, 1.64)
Morasco, 2019	Employed	1 (6%)	3 (9%)	0.67 (0.07, 5.94)
	Other	1 (6%)	4 (12%)	0.50 (0.06, 4.13)
	Receiving disability	12 (71%)	20 (60%)	1.20 (0.79, 1.82)
1.5 Education				
		High-dose	**Low-dose**	**Mean difference, years**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Years of education	15.2 (2.6)	13.5 (2.0)	1.7
1.6 Marriage status				
Morasco, 2019	Married	7 (41%)	11 (32%)	1.27 (0.60, 2.69)
	Separated/ divorced	8 (41%)	16 (47%)	1.00 (0.54, 1.85)
	Single	2 (12%)	5 (15%)	0.80 (0.17, 3.71)
	Widowed	0 (0%)	2 (6%)	0.39 (0.02, 7.68)
1.7 State of residence				
Chang, 2018a	California	47,446 (31%)	1,416,000 (36%)	0.87 (0.86, 0.87)
	Florida	54,338 (36%)	1,207,982 (31%)	1.16 (1.15, 1.17)
	Georgia	20,692 (14%)	689,886 (18%)	0.77 (0.76, 0.78)

	Maryland Washington	12,487 (8%) 15,866 (11%)	250,868 (6%) 330,335 (8%)	1.29 (1.26, 1.31) 1.24 (1.22, 1.26)
1.8 Insurance coverage				
Kobus, 2012	Medicare Medicaid	154 (34%) 1 (0.2%)	1,352 (28%) 3 (0.06%)	1.21 (1.06, 1.39) 3.54 (0.37, 33.99)

2. Treatment-related characteristics

2.1 Coprescription				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Chang, 2018a	Benzodiazepines	61,623 (41%)	314,364 (8%)	5.06 (5.03, 5.10)
Chang, 2018b	Benzodiazepines	1,226 (44%)	8,488 (5%)	9.36 (9.96, 10.28)
Campbell, 2015	Benzodiazepines	172 (40%)	169 (26%)	1.58 (1.33, 1.88)
Kobus, 2012	Sedative-hypnotic prescription 6-months before/ after index visit	276 (61%)	2,022 (42%)	1.45 (1.34, 1.57)
Campbell, 2015	Antidepressants	246 (58%)	323 (49%)	1.18 (1.06, 1.32)
2.2 Opioid schedule				
Campbell, 2015	Australian Schedule 4	146 (34%)	197 (30%)	1.15 (0.97, 1.37)
	OTC analgesic use	259 (61%)	424 (64%)	0.95 (0.86, 1.04)
Kobus, 2012	Long-acting	400 (88%)	1,637 (34%)	2.60 (2.47, 2.74)
2.3 Type of opioid drug				
Campbell, 2015	Past week oxycodone	251 (59%)	400 (61%)	0.91 (0.82, 1.01)
	Past week morphine	86 (20%)	75 (11%)	1.78 (1.34, 2.37)
	Past week buprenorphine	36 (8%)	209 (32%)	0.25 (0.18, 0.35)
2.4 Adverse events and adverse drug reactions				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Number of adverse	91-199: 5	21-90: 4 (1-	Not possible

	events	(2-9.5) ≥200: 6 (3-11)	7) 1-20: 2 (0-6)	
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	ICD-10 lifetime pharmaceutical opioid dependence	49 (12%)	28 (4%)	2.72 (1.7, 4.25)
	ICD-10 12-month pharmaceutical opioid dependence	26 (6%)	13 (2%)	3.11 (1.61, 5.98)
2.5 Duration of opioid use				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Years prescribed opioids	91-199: 6 (2-13) ≥200: 7.8 (3-15)	21-90: 3 (1.1-8) 1-20: 2.5 (0.6-5)	Not possible
2.6 Opioid treatment problems and risks				
		High-dose	**Low-dose**	**Mean difference**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Risk for prescription opioid misuse from the Pain Medication Questionnaire	26.6 (6.4)	25.3 (9.2)	1.3
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	Prescribed opioid difficulty scale (PODS) intermediate- high (≥8)	297 (70%)	367 (56%)	1.26 (1.15, 1.38)
2.7 Treatment-related behaviours				
		High-dose	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Campbell, 2015	Past 3-month tampering	38 (9%)	29 (4%)	2.03 (1.27, 3.25)
	Past 3-month doctor shopping	6 (1%)	5 (1%)	1.86 (0.57, 6.07)
	Past 3-month different drug route	7 (2%)	1 (0.2%)	10.87 (1.34, 88.04)
	Used other person's	12 (3%)	12 (2%)	1.55 (0.70, 3.42)

	opioid medication past 3-months			
2.8 Number of opioid drugs				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Number of opioid drugs	91-199: 1 (1-1) ≥200: 1 (1-2)	21-90: 1 (1-1) 1-20: 1 (1-1)	Not possible

Clinical Characteristics

3. Substance use

3.1 Illicit drug use				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Campbell, 2015	Illicit drug use past 12 months	71 (17%)	67 (10%)	11.03 (5.75, 21.14)
3.2 Non-illicit substance use				
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Days of alcohol use in past 30 days	0.6 (1.3)	2.1 (5.1)	-1.5
3.3 Substance use problems/disorders				
		Count (%)	**Count (%)**	**RR (95% CI)**
Chang, 2018b	Opioid disorders	530 (19%)	1,243 (1%)	28.95 (26.34, 31.82)
Campbell, 2015	Lifetime overdose on any substance	79 (19%)	103 (16%)	1.19 (0.91, 1.55)
Kobus, 2012	Substance use disorder	141 (31%)	1,151 (24%)	1.30 (1.13, 1.51)
		Mean (days)	Mean (days)	
Chang, 2018b	Magnitude of high-risk use in 2012	115.7	-	-
3.4 Potential substance use problems				
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	Past 12 months risky drinking (>5 standard drinks)	96 (23%)	165 (25%)	0.90 (0.73, 1.13)

4. Physical health and patient behaviours

4.1 Morbidity measures						
Study ID	**Variable**	**High-dose**		**Low-dose**		**Mean difference**
		Mean score	**SD**	**Mean score**	**SD**	
Chang, 2018a	Chronic disease score	27.3	21.8	13.3	13.9	14
Chang, 2018b	Aggregated diagnostic cluster morbidity group (ADG) 2012	8.4	4.3	-	-	-
	Aggregated diagnostic cluster morbidity group (ADG) 2013	8.3	4.5	-	-	-
	Rx-defined morbidity groups (Rx-MGs) 2012	8.9	4.5	-	-	-
	Rx-defined morbidity groups (Rx-MGs) 2013	8.8	10.0	-	-	-
	Count of chronic conditions 2012	4.0	3.1	-	-	-
	Count of chronic conditions 2013	4.0	3.3	-	-	-
	Active ingredients 2012	13.1	8.2	-	-	-
	Active ingredients 2013	12.8	8.3	-	-	-
	Concurrent risk score 2012	4.7	6.8	-	-	-
	Concurrent	4.8	47.4	-	-	-

	risk score 2013					
		Median	**IQR**	**Median**	**IQR**	**Mean difference**
Kobus, 2012	Comorbidity (RxRisk) score	895.9	653–2,115	895.9	653–1,432	0
4.2 Smoking						
Study ID		**High-dose**		**Low-dose**		**RR (95% CI)**
		Count (%)		**Count (%)**		
Morasco, 2019		30.7% of the sample endorsed smoking cigarettes				Not possible
Kobus, 2012		256 (57%)		2,489 (52%)		1.09 (1.00, 1.19)
4.3 Body Mass Index (BMI)						
Kobus, 2012	BMI ≥ 30	235 (52%)		2,388 (50%)		1.05 (0.95, 1.15
4.4 Physical health score						
		High-dose		**Low-dose**		**Statistical analysis**
		Median (IQR)		**Median (IQR)**		
Campbell, 2015	SF-12	91-199: 25.9 ≥200: 25.8		21-90: 26.6 1-20: 28.1		Not possible

5. Pain measures

5.1 Duration of pain				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Years living with pain	91-199: 11 (5-22) ≥200: 15 (5-12)	21-90: 10 (2-21) 1-20: 11 (3-23)	Not possible
	12 month chronic pain conditions	91-199: 2 (2-3) ≥200: 2 (2-3)	21-90: 2 (1-3) 1-20: 2 (1-3)	Not possible
5.2 Pain measures				
		High-dose	**Low-dose**	**Linear regression model**
		Slope of function, k	**Slope of function, k**	
Morasco, 2019	Delay discounting	-5.8 (2.3)	-4.8 (2.0)	DD was significantly associated with

				dose (p-value: 0.003)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Pain severity from the Multi-dimensional Pain Inventory	4.5 (1.0)	4.1 (0.9)	0.40
	Pain interference from the Multi-dimensional Pain Inventory	4.7 (1.0)	4.6 (1.0)	0.10
		Mean (SD)	**Mean (SD)**	**RR (95% CI)**
Campbell, 2015	Pain severity from the Brief Pain Inventory	91-199: 5.4 (1.6) ≥200: 5.4 (1.8)	21-90: 4.8 (1.8) 1-20: 4.4 (1.8)	1.21 (1.11, 1.31) 1.21 (1.1, 1.35)
	Pain interference score from the Brief Pain Inventory	91-199: 6.1 (2.1) ≥200: 6.2 (2)	21-90: 5.3 (2.3) 1-20: 4.7 (2.3)	1.18 (1.09, 1.26) 1.23 (1.13, 1.34)
	Pain self-efficacy (PSEQ)	91-199: 27.4 (12.7) ≥200: 24.7 (12.5)	21-90: 31.8 (12.) 1-20: 35.8 (13.8)	0.97 (0.96, 0.99) 0.96 (0.94, 0.97)
5.3 Type of pain conditions				
		High-dose	**Low-dose**	**RR (95% CI)**
		Count, %	**Count, %**	
Campbell, 2015	Arthritis or rheumatism	256 (60%)	424 (64%)	0.94 (0.85, 1.03)
	Back or neck problems	344 (81%)	484 (73%)	1.10 (1.03, 1.18)
	Frequent/severe headaches	134 (32%)	170 (26%)	1.22 (1.01, 1.48)
	Visceral pain	96 (23%)	141 (21%)	1.06 (0.84, 1.33)

6. Healthcare utilisation

6.1 Clinic visits

Study ID	Variable	High-dose	Low-dose	Median difference
		Median	Median	
Kobus, 2012	Clinic visits of any type 6 months before/after index date	22	17	5
		Count (%)	**Count (%)**	**RR (95% CI)**
Kobus, 2012	Any pain clinic visit 6 months before/after index date	104 (23%)	530 (11%)	2.09 (1.73, 2.51)
6.2 Secondary & tertiary care use				
		High-dose	**Low-dose**	**RR (95%)**
		Count (%)	**Count (%)**	
Chang, 2018b	>1 emergency visit in 2012	829 (30%)	51,534 (27%)	1.09 (1.03, 1.16)
	>1 emergency visit in 2013	765 (28%)	34,338 (18%)	1.51 (1.42, 1.61)
Kobus, 2012	ER visit 6 months before/ after index visit	277 (50%)	1,878 (39%)	1.57 (1.45, 1.70)
Chang, 2018b	>1 hospitalisation in 2012	443 (16%)	17,061 (9%)	1.76 (1.62, 1.92)
	>1 hospitalisation in 2013	396 (14%)	11,110 (6%)	2.42 (2.21, 2.66)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Kobus, 2012	Hospitalisation 6 months before/ after index date	1.9 (1.3)	1.5 (1.1)	0.4
		Count (%)	**Count (%)**	**RR (95%)**
	ED visit with back pain diagnosis	131 (29%)	1,348 (28%)	1.03 (0.89, 1.20)
	Filled opioid prescription 5 days after ED visit	285 (63%)	2,696 (56%)	1.12 (1.04, 1.21)

6.3 Multiple prescribers				
Chang, 2018a	Obtain opioids from ≥ 4 unique prescribers & pharmacies over a 90 day period	1,176 (0.78%)	1,948 (0.05%)	15.6 (14.51, 16.76)
		Median	**Median**	**Median difference**
Kobus, 2012	Median opioid prescribers	4	3	1 (p=<0.001)
6.4 Healthcare costs				
		$ (USD)	**$ (USD)**	
Chang, 2018b	Total concurrent cost (2012)	30,486	-	-
	Total prospective cost (2013)	31,045	-	-
	Medical cost 2012	19,275	-	-
	Medical cost 2013	19,663	-	-
	Pharmacy cost 2012	11,211	-	-
	Pharmacy cost 2013	11,382	-	-
	Opioid medication cost 2012	6,169	-	-
	Opioid medication cost 2012	6,079	-	-

7. Mental health

7.1 Depression				
		High-dose	**Low-dose**	

Study ID	Variable & measure/metric	Count (%)	Count (%)	RR (95%)
Campbell, 2015	Moderate-severe depression [score of 10 on the PHQ-9]	221 (52%)	256 (39%)	1.34 (1.17, 1.53)
Kobus, 2012	ICD-9 diagnostic codes for depression: 296.2, 296.3, 300.4, 309.0, 309.1, 311	190 (42%)	1,425 (30%)	1.42 (1.26, 1.59)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Severity of depressive symptoms using the Beck Depression Inventory-2	21.5 (12.1)	20.0 (13.7)	1.5
7.2 Anxiety				
		High-dose	**Low-dose**	**Mean difference**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Severity of anxiety symptoms using the Generalized Anxiety Disorder-7	9.9 (5.6)	9.9 (6.0)	0
		Count (%)	**Count (%)**	**RR (95%)**
Campbell, 2015	Moderate-severe anxiety	98 (23%)	137 (21%)	1.14 (0.85, 1.53)
Kobus, 2012	ICD-9 diagnostic codes for anxiety: 300.0 – 300.09	89 (20%)	510 (11%)	2.06 (1.61, 2.65)
7.3 Post-traumatic stress disorder (PTSD)				
		High-dose	**Low-dose**	
		Count (%)	**Count (%)**	**RR (95%)**
Kobus, 2012	Posttraumatic stress disorder diagnostic code 309.81	20 (4%)	96 (2%)	2.21 (1.38, 3.55)

7.4 Any of depression, anxiety, PTSD or substance use				
Kobus, 2012	Report of depression, anxiety, PTSD and/or substance use disorder	280 (62%)	2,263 (47%)	1.32 (1.22, 1.42)

8. Patient beliefs

8.1 Relief from current medicines			
Study ID	**High-dose**	**Low-dose**	**Statistical analysis**
	Median (IQR)	**Median (IQR)**	
Campbell, 2015	91-199: 6 (5-8) ≥200: 6 (5-8)	21-90: 7 (5-8) 1-20: 7 (5-8)	Not possible

9. Prescriber behaviours

9.1 High-risk prescribers						
Study ID	**Variable**	**High-dose**		**Low-dose**		**RR (95% CI)**
		Mean %	**SD**	**Mean %**	**SD**	
Chang, 2018a	Proportion of prescriptions from high-risk prescribers	122,159 (81%)	31.8	973,865 (25%)	39.4	3.24 (3.23, 3.25)
Percentile group		**Count (%)**		**Count (%)**		**RR (95% CI)**
Chang, 2018a	100% (all opioid prescriptions from high-risk prescribers)	77,217 (51%)		572,633 (15%)		3.48 (3.46, 3.50)
	50-99% of prescriptions from high-risk prescribers	51,277 (34%)		471,351 (12%)		2.81 (2.79, 2.83)
	1-49% of prescriptions from high-risk prescribers	8,747 (6%)		222,041 (6%)		0.10 (0.10, 0.10)
	0% (no prescriptions from high-risk prescribers)	13,573 (9%)		2,629,436 (68%)		0.13 (0.13, 0.15)
9.2 High-volume prescribers						
Study ID	**Variable**	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**
Chang, 2018a	Daily opioid dose per transaction	120	70.8	48	42.7	72
	Days supplied per transaction	27	6.8	25	8.3	2
	Opioid volume per person	56	36.4	3	7.0	53

	Opioid prescription per person	18	11.0	2	5.0	16
		Count (%)		**Count (%)**		**RR (95% CI)**
Chang, 2018a	Proportion of total opioid volume	50,975 (34%)		1,488,066 (38%)		0.88 (0.88, 0.89)
	Proportion of total opioid prescriptions	16,590 (11%)		1,406,261 (36%)		0.31 (0.30, 0.31)
9.3 Low-volume prescribers						
		High-dose		**Low-dose**		**Mean difference**
		Mean	**SD**	**Mean**	**SD**	
Chang, 2018a	Daily opioid dose per transaction	102	70.2	35	27.9	67
	Days supplied per transaction	23	10.2	15	11.2	8
	Opioid volume per person	10	21.4	1	3.6	9
	Opioid prescription per person	4	7.5	3	4.0	1
		Count (%)		**Count (%)**		**RR (95% CI)**
Chang, 2018a	Proportion of total opioid volume	8,747 (6%)		864,792 (22%)		0.26 (0.26, 0.27)
	Proportion of total opioid prescriptions	3,620 (2%)		1,967,208 (51%)		0.05 (0.05, 0.05)