Influence of opioid prescribing standards on health outcomes among patients with long-term opioid use: a longitudinal cohort study

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Abstract:	**Background:** The introduction of College of Physicians and Surgeons of British Columbia (CPSBC) opioid prescribing standards and guidelines in mid-2016 was associated with reduced opioid analgesic use among patients with long-term use of prescription opioids in British Columbia (BC). In this study, we evaluated the impact of the standards and guidelines on health outcomes. **Methods:** We conducted a cohort study with monthly repeated measures using linked administrative data. The study included BC patients with long-term use of prescription opioids, excluding those with a history of long-term residential care, palliative care or cancer. Patients were followed for a 12-month pre-policy period and 10-month post-policy period, and were compared with a historical controls. We evaluated level and trend (slope) changes in rates of opioid overdose hospitalization, and secondary outcomes of all-cause hospitalizations, all-cause emergency room (ER) visits, opioid overdose mortality, and all-cause mortality. **Results:** The study included 68,113 patients in the main cohort and 68,429 historical controls. We found no impact on opioid overdose hospitalizations in level (adjusted rate ratio 0.83; 95% CI 0.45 to 1.54) or in trend (adjusted RR 1.00; 95% CI 0.91 to 1.10). All-cause hospitalizations declined in level but may have increased in trend, suggesting a temporary decrease in hospitalizations occurred. We found no significant changes in all-cause ER visits, opioid overdose mortality, or all-cause mortality. **Interpretation:** Among patients with a history of long-term prescription

	opioid use, the CPSBC regulatory prescribing standards and guidelines were not associated with changes in opioid overdose hospitalizations, all-cause ER visits, opioid overdose mortality, or all-cause mortality, or a sustained reduction in all-cause hospitalizations, over a 10-month post-introduction period.

Influence of opioid prescribing standards on health outcomes among patients with long-term opioid use: a longitudinal cohort study

Short title: Influence of opioid prescribing standards

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ABSTRACT

Background: The introduction of College of Physicians and Surgeons of British Columbia (CPSBC) opioid prescribing standards and guidelines in mid-2016 was associated with reduced opioid analgesic use among patients with long-term use of prescription opioids in British Columbia (BC). In this study, we evaluated the impact of the standards and guidelines on health outcomes.

Methods: We conducted a cohort study with monthly repeated measures using linked administrative data. The study included BC patients with long-term use of prescription opioids, excluding those with a history of long-term residential care, palliative care or cancer. Patients were followed for a 12-month pre-policy period and 10-month post-policy period, and were compared with a historical controls. We evaluated level and trend (slope) changes in rates of opioid overdose hospitalization, and secondary outcomes of all-cause hospitalizations, all-cause emergency room (ER) visits, opioid overdose mortality, and all-cause mortality.

Results: The study included 68,113 patients in the main cohort and 68,429 historical controls. We found no impact on opioid overdose hospitalizations in level (adjusted rate ratio 0.83; 95% CI 0.45 to 1.54) or in trend (adjusted RR 1.00; 95% CI 0.91 to 1.10). All-cause hospitalizations declined in level but may have increased in trend, suggesting a temporary decrease in hospitalizations occurred. We found no significant changes in all-cause ER visits, opioid overdose mortality, or all-cause mortality.

Interpretation: Among patients with a history of long-term prescription opioid use, the CPSBC regulatory prescribing standards and guidelines were not associated with changes in opioid overdose hospitalizations, all-cause ER visits, opioid overdose mortality, or all-cause mortality, or a sustained reduction in all-cause hospitalizations, over a 10-month post-introduction period.

In the context of the opioid overdose crisis in the United States, the US Centers for Disease Control (CDC) published a guideline on opioid prescribing for chronic pain in March 2016.[1] At the same time, British Columbia (BC) was experiencing the highest rates of opioid overdose hospitalizations and apparent opioid-related deaths among Canadian provinces.[2,3] The opioid overdose deaths in BC in recent years are associated with the contamination of street drugs with fentanyl and other potent synthetic opioids.[4] Nevertheless, the overdose deaths raised concerns that the rate of opioid analgesic prescribing was a contributing factor to the province's crisis of opioid-related harms, as rates of opioid prescribing have been associated with opioid-related morbidity and mortality in ecological-level studies of patients in BC, Ontario and the United States.[5-9]

Following the publication of the US CDC guideline, the College of Physicians and Surgeons of British Columbia (CPSBC) first endorsed the guideline[10] and subsequently issued its own standards and guidelines related to prescribing of opioid analgesics which took effect on June 1, 2016.[11] When issuing the standards and guidelines, the College acknowledged that "[t]he public health crisis of prescription drug misuse has developed in part due to the prescribing of physicians" and highlighted the profession's responsibility to limit the over-prescribing of opioids.[11] In addition, the College noted that the potential benefit of long-term opioid therapy for chronic noncancer pain was modest,[11] which is also suggested by a systematic review published since the standards and guidelines were issued.[12] Notably, the CPSBC policy contained both legally enforceable standards and recommended guidelines. The policy was not intended to apply to patients with active cancer or those receiving palliative or end-of-life care.

This study is the second phase of a two-part research project evaluating the impact of the CPSBC opioid standards and guidelines among patients with a history of long-term opioid use. In the first phase of the project, we found that the CPSBC standards and guidelines were associated with a modest reduction in opioid utilization, increased switching from high-dose opioid therapy to lower-dose opioid therapy, and a decrease in concurrent use of opioids and sedative/hypnotic medications.[13] In this study, we evaluated the impact of the CPSBC standards and guidelines on health outcomes, including opioid overdose hospitalizations, all-cause hospitalizations, all-cause emergency room visits, opioid overdose mortality and all-cause mortality.

METHODS

Study setting and design

We described our study design and study population in our report on the first phase of our research project evaluating the impact of the CPSBC standards and guidelines,[13] but here we briefly highlight key aspects of the study design and population and include elements unique to our analysis of health outcomes. We used a longitudinal cohort study design with a historical control group.[14,15] The longitudinal data in our study included monthly repeated outcome measures, which allowed us to evaluate the impact of the introduction of the standards and guidelines on health outcomes while controlling for patient covariates. Analyses included BC residents with a history of long-term use of prescription opioids, where “long-term use” consisted of receiving at least two opioid prescriptions during a 6-month baseline period, with at least one fill in the first 3 months and one fill in the last 3 months, comprising at least 60 days' supply. Opioid analgesic medications included buprenorphine (patch), codeine, fentanyl, hydromorphone, meperidine, oxycodone, tapentadol or tramadol.

Patients who met our criteria for long-term opioid use during an identification period of Dec 1, 2014 – May 31, 2015 were followed for a 12-month prepolicy period prior to the introduction of the standards and guidelines on June 1, 2016, and a 10-month postpolicy period (Figure S1, Supplementary Appendix). We designated these patients as the policy cohort, as their follow-up included a period during which the standards and guidelines applied. Patients who met our criteria for long-term opioid use one year earlier, during Dec 1, 2013 – May 31, 2015, were designated as the historical control cohort. Follow-up of these patients included a 12-month baseline period (June 2014 – May 2015) and a 10-month control period (June 2015 – March 2016), analogous to the prepolicy and postpolicy period of patients in the policy cohort. As the follow-up of historical controls ended prior to the introduction of the standards and guidelines, they provided a comparison group to help control for changes in outcome rates in the absence of the policy of interest. It was possible for patients to be members of both cohorts if they met the inclusion criteria during the identification period for both cohorts. We excluded patients who lacked 1 year of medical services coverage and patients in long-term residential care, and censored patients if their coverage ended or they entered long-term care. As the standards and guidelines were not applicable to treatment of patients receiving palliative care or with active cancer, we also excluded patients who had a record of palliative care or a medical visit with a diagnosis of cancer in the year prior to follow-up, and censored patients who received palliative care or a diagnosis of cancer during follow-up (see Table S1 of Supplementary Appendix for diagnostic codes).

Analyses of the outcome of all-cause emergency room visits applied only to a cohort of patients who were likely to report to the 29 hospitals in BC that supply data on emergency room visits to an ambulatory care database available for analysis (the National Ambulatory Care

Reporting System). We included patients living in areas in which residents were admitted to one of these 29 hospitals for >=95% of all hospital admissions, according to the first 3 digits for patients' postal codes, based on the assumption that we would also capture most emergency room visits for these patients.

The study was approved by the University of British Columbia Clinical Research Ethics Board.

Data sources

We had access to patient-level, de-identified, linked data from the BC Ministry of Health's Health*ideas* data warehouse to conduct the study. This included data from the BC Medical Services Plan, BC PharmaNet, the BC Vital Statistics Agency, the National Ambulatory Care Reporting System, and the Canadian Institute for Health Information Discharge Abstract Database. The data cover most of the BC population but exclude the approximately 4 percent of the population covered by federally insured drug plans for First Nations, members of the military, members of the Royal Canadian Mounted Police and inmates in federal penitentiaries.

Health outcomes

The primary outcome was hospitalization for opioid overdose, which was defined as a hospital admission with an International Classification of Disease, version 10 (ICD-10), diagnostic code for opioid poisoning (Table S2). Secondary health outcomes included all-cause hospitalization, all-cause emergency room visits, opioid overdose mortality, and all-cause mortality. Opioid overdose mortality was defined as a death recorded in vital statistics data with an ICD-10 code for opioid poisoning as a cause of death (Table S2).

Covariates

We identified patient characteristics to describe the cohorts and adjust for confounding, including demographic variables (sex, age category, low-income status, and rural residence); medical history, based on outpatient and inpatient records in the 365 days prior to follow-up; and prescription drug history in the 180 days prior to follow-up. Medical history variables included psychiatric illness, mechanical neck or back problems (excluding low back pain), mechanical low back pain, osteoarthritis, rheumatoid arthritis, diabetic neuropathy, peripheral neuropathy (excluding diabetic neuropathy), lumbar radiculopathy, alcohol dependence or abuse, opioid use disorder, and Romano comorbidity score (an index of the patient's comorbidities based on previous diagnoses).[16,17] (See Tables S3 and S4 for diagnostic codes and definitions for chronic pain conditions.)[18-26] Prescription history variables included opioid substitution therapy (>=1 prescription), use of sedative/hypnotic medication (including benzodiazepines) (>=1 prescription), maximum daily opioid analgesic dose prescribed (<=50 milligrams of morphine equivalents [MME], >50 to 90 MME, >90 to 200 MME, or >200 MME),[27] and intensity of opioid analgesic use (60 to <90 days' supply or >=90 days' supply prescribed).

Statistical analyses

We estimated rate ratios for the effect of the opioid policies on health outcomes, using generalized linear models with a log link function, a Poisson error distribution and an autoregressive correlation structure.[15] Data included multiple observations for most patients due to the longitudinal design with repeated measures and inclusion of some patients in both cohorts, so we used generalized estimating equations in regression models to adjust for clustering effects.[28] In addition, we adjusted estimates by the patient-level covariates to control for confounding. We conducted analyses using SAS Enterprise Guide software, version 6.1.

We estimated rate ratios for changes to the level and trend of each outcome following the introduction of the opioid prescribing standards and guidelines among patients in the policy cohort in comparison to the historical control cohort. Level changes represent a sudden change in event rates following the introduction of the policy, whereas trend (slope) changes reflect gradual monthly changes in outcome rates occurring during each month (Figure S2). Our statistical model used interactions between a binary variable for cohort status (policy cohort v. historical control cohort) and level and trend effect variables to estimate post-policy changes to level or trend.[15,29]

In addition, we conducted pre-planned analyses of our primary outcome in subgroups defined by prescription opioid use during the 180 days prior to follow-up, including by maximum daily dose (<=50 MME vs >50 MME) and intensity of use (<90 days' supply vs >=90 days' supply dispensed).

RESULTS

The policy cohort included 68,113 patients, and the historical control cohort included 68,429 patients; 47,416 patients were in both cohorts, because they met the inclusion criteria at baseline for each cohort. Patients were followed for 1 to 22 months, and 90 percent for at least 16 months. Characteristics of patients in these cohorts were described in our previous report on the impact of the CPSBC opioid policies on drug utilization among these patients and are summarized in Table 1.[13]

The crude rates of opioid overdose hospitalizations were 3.2 hospitalizations per thousand person-years during the pre-policy period in the policy cohort and 3.3 hospitalizations per thousand person-years in the historical control cohort (Table 2 and Figure 1). In our analysis of the primary outcome of hospital admissions involving opioid overdose, we observed no

significant impact of the CPSBC opioid standards and guidelines on either the level of opioid overdose hospitalizations (adjusted RR 0.83; 95% CI 0.45 to 1.54) or the trend in opioid overdose hospitalizations (adjusted RR 1.00; 95% CI 0.91 to 1.10) (Table 2). We also found no change in opioid overdose hospitalizations in subgroup analyses by baseline prescription opioid use (Table 2).

Our results suggest a decrease in the level all-cause hospitalizations occurred in the policy cohort relative to the historical control cohort following the introduction of the CPSBC opioid prescribing standards and guidelines (adjusted RR 0.86; 95% CI 0.82 to 0.91). However, this decrease in level may have been accompanied by an increasing monthly trend of all-cause hospitalizations (RR 1.01; 95% CI 1.00 to 1.02; p=0.002), although the trend estimate's lower confidence limit overlapped 1.00 (Table 2). This mixed finding for all-cause hospitalizations is reflected in Figure 1, which shows that the crude rate of all-cause hospitalizations for the policy cohort declined in level in the initial months of the post-policy period before trending upward without showing a clear difference from historical controls. In addition, we found no change following the introduction of the standards and guidelines in all-cause emergency room visits, opioid overdose mortality, or all-cause mortality (Table 2, Figure 2 and Figure 3).

INTERPRETATION

The CPSBC opioid prescribing standards and guidelines were not associated with a significant change in the primary outcome of opioid overdose hospitalizations among patients with long-term use of prescription opioid analgesics. Our mixed finding that all-cause hospitalizations declined in level but may have increased in trend suggests a temporary decline in hospitalizations may have occurred. In addition, we found no significant change in all-cause emergency room visits, opioid overdose mortality, or all-cause mortality.

Opioid prescribing practices have likely helped to create the current crisis of opioid overdoses and deaths in BC and other jurisdictions in North America, as opioids including high-dose opioids were increasingly prescribed for chronic noncancer pain.[30-32] We previously reported that the CPSBC standards and guidelines were associated with modestly reduced use of opioid analgesics, increased switching from high-dose to lower-dose opioids, and a decrease in concurrent use of opioids and sedative/hypnotic medications, among patients with long-term opioid use.[13] Our current analysis suggests that these modest changes in prescription opioid utilization did not translate into reductions in opioid overdose hospitalizations, all-cause emergency room visits, opioid overdose mortality, or all-cause mortality, or sustained reductions in all-cause hospitalizations.

A major contributing factor to the rise in opioid overdoses and deaths in BC in recent years has been contamination of street drugs with synthetic opioids such as fentanyl.[4] Concern has been expressed that policies focused on reducing prescribing of opioid analgesics could increase opioid-related deaths, if patients unable to access prescription opioids for adequate pain relief turned to street drugs and were exposed to dangerously high levels of synthetic opioids.[33] Our study did not find evidence that the CPSBC standards and guidelines had the unintended consequence of increasing opioid overdose hospitalizations or opioid overdose mortality.

It would be valuable for future research to further investigate how opioid prescribing standards or guidelines influence treatment of chronic non-cancer pain, such as rates of initiation of or switching to non-opioid analgesic medications or non-pharmacologic treatments. The generalizability of our findings may depend on the similarity of other opioid prescribing policies to the CPSBC standards and guidelines, and on contextual factors such as the availability of

alternative treatments and the contamination of the street drug supply. The impact of opioid prescribing standards or guidelines on health outcomes merits additional research.

Limitations

Our study had several limitations. We focused on the impact of the College's opioid prescribing standards and guidelines on patients with a history of long-term opioid use during the 10-month period after they were introduced; impacts over the longer term or on other BC residents were beyond the scope of our study. It is possible that our primary outcome of opioid overdose hospitalization was biased toward the null due to misclassification bias, as opioid overdoses of patients admitted to hospital may not always be accurately identified in administrative data. In addition, our analyses may have been subject to time-varying confounders such as co-interventions or the exposure of some members of the study population to street drugs contaminated with fentanyl or other potent synthetic opioids at levels that varied over time. Co-interventions included the declaration of a public health emergency in BC,[34] the scaling up the provincial take-home naloxone program,[35] and increasing the availability of opioid agonist therapy.[36]

Conclusion

The regulatory opioid prescribing standards and guidelines introduced by the CPSBC in mid-2016 were not associated with reductions in opioid overdose hospitalizations, all-cause emergency room visits, opioid overdose mortality or all-cause mortality, or a sustained reduction in all-cause hospitalizations, over a 10-month post-policy period among patients with a history of long-term opioid use. Conversely, our analyses did not indicate that these policies produced the unintended consequence of increasing risk of these adverse events in this population.

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The British Columbia Ministry of Health and the British Columbia Vital Statistics Agency approved access to and use of British Columbia data. British Columbia data sources were as follows (http://www.popdata.bc.ca/data):

- British Columbia Ministry of Health [creator] (2017): Medical Services Plan (MSP) Payment Information File. BC Ministry of Health [publisher]. MOH (2017);
- British Columbia Ministry of Health [creator] (2017): PharmaNet. BC Ministry of Health [publisher]. Data Stewardship Committee (2017);
- Canadian Institute for Health Information [creator] (2017): Discharge Abstract Database (Hospital Separations). BC Ministry of Health [publisher]. MOH (2017);
- British Columbia Ministry of Health [creator] (2017): Consolidation File (MSP Registration & Premium Billing). BC Ministry of Health [publisher]. MOH (2017);
- BC Vital Statistics Agency [creator] (2017): Vital Statistics Deaths. BC Ministry of Health [publisher]. Vital Statistics Agency (2017).

All inferences, opinions, and conclusions drawn in this article are those of the authors, and do not reflect the opinions or policies of the BC Ministry of Health or other Data Stewards.

Author contributions: RLM, KB, GC, JW and CRD contributed to the study design. RLM had full access to all of the data in the study, conducted the data analysis and drafted the manuscript. All authors contributed to the interpretation of the data, revised the work for important

intellectual content, provided final approval for the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement: The authors do not have permission to share data from this study.

Ethics: The study was approved by the University of British Columbia Clinical Research Ethics Board.

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Table 1. Characteristics of patients with long-term opioid use in British Columbia, historical control cohort vs policy cohort

Characteristic	Historical cohort, patients (%) (n=68,429)	Policy cohort, patients (%) (n=68,113)
Demographic characteristics		
Sex		
Female	36,894 (53.9)	36,903 (54.2)
Male	31,535 (46.1)	31,210 (45.8)
Age, years		
Under 25	473 (0.7)	388 (0.6)
25 to 39	6,376 (9.3)	5,925 (8.7)
40 to 54	20,946 (30.6)	19,848 (29.1)
55 to 64	18,779 (27.4)	19,249 (28.3)
65 to 74	11,670 (17.1)	12,391 (18.2)
75 to 84	6,921 (10.1)	7,015 (10.3)
85 or older	3,264 (4.8)	3,297 (4.8)
Low income	13,222 (19.3)	12,683 (18.6)
Place of residence		
Rural	10,766 (15.7)	10,726 (15.7)
Urban	57,663 (84.3)	57,387 (84.3)
Medical history in 365 days prior to follow-up		
Psychiatric illness	14,994 (21.9)	14,152 (20.8)
Chronic pain conditions:		
Mechanical neck or back pain*	9,738 (14.2)	9,815 (14.4)
Mechanical low back pain	12,900 (18.9)	13,477 (19.8)
Osteoarthritis	6,778 (9.9)	6,723 (9.9)
Rheumatoid arthritis	1,619 (2.4)	1,566 (2.3)
Diabetic neuropathy	239 (0.3)	262 (0.4)
Peripheral neuropathy	230 (0.3)	262 (0.4)
Lumbar radiculopathy	182 (0.3)	221 (0.3)
Alcohol dependence or abuse	1,307 (1.9)	1,311 (1.9)
Opioid use disorder	821 (1.2)	931 (1.4)
Romano comorbidity score		
Zero	36,447 (53.3)	36,000 (52.9)
One	17,146 (25.1)	16,965 (24.9)
Two	7,074 (10.3)	7,320 (10.7)
Three or more	7,762 (11.3)	7,828 (11.5)
Prescription history in 180 days prior to follow-up		
Opioid substitution therapy	943 (1.4)	909 (1.3)
Maximum daily opioid analgesic dose dispensed		
Lower dose (<=50 MME)	41,679 (60.9)	42,565 (62.5)
Intermediate dose (>50 to 90 MME)	12,987 (19.0)	12,753 (18.7)
High dose (>90 to 200 MME)	8,598 (12.6)	8,144 (12.0)
Very high dose (>200 MME)	5,165 (7.5)	4,651 (6.8)
Intensity of opioid analgesic use†		
Lower intensity use (<90 days' supply)	10,648 (15.6)	10,471 (15.4)
Higher intensity use (>=90 days' supply)	57,781 (84.4)	57,642 (84.6)
Sedative/hypnotic medication use	30,291 (44.3)	28,737 (42.2)

Patient characteristics were evaluated prior to cohort entry (1 June 2014 for the historical control cohort and prior 1 June 2015 for the policy cohort). *Excluded low back pain. †Based on days' supply dispensed. MME=milligrams of morphine equivalent

Table 2. Impact of opioid prescribing standards and guidelines policy on health outcomes among patients with long-term opioid use

Analysis	Patients		Crude event rates per 1,000 person-years*†				Adjusted rate ratios (95% CI)	
			Months 1 to 12		Months 13 to 22			
	Historical cohort	Policy cohort	Historical cohort	Policy cohort	Historical cohort	Policy cohort	Impact on outcome level	Impact on outcome trend
(a) Primary outcome:								
Opioid overdose hospitalization	68,429	68,113	3.3	3.2	3.3	2.8	0.83 (0.45,1.54)	1.00 (0.91,1.10)
(b) Secondary outcomes:								
All-cause hospitalization	68,429	68,113	522	530	497	497	0.86 (0.82,0.91)	1.01 (1.00,1.02)‡
All-cause emergency room visits	27,778	27,713	828	848	829	815	0.94 (0.88,1.00)	1.00 (0.99,1.01)
Opioid overdose mortality§	68,429	68,113	1.0	1.3	1.4	2.1	1.38 (0.60,3.21)	0.97 (0.87,1.09)
All-cause mortality	68,429	68,113	17.2	17.5	17.2	19.3	1.08 (0.87,1.35)	1.01 (0.98,1.04)
(c) Opioid overdose hospitalization, by baseline opioid analgesic use:								
Maximum daily dose received§¶								
Lower dose (<=50 MME)	41,679	42,565	1.8	2.1	1.9	1.7	0.54 (0.21,1.35)	1.07 (0.93,1.24)
Higher dose (>50 MME)	26,750	25,548	5.7	4.9	5.5	4.7	0.96 (0.44,2.10)	0.98 (0.87,1.10)
Intensity of opioid use‡§								
Lower (<90 days' supply)	10,648	10,471	1.7	1.6	1.1	1.3	1.03 (0.16,6.84)	1.05 (0.72,1.51)
Higher (>=90 days' supply)	57,781	57,642	3.7	3.5	3.7	3.1	0.79 (0.42,1.49)	1.00 (0.91,1.10)

*May include multiple events of the same type for the same patient, but not in the same month. †Months 1 to 12 and months 13 to 22 represent the pre- and post-policy periods for the policy cohort and analogous periods for the historical cohort. ‡p=0.002 §It was not feasible to include covariates for neuropathic pain, due to small numbers of patients with these conditions, in analyses of opioid overdose mortality or in subgroup analyses of opioid overdose hospitalization. ¶Patient subgroups were defined by opioid analgesic medication use in the 180 days prior to follow-up. ME=milligrams of morphine equivalents CI=confidence interval

Figure 1. Opioid overdose (OD) hospitalization and all-cause (AC) hospitalization rates per 1,000 person-years in policy cohort (PC) vs historical control cohort (HCC)

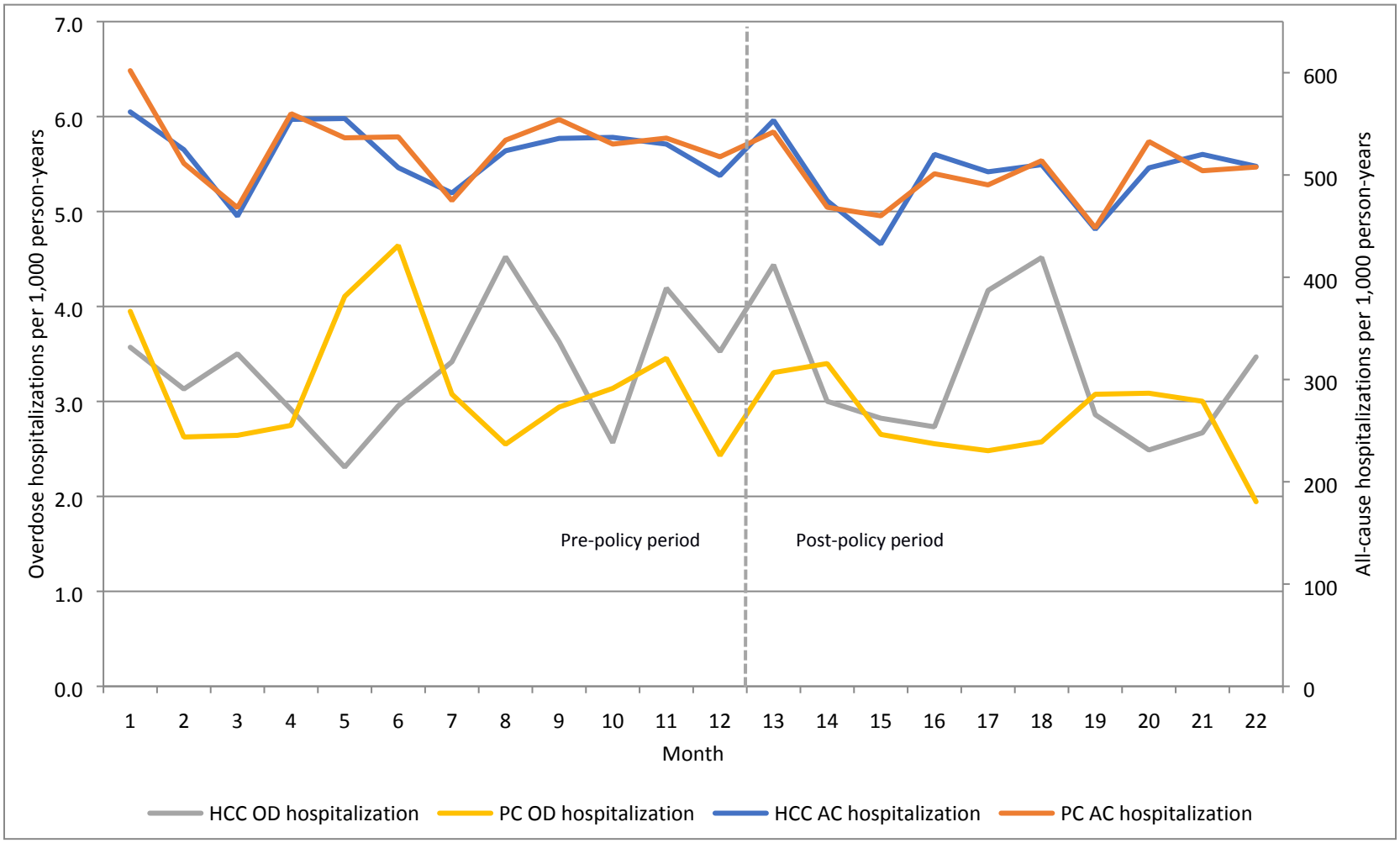


Figure 2. All-cause emergency room (ER) visit rates per 1,000 person-years in policy cohort (PC) vs historical control cohort (HCC), among patients 95% likely to report to a hospital in NACRS database

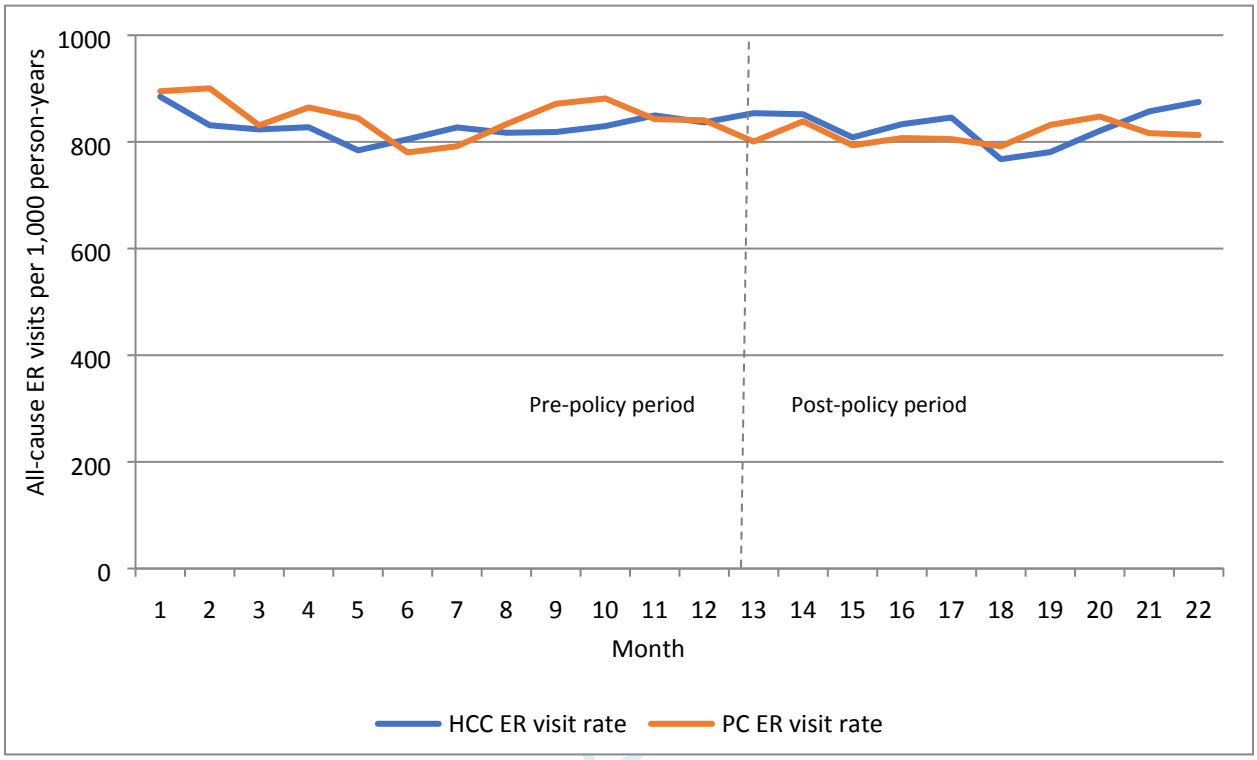
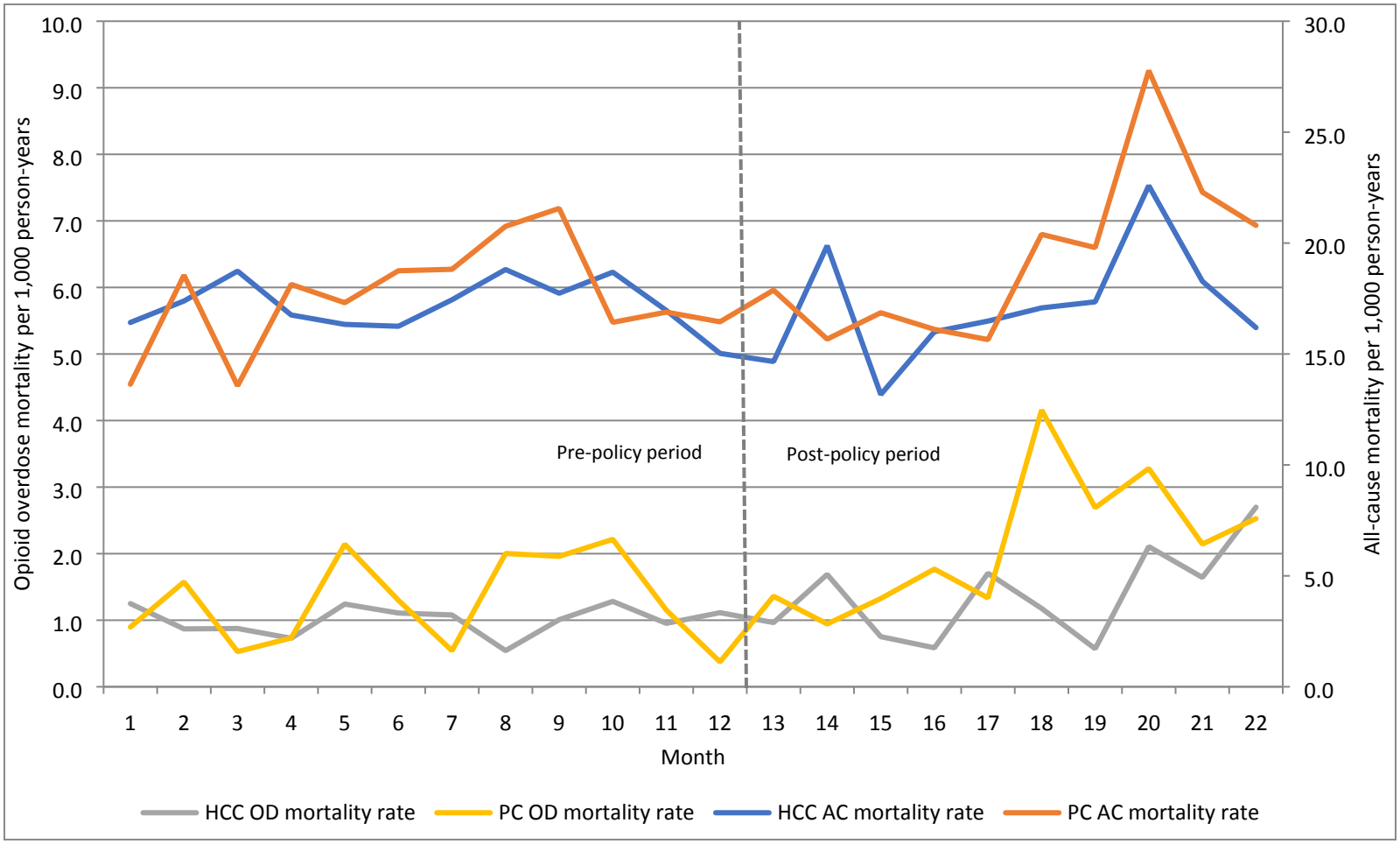


Figure 3. Opioid overdose (OD) mortality and all-cause (AC) mortality rates per 1,000 person-years in policy cohort (PC) vs historical control cohort (HCC)



SUPPLEMENTARY APPENDIX

Figure S1. Longitudinal cohort study design with cohort identification and follow-up periods for policy cohort and historical control cohort. Patients were selected for each cohort during a 6-month identification period. The policy cohort was followed for a 12-month pre-policy period and a 10-month post-policy period. Historical controls were followed for an analogous 12-month baseline period and 10-month control period, but not exposed to the policy.

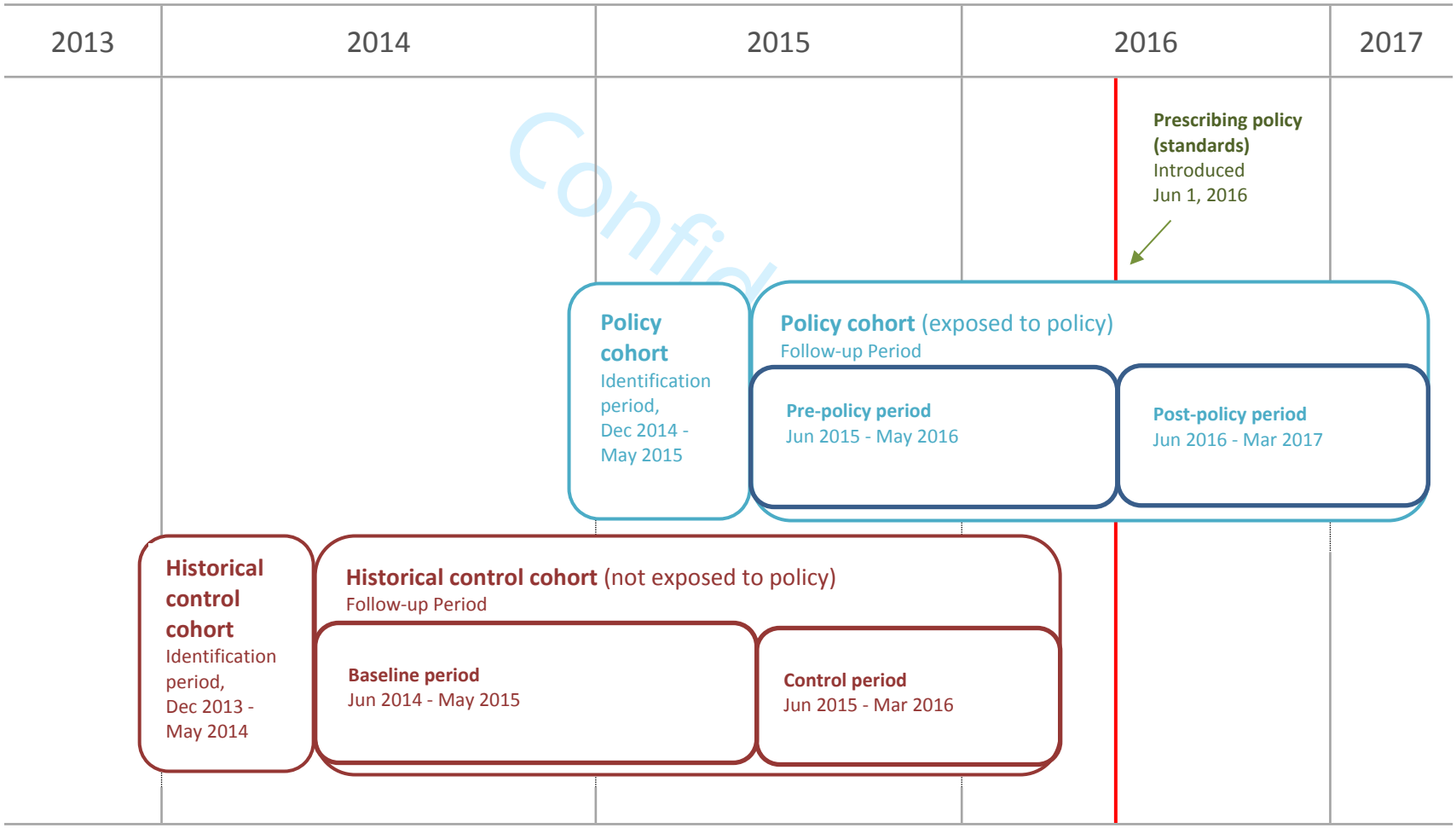


Figure S2. Potential changes in event rate following a change in policy

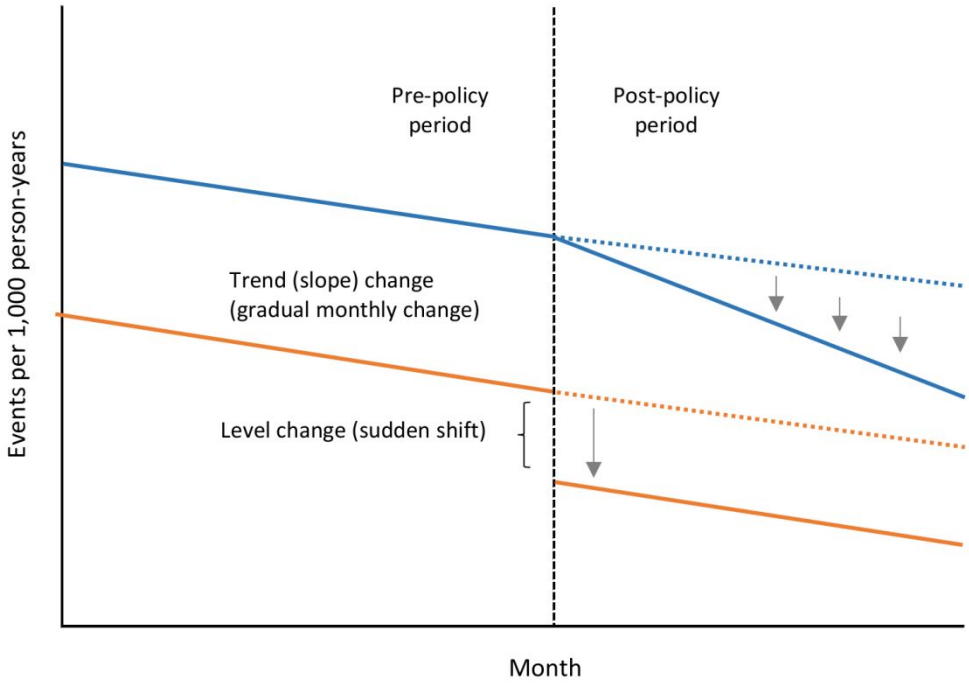


Table S1. Cancer diagnostic codes for exclusions

Description	ICD codes
ICD-9 codes:	
Malignant neoplasm of lip, oral cavity, and pharynx	140–149
Malignant neoplasm of digestive organs and peritoneum	150-159
Malignant neoplasm of respiratory and intrathoracic organs	160-165
Malignant neoplasm of bone, connective tissue, skin, and breast	170-175
Kaposi's sarcoma	176
Malignant neoplasm of genitourinary organs	179-189
Malignant neoplasm of other and unspecified sites	190-199
Malignant neoplasm of lymphatic and hematopoietic tissue	200-208
Neuroendocrine tumors	209
ICD-10 codes:	
Malignant neoplasms of lip, oral cavity and pharynx	C00-C14
Malignant neoplasms of digestive organs	C15-C26
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39
Malignant neoplasms of bone and articular cartilage	C40-C41
Melanoma and other malignant neoplasms of skin	C43-C44
Malignant neoplasms of mesothelial and soft tissue	C45-C49
Malignant neoplasm of breast	C50
Malignant neoplasms of female genital organs	C51-C58
Malignant neoplasms of male genital organs	C60-C63
Malignant neoplasms of urinary tract	C64-C68
Malignant neoplasms of eye, brain and other parts of central nervous system	C69-72
Malignant neoplasms of thyroid and other endocrine glands	C73-C75
Malignant neoplasms of ill-defined, secondary and unspecified sites	C76-C80
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81-C96

Table S2. Opioid poisoning codes

Description	ICD-10 codes
Poisoning by opium	T40.0
Poisoning by heroin	T40.1
Poisoning by other opioids	T40.2
Poisoning by methadone	T40.3
Poisoning by synthetic opioids	T40.4
Poisoning by unspecified/other opioids	T40.6

Opioid poisoning definitions:

Opioid overdose hospitalization is defined as occurring on the date of hospital admission, when a hospital admission record is coded with an ICD-10 code opioid poisoning (**T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6**) and the hospital diagnosis type is coded as M (most responsible diagnosis); 1 (pre-admit comorbidity); W, X or Y (service transfer diagnoses); or 6 (proxy most responsible diagnosis).

Opioid overdose death is defined as occurring on the date of death recorded in vital statistics data, when the death is accompanied by a cause of death coded with an ICD-10 code opioid poisoning (**T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6**).

Table S3. Chronic non-cancer pain covariates

Chronic pain condition	Diagnostic codes (ICD-9, ICD-10)	Definition (algorithm)
Nociceptive pain:		
Mechanical neck and back problems (excluding low back pain)	ICD-9: 721.0, 721.1, 721.2, 721.3, 721.4, 721.5, 721.6, 721.7, 721.8, 721.9, 722.0, 722.1, 722.2, 722.3, 722.4, 722.5, 722.6, 722.7, 722.8, 722.9, 723.0, 723.1, 723.2, 723.3, 723.4, 723.5, 723.7, 723.8, 723.9, 737.1, 737.2, 738.2, 738.4, 738.5, 739.1, 739.2, 739.3, 739.4, 756.1, 846.0, 846.1, 846.2, 846.3, 846.8, 846.9, 847.0, 847.1, 847.2, 847.3, 847.9 ICD-10: M47, M48.1, M48.2, M48.3, M48.9	>=1 healthcare encounter with any of the ICD codes listed during previous 365 days [Adapted from an algorithm created by Lavis et al, 1998,[18] and validated by Lacasse et al, 2015][19]
Low back pain, mechanical	ICD-9: 724.0, 724.1, 724.2, 724.3, 724.5, 724.6, 724.8, 724.9, ICD-10: M43.2, M43.5, M48.0, M53.2, M53.8, M53.9, M54.5	>=1 healthcare encounter with any of the ICD codes listed during previous 365 days [Adapted from an algorithm validated by Lacasse et al, 2015]
Osteoarthritis	ICD-9: 715.00–715.99 ICD-10: M15, M16, M17, M18, M19	>=1 hospital admission or >=3 physician visits with any of the ICD codes listed during previous 365 days [Adaptation of an algorithm of Harrold et al, 2000,[20] who tested >=3 ambulatory visits]
Rheumatoid arthritis	ICD-9: 714 ICD-10: M05-M06	>=1 hospital admission or >=3 physician visits with any of the ICD codes listed during previous 365 days [Adaptation of algorithms of Widdifield et al, 2013,[21] who tested 1 hospitalization ever as one algorithm and >=3 physician visits as another algorithm]

Neuropathic pain:		
Diabetic neuropathy	ICD-9: 250.6, 357.2 ICD-10: E10.4, E11.4	>=1 hospital admission or >=2 physician visits with any of the ICD codes listed during previous 365 days [Cf. Dworkin et al, 2010;[22] Berger et al, 2003;[23] Kostev et al, 2014][24]
Peripheral neuropathy (excluding diabetic neuropathy)	ICD-9: 354.5, 356.0, 357.0, 357.1, 357.3, 357.4, 357.5, 357.6, 357.7, 357.8, 357.9 ICD-10: G58.7, G60.0, G61.0, G61.9, G63, G62.0, G62.1, G62.2, G62.8	>=1 hospital admission or >=2 physician visits with any of the ICD codes listed during previous 365 days [Adaptation of algorithm of Callaghan et al, 2015][25]
Lumbar radiculopathy	ICD-9: 724.4 ICD-10: M54.16	>=1 hospital admission or >=2 physician visits during previous 365 days [Adapted from Schoenfeld et al, 2012][26]

Table S4. Diagnostic codes for other covariates

Description	Subcategory (if applicable)	ICD codes
Opioid use disorder		ICD-9: 304.0 ICD-10: F11
Alcohol dependence or abuse		ICD-9: 303 ICD-10: F10.1, F10.2
Psychiatric illness	Depression	ICD-9: 311, 296.2, 296.3 ICD-10: F32, F33
	Bipolar disorder/ mixed mania	ICD-9: 296.0, 296.1, 296.4, 296.9 ICD-10: F31
	Schizophrenia	ICD-9: 295 ICD-10: F20
	Personality disorders	ICD-9: 301 ICD-10: F60
	Other psychosis	ICD-9: 297 - 299 ICD-10: F21 – F29

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) title (p. 1) and abstract (p. 2) (b) abstract (p. 2)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract (p. 2) Abstract (p. 2) Abstract (p. 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	pp. 3-4		
Objectives	3	State specific objectives, including any prespecified hypotheses	p. 4		
Methods					
Study Design	4	Present key elements of study design early in the paper	pp. 4-6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	pp. 4-6		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	pp. 4-6 n/a	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	pp. 4-6 n/a Not included
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	pp. 6-8, 10-11 (exposures, predictors, confounders); Supplemental appendx, pp. 26-28	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	pp. 6-8, 10-11 (exposures, predictors, confounders); Supplemental appendx, pp. 26-28
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	pp. 6-8, 10-11 (exposures, predictors, confounders); Supplemental appendx, pp. 26-28		

Bias	9	Describe any efforts to address potential sources of bias	Control group (pp. -4-5), covariates (pp. 6-7)		
Study size	10	Explain how the study size was arrived at	Description of study cohorts (pp. 4-6)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	pp. 6-7		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(a) Control group (pp. 4-5), covariates (pp. 7), statistical analyses (pp. 7-8) (b) Statistical analyses (pp. 7-8) (c) n/a (d) Censoring (p. 5) (e) n/a		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	'Author contributions' section (p. 12)

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	n/a
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	'Data sources' (p. 6)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) Results (p. 8) (b) Censoring criteria described (p. 5) (c) Not included	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	p. 8
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) Table 1, p. 19 (b) n/a c) p. 9		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	pp. 8-9; Table 2, p. 20		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a) pp. 8-9; Table 2, p. 20 (b) n/a c) Not included, except crude event rates are provided in Table 2, p. 20		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Subgroup analyses – p. 9 and in Table 2, p. 20		
Discussion					
Key results	18	Summarise key results with reference to study objectives	p. 9		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	pp. 10-11	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	pp. 10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	pp. 9-11		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	p. 10		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page, p. 1		
Accessibility of protocol, raw data, and programming code		..	Data sharing statement, p. 13	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data sharing statement, p. 13

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.