Influence of opioid prescribing standards on drug utilization among patients with chronic opioid use: a retrospective cohort study

Short title: Influence of opioid prescribing standards

Richard L. Morrow, MA[1], Ken Bassett, MD, PhD[1,2], James M. Wright, MD, PhD[1,3], Greg Carney, BSc[1], Colin R. Dormuth, ScD[1]

Author information:

1. Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, British Columbia
2. Department of Family Practice, University of British Columbia, Vancouver, British Columbia
3. Department of Medicine, University of British Columbia, Vancouver, British Columbia

Corresponding author: Richard L. Morrow, Therapeutics Initiative, University of British Columbia, 210-1110 Government St., Victoria, BC V8W 1Y2 Canada. Tele: 250-590-5955, Fax: 250-590-5954, email: richard.morrow@ti.ubc.ca. (This email address can be published.)

Funding statement: This work was supported by a 5-year renewable grant to the University of British Columbia from the British Columbia Ministry of Health. Individuals employed by or consulting for the Ministry of Health at the time the research project was planned provided ideas and feedback on development of the research protocol. The analyses and interpretations in this study are those of the authors and do not reflect the opinions or policies of the Ministry of Health.

Competing interests: The authors have no competing interests to declare.

ABSTRACT

Background: In mid-2016, the College of Physicians and Surgeons of British Columbia (CPSBC) issued prescribing standards and guidelines relating to opioid drugs, and a policy to allow prescribing of buprenorphine/naloxone by physicians not officially authorized to prescribe methadone for opioid use disorder. We evaluated the impact of the College's policies on prescription drug utilization.

Methods: We used a cohort study design with monthly repeated outcome measures using linked administrative health data in British Columbia. Patients with chronic prescription opioid use were followed for a 12-month pre-policy period and 10-month post-policy period, and compared to historical controls not exposed the policies. We excluded patients with a history of long-term care, palliative care or cancer. The study included 68,113 patients in the main cohort and 68,429 historical controls. We estimated changes in utilization of opioids, high-dose opioids (>90 milligrams of morphine equivalents (MME)/day), opioids with sedatives/hypnotics, opioid discontinuation, and opioid substitution therapy (methadone or buprenorphine/naloxone).

Results: Following the opioid policies, average monthly utilization of opioids declined (adjusted difference -63 MME; 95% confidence interval [CI] -81 to -45) and discontinuation of opioids increased (odds ratio [OR] 1.24; 95% CI 1.16 to 1.32). Among patients prescribed high-dose opioids, switching to lower dose opioids increased (OR 1.88; 95% CI 1.63 to 2.17), but discontinuation did not (OR 1.21; 95% CI 0.91 to 1.59). We observed an increase in opioid substitution and an increase in discontinuation of concurrent use of opioids and sedatives/hypnotics.

Interpretation: The CPSBC opioid policies modestly reduced utilization of opioids and increased switching from high-dose to lower dose opioids among patients with chronic use of prescribed opioids while increasing use of opioid substitution therapy.

The increasing number of opioid overdoses and illicit drug overdose deaths in British Columbia (BC) led the provincial health officer to declare a public health emergency in April 2016.[1] The rate of hospitalizations for opioid overdose had been rising steadily for several years,[2] and the rate of illicit drug overdose deaths had risen rapidly since 2012.[3] Although the rise in illicit drug overdose deaths was closely linked to the contamination of street drugs with fentanyl and other synthetic opioids,[3] it was likely that the growth in opioid-related harms was related in part to high rates of opioid prescribing.[4-6]

The College of Physicians and Surgeons of British Columbia (CPSBC) issued two policies in mid-2016 to help promote best prescribing practices, for opioid treatment of pain and for opioid substitution to treat opioid use disorder. First, CPSBC issued "Professional standards and guidelines: safe prescribing of drugs with potential for misuse/diversion,"[7] a policy which took effect on June 1, 2016. Second, it issued a policy which allowed for prescribing of buprenorphine/naloxone by physicians not officially authorized to prescribe methadone for opioid use disorder.[8] This policy took effect on July 1, 2016, soon followed by a related clinical practice guideline.[9] The CPSBC standards and guidelines contained both legally enforceable requirements ('standards') and recommended courses of action ('guidelines') allowing for more discretion on the part of the physician.[7] The standards and guidelines did not apply to patients with active cancer or those receiving palliative care or end-of-life care.[7]

In this study, we evaluated whether the CPSBC prescribing standards and guidelines policy and the buprenorphine/naloxone policy influenced prescription drug utilization among BC patients with chronic prescription opioid use, excluding patients who had a record of long-term residential or palliative care or a medical visit with a cancer diagnosis in the previous year. The standards and guidelines policy and the buprenorphine/naloxone policy were introduced within

one month during 2016, so the impact of both — referred to below as the "CPSBC opioid policies" — are considered together in this study except when indicated below.

METHODS

Study setting and design

We used a longitudinal cohort study design with monthly repeated outcome measures to investigate the influence of the CPSBC opioid prescribing policies on drug utilization.[10] The study cohort consisted of BC residents with chronic use of prescription opioids: buprenorphine patch, codeine, fentanyl, hydromorphone, meperidine, morphine, oxycodone, tapentadol or tramadol. We defined "chronic opioid use" as filling at least two opioid prescriptions during a 6-month identification 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.

We identified a cohort of patients who met the chronic opioid use criteria during an identification period of December 1, 2014 - May 31, 2015. We refer to these patients as the policy cohort, because their follow-up included a 12-month "pre-policy period" (June 1, 2015 - May 31, 2016) and a 10-month "post-policy period" (June 1, 2016 - March 31, 2017) during which the CPSBC opioid policies applied. We also identified a historical control cohort that met the criteria for chronic opioid use one year earlier during December 1, 2013 - May 31, 2014. Follow-up for the historical cohort included analogous 12- and 10-month periods, between June 1, 2014, and March 31, 2016. The historical control cohort provided a comparison group not affected by the CPSBC opioid policies. It was possible for patients to be members of both cohorts, which could reduce confounding related to patient characteristics that do not vary with time. We excluded patients who lacked 1 year of medical services coverage, had a record of long-term residential care or palliative care, or had a medical visit with a diagnosis of cancer in

the year prior to the start of follow-up (see Table S1 of Supplementary Appendix for diagnostic codes). We censored patients during follow-up if they lost medical services coverage, entered long-term or palliative care, died, or were diagnosed with cancer.

Data sources

We used linked data from the BC Ministry of Health's Healthideas data warehouse, including patient-level, de-identified data from the BC Medical Services Plan, BC PharmaNet, the BC Vital Statistics Agency, and the Canadian Institute for Health Information Discharge Abstract Database. These datasets include most of the BC population but exclude about 4 percent of the population covered by federally insured drug plans for First Nations, members of the military, veterans, members the RCMP, and inmates in federal penitentiaries.

Outcome measures

Outcomes included monthly opioid analgesic medication use, discontinuation of opioids, discontinuation of high-dose opioids, switching from high-dose to lower dose opioids, discontinuation and initiation of concurrent use of opioids and sedatives/hypnotics, and initiation of opioid substitution. To determine a patient's monthly opioid analgesic use (in MME), we calculated each prescription's daily MME[11] and assumed that use was evenly distributed across the prescribed days' supply. Analysis of discontinuation of opioids included only patients who had a prescription with sufficient days' supply to end in a given month. Similarly, analyses of discontinuation of high-dose opioids and switching from high-dose to lower dose opioids included patients who had received a high-dose prescription (with a daily dose of >90 MME) ending in a given month. We defined discontinuation as occurring if no additional prescription was filled within 90 days of the end of the prescription. We deemed a patient to have discontinued high-dose opioid therapy if no additional opioid prescription of any dose was filled

within 90 days, or to have switched to a lower dose if a prescription with a daily dose <=90 MME, but no prescription of >90 MME/day, was filled within 90 days. Analysis of discontinuation of concurrent use of opioids and sedatives/hypnotics included patients with concurrent use and an opioid or sedative/hypnotic prescription ending in a given month; analysis of initiation of concurrent use of these medications included only patients without concurrent use in the 180 days prior to the current month. We defined concurrent use as overlapping days' supply of these medications (sedatives/hypnotics were identified by ATC codes N05C, N03AE and N05BA).[12] We deemed a patient to have discontinued concurrent use after 90 days with no concurrent supply. Analysis of initiation opioid substitution included only patients without prescriptions of methadone with this indication or buprenorphine/naloxone in the previous 180 days.

Covariates

We defined patient variables to control for confounding in adjusted analyses. Demographic variables included sex, age category, low-income status, and rural residence. We included medical history variables, based on diagnoses from outpatient and inpatient records in the 365 days prior to follow-up: 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).[13-14] (See Tables S2 and S3 for diagnostic codes and definitions for chronic pain conditions.)[15-23] We also included variables for prescription drug use in the 180 days prior to follow-up: opioid substitution therapy (>=1 prescription), use of sedative/hypnotic medication (including benzodiazepines) (>=1

prescription), maximum daily opioid analgesic dose prescribed (<=50 MME, >50 to 90 MME, >90 to 200 MME, or >200 MME), and intensity of opioid analgesic use (60 to <90 days' supply or >=90 days' supply prescribed).

Statistical analyses

We estimated absolute differences due to the effect of the CPSBC opioid policies on monthly opioid analgesic medication use, using a generalized linear model with an identity link function and a normal error distribution. We estimated odds ratios of the effect of the CPSBC opioid policies on outcomes involving discontinuation, switching or initiation, using generalized linear models with a logistic link function and a binomial error distribution. Analyses used generalized estimating equations in the regression models to adjust for "clustering effects" due to multiple observations from the same patients.[24]

We estimated absolute differences or odds ratios for changes to the level and trend of each outcome following the opioid prescribing policies by including interactions in each model between a binary variable for cohort status (policy cohort vs historical control cohort) with level effect and trend effect variables. Level changes represented a sudden change in the outcome affecting the whole post-policy period, whereas trend changes represented gradual changes occurring in each month of the post-policy period. We modified our approach for the outcome of monthly opioid use by including a 3-month transition period and using a shorter post-policy period, because days' supply from prescriptions pre-dating the opioid policies might carry forward for approximately 3 months and attenuate this measure. Similarly, we included a 1-month transition period in our analysis of opioid substitution, because the buprenorphine/naloxone policy was likely more influential on this outcome and was introduced 1 month after the opioid standards and guidelines.

RESULTS

Patient characteristics

The study population included 68,113 patients in the policy cohort and 68,429 patients in the historical control cohort (Table 1); 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. Patient characteristics were similar across the two cohorts (Table 1). However, slightly fewer patients in the policy cohort compared with historical controls had been prescribed high-dose opioids (12.0% vs 12.6%) or very high dose opioids (6.8% vs 7.5%) prior to follow-up. Over 40% of patients had been prescribed a sedative or hypnotic medication in the 180 days prior to follow-up.

Impact on drug utilization

Average monthly use of opioids was 1,625 MME during the pre-policy period in the policy cohort and 1,770 MME in the historical control cohort (Table 2). We observed a small decrease in the level of monthly opioid use following the introduction of the opioid prescribing policies in the policy cohort relative to historical controls (adjusted difference -57 MME; 95% CI -74 to -39), and a decreasing trend in opioid use (Table 2). The trend lines for monthly opioid use for both the policy cohort and historical control cohort decline over time in part because some patients in both cohorts stopped opioids over time (Figure 1). However, the decline in opioid use as a result of the policy can be observed in the divergence of trend lines during the post-policy period.

The average monthly rate of discontinuation was 2.6% in the policy cohort 2.5% among historical controls in the pre-policy period. Following the policies, we found an increase in the level of opioid discontinuation in the policy cohort relative to historical controls (adjusted OR

1.24; 95% CI 1.16 to 1.32) (Table 2), as shown in Figure 1. In contrast, the rate of discontinuation of high-dose opioids did not increase in the post-policy period, while the rate of switching from high-dose to lower dose opioids did increase (adjusted OR 1.88; 95% CI 1.63 to 2.17) (Table 2 and Figure 2).

Discontinuation of concurrent use of opioids and sedatives/hypnotics increased in the post-policy period (adjusted OR 1.37; 95% CI 1.27 to 1.49). However, the potential change in initiation of concurrent use of opioids and sedatives/hypnotics following the policy was unclear, with the impact on the level suggesting an increase (adjusted OR 1.10; 95% CI 1.02 to 1.18) and the impact on trend suggesting a monthly decline (adjusted OR 0.98; 95% CI 0.97 to 0.99) (Table 2 and Figure 3). Monthly rates of initiation of opioid substitution were slightly less than one per thousand population in both cohorts during the pre-policy period. Following the policies, the rate of opioid substitution increased in the policy cohort relative to historical controls (OR 1.87; 95% CI 1.44 to 2.42).

INTERPRETATION

The CPSBC opioid policies issued in mid-2016 had a modest effect on opioid utilization among patients with chronic prescription opioid use. The policies led to a small reduction in the level and trend of prescription opioid analgesic use (measured in MME), which appeared to result from both increased discontinuation of lower dose opioids and increased switching from high-dose to lower dose opioids. The rate of opioid discontinuation among patients with high-dose opioid prescriptions did not increase following the policy. The opioid policies increased discontinuation of concurrent use of opioids and sedative/hypnotic medications and increased initiation of opioid substitution therapies, but did not have a clear impact on initiation of concurrent use of opioids and sedative/hypnotic medications.

The increase in the rate of switching from high-dose to lower dose opioids appears to reflect the CPSBC's advice to avoid prescribing daily doses above 90 MME in most cases and to prescribe opioids at the 'lowest effective dosage.'[7] While our analyses did not directly examine tapering of medications, our finding that the rate of discontinuation of high-dose opioids did not increase following the policy appears to be consistent with the policy's concern about abrupt stopping of opioids.[7] Similarly, the CPSBC standards discouraged prescribing of sedatives/hypnotics to patients on long-term opioid therapy,[7] and this appears to be reflected in the increased discontinuation of concurrent use of opioids and sedatives/hypnotics in the post-policy period. Previous research has suggested that use of higher-dose opioids and concurrent use of opioids and sedative/hypnotic medications are risk factors for overdose.[25-27] Revisions of the CPSBC standards and guidelines (now simply a 'practice standard') have retained the elements mentioned above.[28] The increased initiation of opioid substitution in the post-policy period likely resulted primarily from the CPSBC policy change facilitating wider physician prescribing of buprenorphine/naloxone.

Our findings were consistent with two previous studies that evaluated the impact of opioid prescribing guidelines on drug utilization. A study of workers' compensation claimants in Washington State found that an opioid prescribing guideline reduced the prevalence of opioid use among claimants.[29] Similarly, results of a study of Ontario residents aged 15 to 64 who were eligible for public drug coverage suggested that the introduction of Canadian clinical practice guidelines in May 2010 reduced the rate of opioid use in that province.[30]

Limitations

Our study has a number of limitations. We focused on impacts of the CPSBC opioid policies on drug utilization among patients with chronic opioid use, but we did not evaluate the

impact of the policy on pain management or health outcomes. Our analyses of drug utilization relied on prescription drug dispensing data, which may differ from actual medication use (for example, overlapping supply of opioids and sedatives/hypnotics could differ from concurrent use for some patients). While we included a historical control group and adjusted for demographic and medical characteristics, opioid prescribing and utilization may have been influenced by factors not controlled for in our study, such as news reports and public debate on the opioid crisis.

Conclusion

The opioid prescribing standards and guidelines introduced by CPSBC in mid-2016 modestly reduced opioid analgesic use, increased discontinuation of lower dose opioids, increased switching from high-dose to lower dose opioid use, and increased discontinuation of concurrent use of opioids and sedative/hypnotic medications among patients with chronic use of prescribed opioids in BC. The CPSBC's policy to allow prescribing of buprenorphine/naloxone by physicians not officially authorized to prescribe methadone for opioid use disorder was associated with an increase in use of opioid substitution therapy.

Acknowledgements: The authors thank Brian Emerson (BC Ministry of Health), Kathleen Perkin (BC Ministry of Health), Mikhail Torban (advised while at the BC Ministry of Health, now at the BC Ministry of Mental Health and Addictions) and Kenneth Tupper (advised while at the British Columbia Ministry of Health, now at the British Columbia Centre on Substance Use), who provided ideas and feedback during the development of the research protocol; and Tom Perry (Therapeutics Initiative, University of British Columbia) for feedback on the manuscript and interpretation of results.

Author contributions: RM, CD, KB and JW contributed to the study design. RM 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.

REFERENCES

1. Government of British Columbia. Provincial health officer declares public health emergency. News release. (14 Apr 2016) https://news.gov.bc.ca/releases/2016HLTH0026-000568
2. Canadian Institute for Health Information. Opioid-related harms in Canada. Ottawa: CIHI; 2017.
3. British Columbia Coroners Service. Illicit drug overdose deaths in BC: January 1, 2007 - December 31, 2017. Burnaby, BC; 2018 January 31, 2017.
4. Gladstone EJ, Smolina K, Weymann D, Rutherford K, Morgan SG. Geographic Variations in Prescription Opioid Dispensations and Deaths Among Women and Men in British Columbia, Canada. Med Care. 2015;53(11):954-9.
5. Fischer B, Jones W, Rehm J. High correlations between levels of consumption and mortality related to strong prescription opioid analgesics in British Columbia and Ontario, 2005-2009. Pharmacoepidemiol Drug Saf. 2013;22(4):438-42.
6. Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005-2011. Drug Alcohol Rev. 2014;33(1):19-26.
7. College of Physicians and Surgeons of British Columbia. Professional standards and guidelines: Safe prescribing of drugs with potential for misuse/diversion. (1 June 2016) https://www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf
8. ---. Important notice regarding Suboxone®. (4 July 2016) https://www.cpsbc.ca/important-notice-regarding-suboxone%C2%AE
9. ---. Methadone and buprenorphine: Clinical practice guideline for opioid use disorder. (6 July 2016) https://www.cpsbc.ca/files/pdf/MBMT-Clinical-Practice-Guideline.pdf

10. Schneeweiss S, Maclure M, Dormuth CR. On the evaluation of drug benefits policy changes with longitudinal claims data: Concepts of income-based deductibles and issues related to causal inference. Dis Manage Health Outcomes 2002; 10(12):763-769.
11. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf. 2016;25(6):733-7.
12. ATC/DDD Index 2018. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2018 [Available from: https://www.whocc.no/atc_ddd_index/].
13. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol. 2001;154(9):854-64.
14. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993;46(10):1075-9; discussion 81-90.
15. Lavis JN, Malter A, Anderson GM, et al. Trends in hospital use for mechanical neck and back problems in Ontario and the United States: discretionary care in different health care systems. *Cmaj* 1998;158(1):29-36.
16. Lacasse A, Ware MA, Dorais M, et al. Is the Quebec provincial administrative database a valid source for research on chronic non-cancer pain? *Pharmacoepidemiol Drug Saf* 2015;24(9):980-90.
17. Harrold LR, Yood RA, Andrade SE, et al. Evaluating the predictive value of osteoarthritis diagnoses in an administrative database. *Arthritis Rheum* 2000;43(8):1881-5.

18. Widdifield J, Bernatsky S, Paterson JM, et al. Accuracy of Canadian health administrative databases in identifying patients with rheumatoid arthritis: a validation study using the medical records of rheumatologists. *Arthritis Care Res (Hoboken)* 2013;65(10):1582-91.

19. Dworkin RH, Malone DC, Panarites CJ, et al. Impact of postherpetic neuralgia and painful diabetic peripheral neuropathy on health care costs. *J Pain* 2010;11(4):360-8.

20. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004;5(3):143-9.

21. Kostev K, Jockwig A, Hallwachs A, et al. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. *Prim Care Diabetes* 2014;8(3):250-5.

22. Callaghan B, Kerber K, Langa KM, et al. Longitudinal patient-oriented outcomes in neuropathy: Importance of early detection and falls. *Neurology* 2015;85(1):71-9.

23. Schoenfeld AJ, Laughlin M, Bader JO, et al. Characterization of the incidence and risk factors for the development of lumbar radiculopathy. *J Spinal Disord Tech* 2012;25(3):163-7.

24. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986;42(1):121-30.

25. Dilokthornsakul, P., G. Moore, J. D. Campbell, R. Lodge, C. Traugott, J. Zerzan, R. Allen and R. L. Page, 2nd (2016). "Risk Factors of Prescription Opioid Overdose Among Colorado Medicaid Beneficiaries." Journal of Pain 17(4): 436-443.

26. Dunn, K. M., K. W. Saunders, C. M. Rutter, C. J. Banta-Green, J. O. Merrill, M. D. Sullivan, C. M. Weisner, M. J. Silverberg, C. I. Campbell, B. M. Psaty and M. Von Korff "Opioid prescriptions for chronic pain and overdose: a cohort study.[Summary for patients in Ann

Intern Med. 2010 Jan 19;152(2):I-42; PMID: 20083811]." Annals of Internal Medicine 152(2): 85-92.

27. Bohnert, A. S., M. Valenstein, M. J. Bair, D. Ganoczy, J. F. McCarthy, M. A. Ilgen and F. C. Blow (2011). "Association between opioid prescribing patterns and opioid overdose-related deaths." JAMA 305(13): 1315-1321.
28. College of Physicians and Surgeons of British Columbia. Practice standard: safe prescribing of opioids and sedatives. June 4, 2018. https://www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf
29. Garg RK, Fulton-Kehoe D, Turner JA, Bauer AM, Wickizer T, Sullivan MD, et al. Changes in opioid prescribing for Washington workers' compensation claimants after implementation of an opioid dosing guideline for chronic noncancer pain: 2004 to 2010. J Pain.14(12):1620-8.
30. Spooner L, Fernandes K, Martins D, Juurlink D, Mamdani M, Paterson JM, et al. High-Dose Opioid Prescribing and Opioid-Related Hospitalization: A Population-Based Study.[Erratum appears in PLoS One. 2017 Jan 20;12 (1):e0170834; PMID: 28107478]. PLoS ONE. 2016;11(12):e0167479.

Table 1. Characteristics of patients with chronic 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 follow-up; the policy cohort was followed from June 1, 2015, to March 31, 2017, and the historical control cohort was followed from June 1, 2014, to March 31, 2016. †Excluded low back pain. ‡Based on days' supply dispensed. MME=milligrams of morphine equivalents

Table 2. Impact of opioid prescribing policies on drug utilization among patients with chronic opioid use

Analysis	Patients: Historical cohort	Patients: Policy cohort	Measures in pre-policy period*		Impact on outcome level†	Impact on outcome trend†
			Monthly MME, mean (SD)			
a) Opioid analgesic use (MME/ month)	68,429	68,113	Historical cohort: 1,770 (4,200)	Policy cohort: 1,625 (3,860)	Adj difference (95% CI): -57 (-74,-39)	Adj difference (95% CI): -6.8 (-9.9,-3.8)
b) Discontinuation:			Monthly discontinuation (%)			
Discontinuation of opioid use	66,203	65,791	Historical cohort: 2.5	Policy cohort: 2.6	Adj odds ratio (95% CI): 1.24 (1.16,1.32)	Adj odds ratio (95% CI): 1.00 (0.98,1.01)
Discontinuation among high-dose opioid users‡	13,922	12,409	0.6	0.6	1.21 (0.91,1.59)	0.98 (0.94,1.03)
Discontinuation of concurrent opioid and sedative/hypnotic use§	28,483	26,506	9.2	9.4	1.37 (1.27, 1.49)	0.99 (0.97, 1.00)
c) Switching:			Monthly switching (%)			
Switching from high dose opioid‡ to lower dose	13,922	12,409	Historical cohort: 2.5	Policy cohort: 2.6	Adj odds ratio (95% CI): 1.88 (1.63,2.17)	Adj odds ratio (95% CI): 0.99 (0.97,1.01)
d) Initiation:			Monthly initiation (%)			
Initiation of concurrent opioid and sedative/hypnotic use§	54,934	56,441	Historical cohort: 2.1	Policy cohort: 2.0	Adj odds ratio (95% CI): 1.10 (1.02,1.18)	Adj odds ratio (95% CI): 0.98 (0.97,0.99)
			Monthly initiation per 1,000 cohort members			
Initiation of opioid substitution therapy‖	67,784	67,482	Historical cohort: 0.8	Policy cohort: 0.9	Adj odds ratio (95% CI): 1.87 (1.44,2.42)	Adj odds ratio (95% CI): 0.98 (0.94,1.03)

*These measures were calculated based on all monthly observations during the 12-monthly pre-policy period for the policy cohort and corresponding period for historical controls.
†'Impact on outcome level' measures a sudden change following a policy, whereas 'impact on outcome trend' measures gradual change occurring each month following a policy. ‡High dose was defined as a daily dose of >90 MME. §Concurrent use was defined as overlapping supply according to date and days' supply dispensed. ‖Opioid substitution medications included methadone and buprenorphine/naloxone. MME=milligrams of morphine equivalents Adj =Adjusted

Figure 1. Average monthly opioid analgesic use (mean milligrams of morphine equivalents) and opioid stopping rate (%) in policy cohort (PC) vs historical control cohort (HCC). (Note: The analysis of opioid use included a 3-month transition period after prescribing standards were introduced to account for medication supply that would carry forward from the pre-policy period; this did not apply to the stopping analysis.)

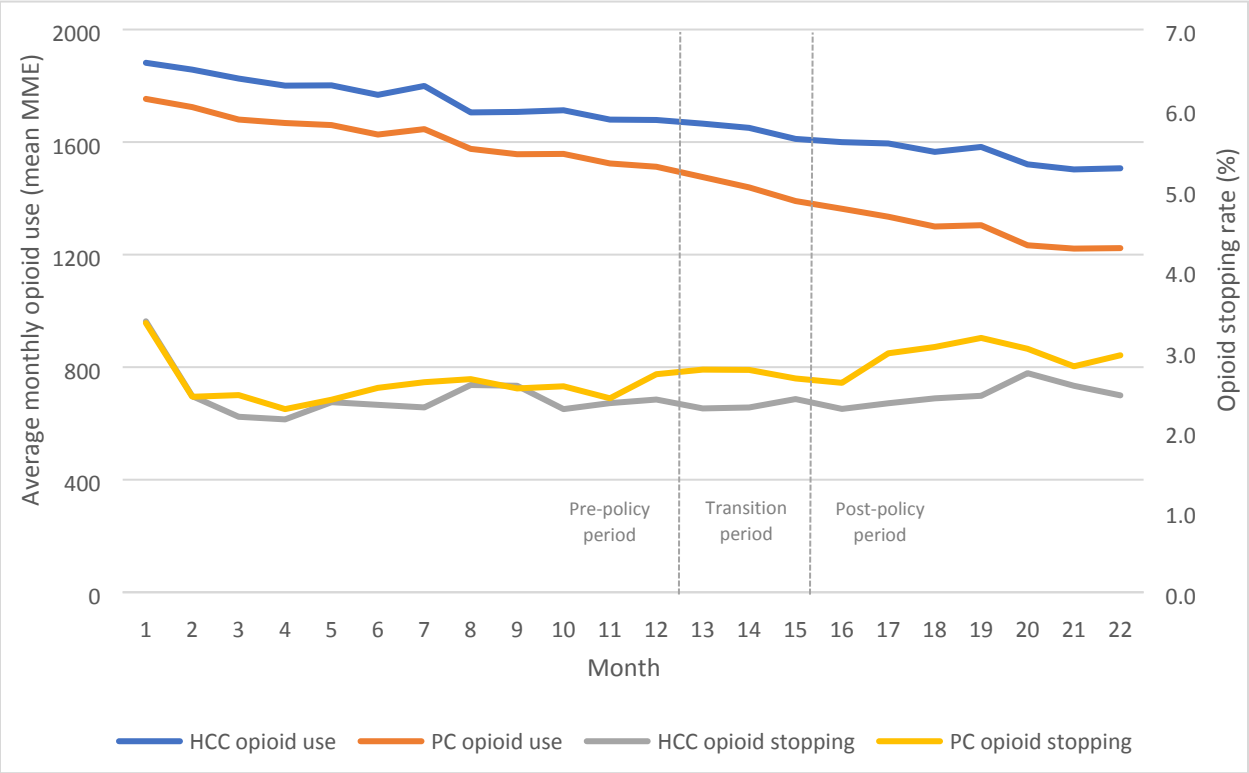


Figure 2. Monthly rates of switching from high-dose (>90 MME daily) to lower dose opioid medication and rates of stopping high-dose opioid medication, in policy cohort (PC) vs historical control cohort (HCC). MME=milligrams of morphine equivalents

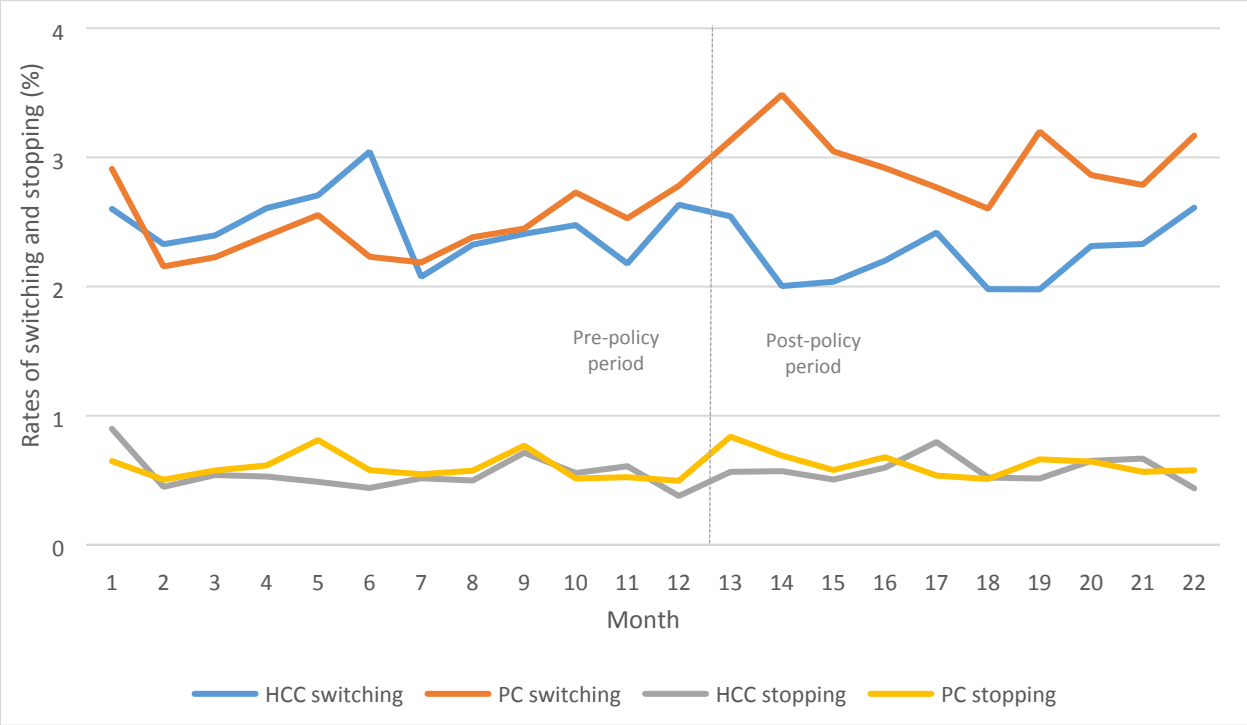
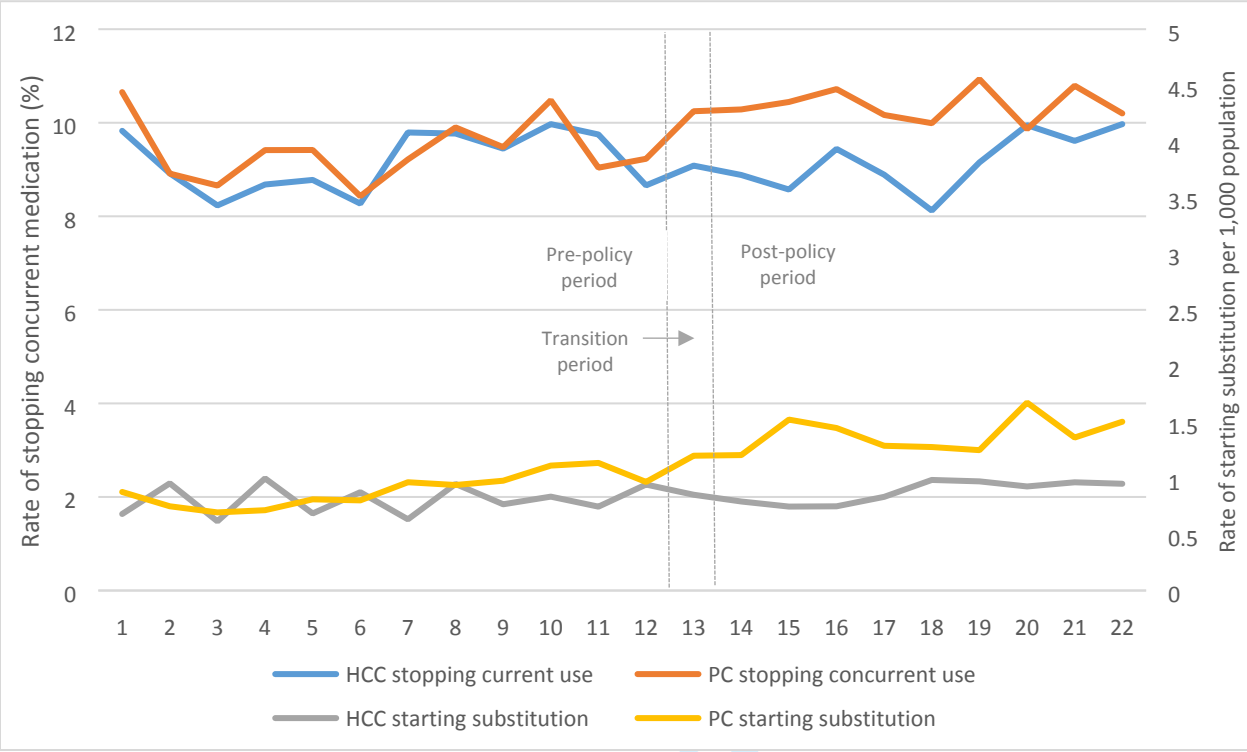


Figure 3. Monthly rates of (a) discontinuing concurrent use of opioid and sedative/hypnotic medications (%), and (b) initiating opioid substitution therapy (per 1,000 population), in policy cohort (PC) vs historical control cohort (HCC). (Note: The analysis of opioid substitution included a one-month transition period between the introduction of prescribing standards and the opioid substitution policy; this did not apply to the analysis of concurrent use.)



SUPPLEMENTARY APPENDIX

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. 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,	>=1 healthcare encounter with any of the ICD codes listed during previous 365 days [Adapted from an algorithm created by Lavis et al, 1998,[7] and validated by Lacasse et al, 2015][8]

	846.9, 847.0, 847.1, 847.2, 847.3, 847.9 ICD-10: M47, M48.1, M48.2, M48.3, M48.9	
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,[9] 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,[10] 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;[11] Berger et al, 2003;[12] Kostev et al, 2014][13]
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][14]
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][15]

Table S3. 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. 3		
Methods					
Study Design	4	Present key elements of study design early in the paper	pp. 4-5		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	pp. 4-5		

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. 4-5 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. 4-5 n/a Not included
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	pp. 5-7, 11 (exposures, predictors, confounders); Supplemental appendx, pp. 22-24	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. 5-7, 11 (exposures, predictors, confounders); Supplemental appendx, pp. 22-24
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. 5-7, 11 (exposures, predictors, confounders); Supplemental appendx, pp. 22-24		

Bias	9	Describe any efforts to address potential sources of bias	Control group (p. 4), covariates (pp. 6-7)		
Study size	10	Explain how the study size was arrived at	Description of study cohorts (p. 4)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	pp. 5-7		
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 (p. 4), covariates (pp. 6-7), statistical analyses (p. 7) (b) Outcome measures (pp. 6-7), statistic analyses (p. 7) (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. 5)
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) Patient characteristics (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) p. 8; Table 1, p. 17 (b) n/a c) p. 8		
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. 18		

		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. 18 (b) n/a c) Not included, but pre-policy measurs are provided in Table 2, p. 18		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a		
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. 12	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. 12

*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.