Opioid-related harms and socioeconomic inequalities in Ontario: A population health assessment

Zoe F. Cairncross BScH[1,2], Jeremy Herring MSc[2], Trevor van Ingen MPH[2],

Brendan T. Smith MSc PhD[1,2], Pamela Leece MD MSc[1,2],

Brian Schwartz MD MScCH[1,2], Karin Hohenadel MSc[2]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada,

[2]Public Health Ontario, Toronto, Canada

Corresponding Author:

Zoe Cairncross

zoe.cairncross@mail.utoronto.ca

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ABSTRACT

BACKGROUND: Negative health outcomes associated with the use of both prescribed and non-prescribed opioids are increasingly prevalent. This study examines long-term trends in opioid-related harms in Ontario and the relationship between harms and neighbourhood income.

METHODS: We examined rates of neonatal abstinence syndrome (NAS), opioid poisonings (fatal and non-fatal), and non-poisoning opioid-related harms from 2003 to 2016 in Ontario using population-based health administrative databases. Rates were calculated for harm indicators across neighbourhood income quintiles. Social inequalities in opioid-related harms were examined on both relative (prevalence ratios) and absolute (potential rate reductions) scales.

RESULTS: Rates of opioid related harms increased dramatically between 2003 and 2016. After stratifying by income, NAS, opioid poisoning, and non-poisoning events demonstrated a strong social gradient with harm rates being lowest in high-income neighbourhoods and highest in low-income neighbourhoods. Prevalence ratios for low-income neighbourhoods compared to high-income neighbourhoods ranged from 2.36 (95% CI: 2.15-2.58) for opioid poisoning emergency department visits to 3.70 (95% CI: 2.62-5.23) for NAS. Potential rate reductions for these harms ranged from 34.8% to 49.9%, suggesting that at least one third of all harmful events could be prevented if all neighbourhoods had the same socio-economic profile as the highest quintile.

INTERPRETATION: Rates of opioid-related harms are increasing in Ontario. Neighbourhoods with a high proportion of low-income residents are experiencing substantially higher rates of opioid-related harms. This finding can inform planning for opioid-related public health interventions.

INTRODUCTION

In the past 25 years, opioid-related mortality in Ontario has increased by 285 percent, with over 730 deaths in 2015 alone.[1,2] Contributing to the high mortality rates from opioids is the widespread dispensing of prescription opioids, which have also been shown to be a major cause of mortality across Canada and internationally.[3-6] Globally, Canada is the second largest consumer of prescription opioids, with the province of Ontario having the highest dispensing rates of strong opioids in the country.[7,8] Adding to the challenge that ensues from high rates of opioid prescription is the availability of fentanyl in the illicit drug supply, which is leading to a rapidly growing number of opioid-related deaths in both the United States and Canada.[1,2,9,10]

Opioid morbidity and mortality have been found to be positively associated with social marginalization: harms from opioids are especially common among the unemployed and those living in poverty [11-15]. However, the increasingly widespread prescription of opioid medications for non-cancer pain and other conditions has led to speculation that the socioeconomic profiles of those dying or suffering significant other harms related to opioids might be shifting from marginalized populations to the middle-class.[16] Supporting this viewpoint are the results of a recent Ontario-based analysis of the dispensing patterns of prescription opioids. In 2016, the 1.7 million Ontarians who were prescribed an opioid medication for the treatment of pain were evenly distributed across income quintiles.[17] Furthermore, well-publicized opioid-related deaths of individuals from more affluent backgrounds would seem to support this theory of demographic shift. To test the hypothesis that harm rates from opioids are shifting in Canada, we analyzed population-based trends in opioid-related morbidity and mortality in Ontario,

Canada from 2003 to 2016, and estimated the extent to which socioeconomic inequalities in opioid related morbidity and mortality exist in Ontario.

Six indicators of opioid-related harms were evaluated in this study: neonatal abstinence syndrome (NAS); opioid poisonings (emergency room (ED) visits, hospitalizations, and deaths); and non-poisoning opioid-related events (ED visits and hospitalizations). Previous analyses have focused solely on the burden of accidental and intentional opioid poisonings in Ontario, but we chose to assess a broad range of events to include non-poisoning opioid-related harms such as opioid withdrawal and opioid use disorder.[1,2,18] Likewise, although maternal opioid use is not the only cause of NAS, previous studies have found that at least 60% of infants born to opioid-dependent women show associated symptoms of NAS.[19-23]

METHODS

Data Sources and Case Identification

We conducted a population-based assessment including all cases of opioid morbidity (NAS, non-fatal opioid poisonings, and non-poisoning events) and mortality identified in population-based health administrative datasets in the province of Ontario, Canada from 2003 to 2016.

Cases of NAS were identified using the Discharge Abstract Database (DAD). NAS is defined by withdrawal symptoms an infant may experience after birth if the mother used certain medications or other substance during pregnancy.

Opioid poisonings resulting in emergency department visits, hospitalizations, and death were identified from three sources, respectively: the National Ambulatory Care Reporting System (NACRS), DAD, and the Ontario Opioid-Related Death Database (OORDD). Opioid

poisoning includes any therapeutic, intentional, accidental, or unknown use of opioids resulting in poisoning.

Non-poisoning opioid-related events include any harmful effect of opioid use that does not result in poisoning, such as opioid use disorder or opioid withdrawal. Non-poisoning ED visits were identified from NACRS. Non-poisoning hospitalizations were identified from DAD and the Ontario Mental Health Reporting System (OMHRS). Unique cases of non-poisoning opioid-related events resulting in ED visits or hospitalization were identified by ICD-10-CA codes for mental and behavioural disorders due to use of opioids.

Full details of the case definitions and ICD codes used for the analysis can be found in Appendix 1. This project was approved by the Public Health Ontario Ethics Review Board. Age, sex, date of admission, postal code of residence, and all diagnosis codes were extracted for all cases.

Quantifying Neighbourhood Income

Neighbourhood income was determined using 2011 Statistics Canada Annual Estimates for Census Families and Individuals (T1 Family File) after-tax low income measures (LIMs). LIMs are a relative measure of low income, defined as 50% of the median census family income for a given family type and size. Tax filer data from 2011 was used on the basis of availability, and due to Statistics Canada data showing that proportions of low-income residents in Ontario have not changed significantly from 2011 to 2015.[24]

For the purposes of this investigation, Ontario dissemination areas (DAs) were ranked by the percent of census families in the area earning less than the after-tax LIM, and divided into fifths, where the first quintile represented an area with high income, and the fifth quintile

represented an area of low income. There were 327 DAs not included in the quintile calculation as they either had a population of zero, or tax information was suppressed in the data due to having fewer than 100 individuals in the area that filed taxes. Descriptive characteristics of each income quintile are included in Appendix 2 (Table 1).

Geocoding of Cases to Income Quintiles

Postal code boundaries in Canada do not directly align with DA boundaries. To mitigate this, cases of NAS, opioid poisoning, or non-poisoning events were geocoded to their corresponding census dissemination areas by joining their postal code of residence with the Statistics Canada Postal Code Conversion File (PCCF).[25] The single-link indicator (SLI) was used if the postal code of a case corresponded to more than one DA. The SLI determines the postal code to which a DA corresponds by determining where the majority of dwellings in a given postal code reside. Hence some cases may not have been assigned to their correct DA, and could therefore potentially be assigned to the incorrect income quintile. However, as it is unlikely that neighbouring DAs have drastically different socioeconomic profiles, this should not have a large impact on the results of our study.

Rate Calculations

Annual counts of live births in Ontario hospitals from 2003 to 2016 were obtained from DAD and used as the denominator to calculate yearly rates of NAS. Ontario population estimates for 2003 to 2015, and projections for 2016, were obtained from IntelliHealth Ontario and used as the denominator to calculate yearly rates of opioid-related poisoning and non-poisoning events.[26,27]

To calculate quintile-specific rates for NAS, opioid poisonings and non-poisoning events, we first created our quintiles as determined by the 2011 Statistics Canada T1 Family File. However, because the Ontario population has grown by approximately 700,000 people between 2011 and 2016, the total population estimated by the T1 Family File is markedly smaller than the current Ontario population. Therefore if we were to create quintile-specific rates of NAS, opioid poisonings, or non-poisoning events using this measure of population, they would be overestimates of the true incidence. To account for this, we calculated the percent of the population in each income quintile as estimated by the T1 Family File, and applied it to the total Ontario 2016 population used in our yearly rates to create a more accurate denominator. We were then able to compare our annual rates for NAS, opioid poisonings, and non-poisoning events, to our quintile-specific rates. Due to a lack of data on opioid-related deaths for 2016, quintile-specific rates for deaths were calculated for 2015.

Statistical Analyses

We calculated crude rates and 95% confidence intervals of NAS, opioid poisonings and non-poisoning events in the population and across income quintiles. Age-standardized rates were not calculated because age-specific rates of opioid morbidity and mortality over time have neither been constant over time, nor have they held a consistent relationship between age-groups.[1,2,28,29]

Prevalence ratios and corresponding 95% confidence intervals were calculated by comparing NAS, opioid poisonings and non-poisoning rates in the least advantaged quintile to those in the most advantaged quintile. Potential rate reductions (PRR) and corresponding 95% confidence intervals were calculated for each opioid indicator.[30] The PRR represents the

potential reduction in rates of a health outcome if all groups had the same income profile as the highest income quintile. A higher PRR represents greater inequality in the population. Attributable cases and corresponding 95% confidence intervals were calculated by multiplying each PRR by the total number of cases in the population for a given indicator. The attributable cases represent the absolute number of cases in a population that could be prevented if all groups experienced the same rate as the highest income quintile.

All statistical analyses were completed using SAS version 9.3 statistical software.

RESULTS

Descriptive Statistics

Our analysis included trends for NAS, opioid poisonings, and non-poisoning events occurring in Ontario between 2003 and 2016. Table 1 presents the distribution of NAS, ED visits and hospitalizations for opioid poisonings and non-poisoning events (2016) and opioid-related deaths (2015) by age, sex, and income quintile related to the most recent available data.

Opioid poisonings and non-poisonings events occurred primarily in individuals aged 25 to 64. Hospitalizations for both opioid poisonings and non-poisonings had a relatively even distribution of events across sex, while deaths, poisoning, and non-poisoning ED visits had higher distributions of events for males as compared to females. Low-income quintiles were more likely to experience opioid events across all indicators compared to high-income quintiles.

Table 1. Descriptive characteristics of NAS, opioid poisonings, and non-poisoning events in 2016, and opioid-related deaths in 2015.

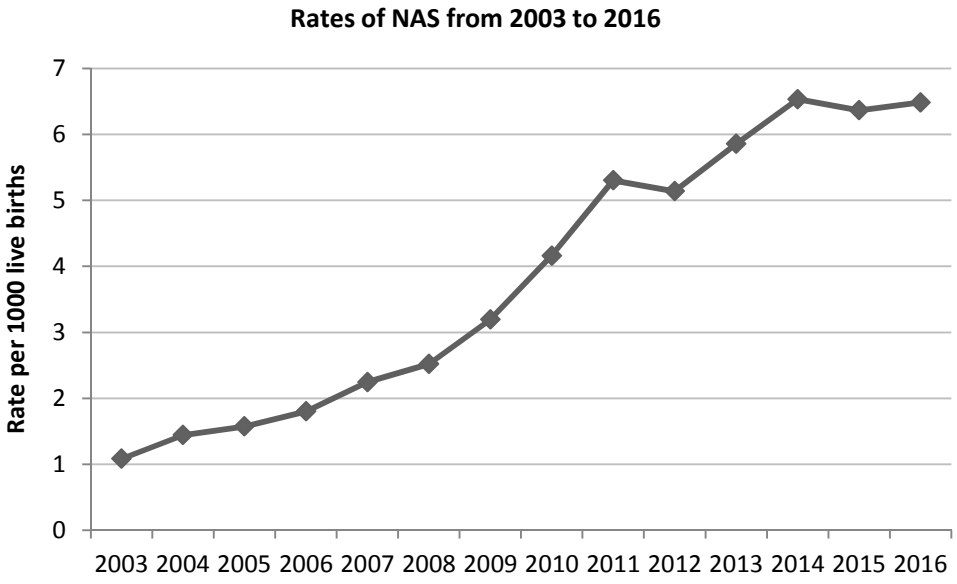
Variable	NAS, n (%)	Opioid Poisonings, n (%)			Non-Poisoning Events, n (%)	
		ED Visits	Hosp.	Deaths	ED Visits	Hosp.
Total	882	4420	1893	730	7575	3886
Age	N/A					
< 14		89 (2.0)	42 (2.2)	1 (0.1)	11 (0.1)	33 (0.8)
15-24		701 (15.9)	164 (8.7)	71 (9.7)	1226 (16.2)	445 (11.5)
25-44		1898 (42.9)	533 (28.2)	303 (41.5)	4307 (56.9)	1804 (46.4)
45-64		1257 (28.4)	721 (38.1)	318 (43.6)	1701 (22.5)	1140 (29.3)
65+		475 (10.8)	432 (22.8)	34 (4.7)	325 (4.3)	464 (11.9)
Sex	N/A					
Male		2461 (55.7)	910 (48.1)	474 (64.9)	4610 (60.9)	1881 (48.4)
Female		1958 (44.3)	982 (51.9)	256 (35.1)	2965 (39.1)	2005 (51.6)
Not identified		1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Income Quintile						
Q1	64 (7.3)	480 (10.9)	208 (11.0)	74 (10.1)	638 (8.4)	384 (9.9)
Q2	103 (11.7)	728 (16.5)	335 (17.7)	102 (14.0)	1021 (13.5)	572 (14.7)
Q3	135 (15.3)	790 (17.9)	350 (18.5)	109 (14.9)	1653 (21.8)	634 (16.3)
Q4	176 (20.0)	806 (18.2)	364 (19.2)	148 (20.3)	1381 (18.2)	692 (17.8)
Q5	384 (43.5)	1283 (29.0)	562 (29.7)	251 (34.4)	2214 (29.2)	1456 (37.5)
Undetermined[†]	20 (2.3)	333 (7.5)	74 (3.9)	46 (6.3)	668 (8.8)	148 (3.8)

[†]Due to missing postal code, invalid postal code, or suppressed DA information.

Long-Term Rates of Opioid Use Indicators

Figure 1 presents crude rates of NAS, opioid poisonings, and non-poisoning events in Ontario from 2003 to 2016. Annual rates and corresponding 95% confidence intervals for NAS, opioid poisonings, and non-poisoning events can be found in Appendix 2 (Table 2).

Over the study period, the percent change in indicator rates ranged from a 39.8% increase in opioid poisoning hospitalizations, to a 499.9% increase in NAS. From 2014 to 2016, however, rates of NAS in Ontario have held relatively constant around 6.5 cases per 1,000 live births. Rates of ED visits for non-poisoning events increased by 286.0%, from 14.06 in 2003 (n=1721) to 54.26 in 2016 (n=7575). Despite a large absolute decrease in ED visits between 2011 (n=7046) and 2014 (n=5659), rates returned to their previous levels in 2016.



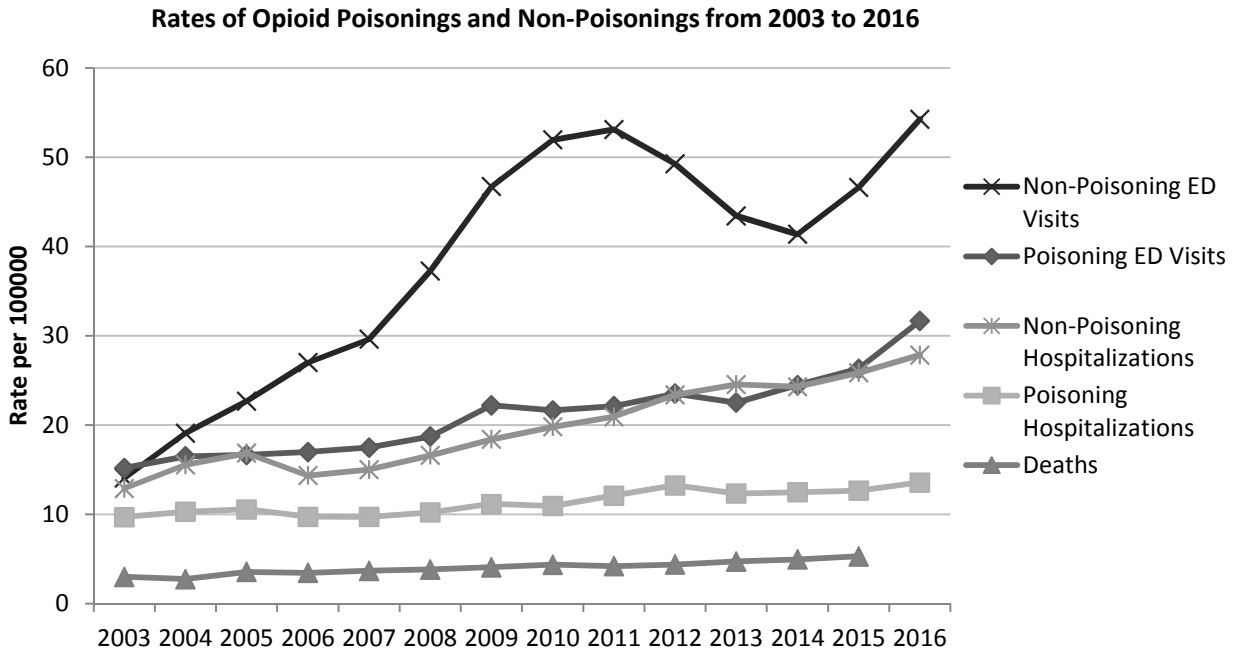


Figure 1. Crude rates of NAS, opioid poisonings, and non-poisoning events in Ontario, 2003-2016.

Rates by Income Quintile

Figure 2 presents crude rates of NAS, opioid poisoning and non-poisoning ED visits and hospitalizations and opioid-related deaths by income quintile, where Q1 represents the highest income neighbourhoods and Q5 represents the lowest income neighbourhoods. Results show that NAS, opioid poisoning, and non-poisoning events all demonstrated the social gradient, with rates of opioid-related harms increasing from highest to lowest income quintiles.

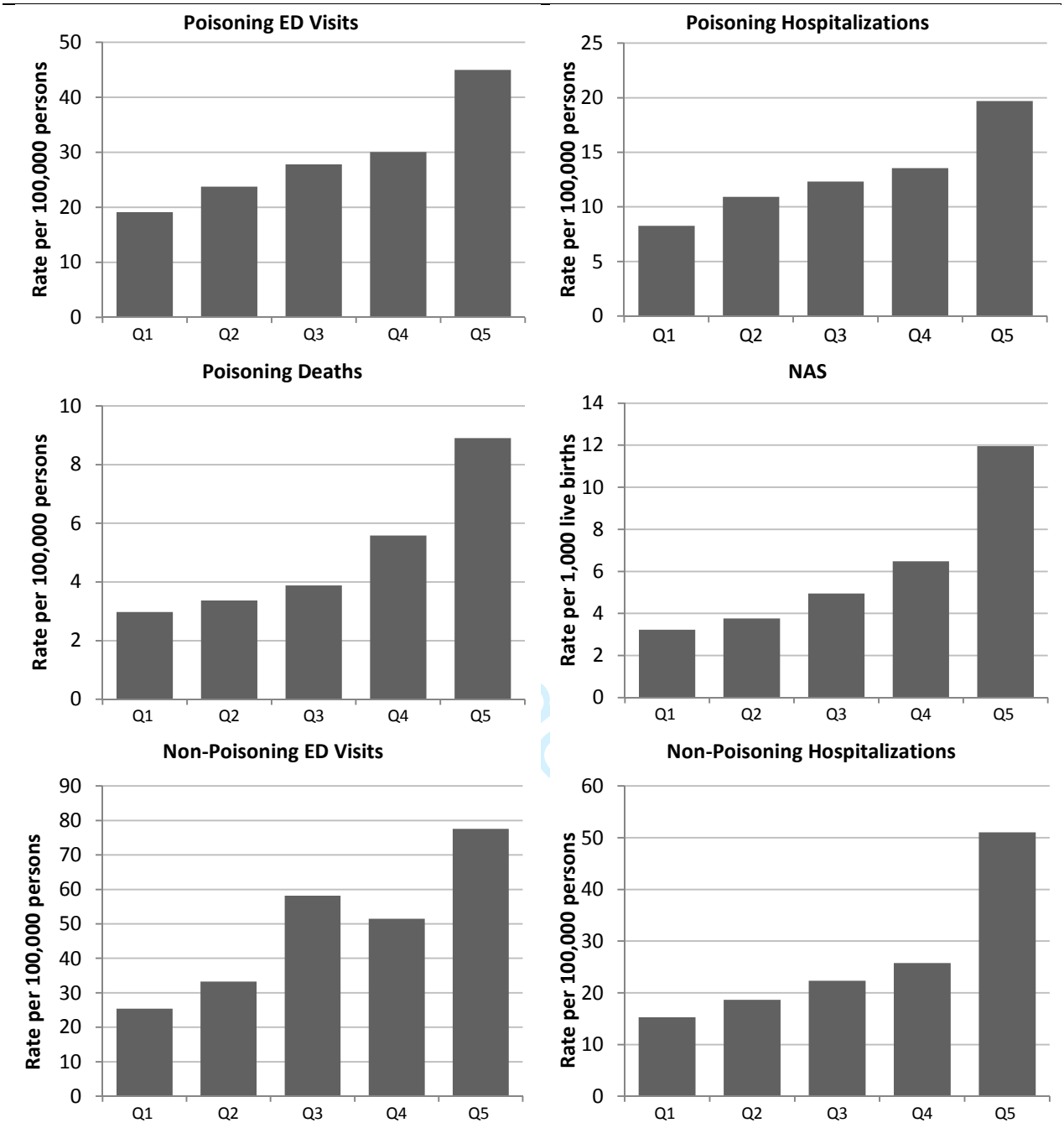


Figure 2. Crude rates of opioid poisoning ED visits and hospitalizations, non-poisoning ED visits and hospitalizations by neighbourhood income quintile in Ontario in 2016, and crude rates of opioid-related deaths by neighbourhood income quintile in Ontario in 2015, where Q1 represents high-income neighbourhoods and Q5 represents low-income neighbourhoods.

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Absolute and Relative Calculations

Table 2 presents the prevalence ratio, PRR, and the absolute number of cases attributable to socioeconomic inequalities in the population for NAS, opioid poisonings, and non-poisoning events. Significant social inequalities were observed on both absolute and relative scales. Living in the lowest income neighbourhoods was associated with at least double the prevalence of opioid-related harms for NAS, opioid poisonings, and non-poisoning events, compared to those living in the highest income neighbourhoods.

PRRs in opioid-related harms were demonstrated for all cases of NAS, opioid poisonings, and non-poisoning events, if all groups were to experience the same rates as the highest income neighbourhoods. In absolute terms, this would mean a significant annual reduction in the number of ED visits, hospitalizations, and deaths due to NAS, opioid poisonings, and non-poisoning events.

Table 2. Prevalence ratios, PRRs, and cases attributable to socioeconomic inequality of NAS, opioid poisoning and non-poisoning ED visits and hospitalizations in 2016, and opioid-related deaths in 2015.

Indicator	Prevalence Ratio (95% CI)	PRR% (95% CI)	Attributable Cases (95% CI)
NAS	3.70 (2.62-5.23)	49.9 (36.7-60.5)	440.1 (324.0-533.7)
Opioid Poisonings			
ED Visits	2.36 (2.15-2.58)	34.8 (29.1-40.1)	1538.9 (1287.8-1772.4)
Hospitalizations	2.38 (2.07-2.73)	36.5 (28.0-44.2)	691.6 (529.2-836.9)
Deaths	2.99 (2.25-3.97)	40.0 (25.8-51.7)	291.7 (188.1-377.5)
Non-Poisoning Events			
ED Visits	3.06 (2.77-3.38)	48.7 (44.8-52.4)	3691.6 (3394.9-3969.3)
Hospitalizations	3.34 (2.92-3.83)	43.0 (37.4-48.2)	1670.4 (1451.5-1871.7)

INTERPRETATION

Rates of opioid-related harms have markedly increased from 2003 to 2016. After stratifying by neighbourhood income quintile, rates of NAS, opioid poisonings, and non-poisoning events all demonstrate increasing rates with decreasing neighbourhood income. Furthermore, the lowest neighbourhood income quintile is particularly at risk of opioid-related harms, with rates of NAS, opioid poisonings, and non-poisoning events at least double that of the highest income group. PRR calculations indicated that at least 30% of the cases of opioid poisoning, non-poisoning events, and NAS could be prevented if all groups experienced the same rates as those in the highest income group. Together, these results suggest there may be significant health disparities between low and high-income areas in Ontario with respect to opioid-related morbidity and mortality.

Our study was successful in replicating a well-established pattern in the literature showing relatively constant increases in rates of NAS, as demonstrated in Ontario and the United States.[31-34] For example, Brogly et al. (2017) found a 16-fold increase in infants born to opioid-dependent mothers from 2002 to 2014 in Ontario, while in the United States, Tolia et al. (2015) found a 286% increase from 2004 to 2013 in neonatal ICU admissions due to NAS.[31,32] Results from our study further examine this trend, demonstrating that NAS is disproportionately experienced by women from low-income neighbourhoods. These findings from Ontario are consistent with other jurisdictions.[34-35] A study by Patrick et al. (2012) found that state Medicaid programs (social health care programs for low income and disabled individuals who cannot afford health care) were the predominant payer for 60% of mothers using opiates, and 78% of newborns diagnosed with NAS in the United States in 2009.[34]

Rates of other opioid poisonings and non-poisoning events also fit with what is known on opioid-related harms in Ontario.[1,2,18] One particular trend of interest is that of the non-poisoning opioid-related ED visits, which show a large decrease around 2011, and a subsequent rise in 2014. Though it could not be causally connected, we speculate that this could be related to the February 2012 introduction of tamper-resistant oxycodone in Ontario, as this trend maps with the decrease in oxycodone-related deaths in Ontario, and the rise in fentanyl and hydromorphone related deaths soon after.[2] It could also be related to changed opioid prescribing guidelines in 2010, and the expansion of methadone and buprenorphine programs.[36,37]

Results for opioid-related harms by neighbourhood income also fit with findings from the United States, in which oxycodone poisoning deaths and ED visits for drug-related poisonings have been found to increase with decreasing neighbourhood income.[38-41]

There are several limitations to our study. The use of administrative databases means we have only captured Ontario residents who visited an ED, were admitted to a hospital, or died in the province over our study period. Individuals could not be included if a postal code of residence was not recorded, had an invalid postal code recorded, or were geocoded to a suppressed DA. By excluding these cases from our analysis, 6.6% (n=1289) of all cases were not included. Given that people who use opioids may not pursue medical help at a hospital for a variety of reasons, reported values are likely to be an underestimate of the true rates and income inequalities in opioid-related harms in Ontario. We are also not able to determine whether individuals identified in the database used opioids acquired by prescription, obtained them through diversion of prescription medication, or used an illicit opioid. While this limits the

specificity of our analysis, it at the same time captures the overall burden in the entire population, rather than only those who were prescribed opioids. Finally, our analysis assumes that the socioeconomic structuring of Ontario neighbourhoods has remained stable from 2011 to 2016.

In summary, the present study found that all opioid use indicators studied have demonstrated steady increases from 2003 to 2016 in Ontario. Our results suggest low-income neighbourhoods experience higher rates of opioid-related harms in Ontario.

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APPENDIX 1

Inclusion and exclusion criteria

Unique cases of NAS were identified by ICD-10-CA code P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction). Cases of NAS were excluded if they had a query or suspected diagnosis, or if they were beyond the neonatal age range of 0 to 28 days. One case was counted per infant regardless of how many times they were hospitalized in those 28 days. Cases of NAS were identified using the Discharge Abstract Database (DAD). DAD is housed at the Canadian Institute for Health Information (CIHI) and captures administrative, clinical, and demographic information on all Canadian hospital discharges.

Unique cases of opioid poisoning resulting in unscheduled ED visits and hospitalizations were identified by ICD-10-CA codes T40.0 (poisoning by opium), T40.1 (poisoning by heroin), T40.2 (poisoning for other opioids), T40.3 (poisoning by methadone), T40.4 (poisoning by other synthetic narcotics), and T40.6 (poisoning by other and unspecified narcotics). Cases were excluded if they had a query or suspected diagnosis. Opioid poisonings were identified from the National Ambulatory Care Reporting System (NACRS), DAD, and the Ontario Opioid-Related Death Database (OORDD). NACRS is housed at CIHI and contains data on all hospital and community based ambulatory care, including emergency department utilization, day surgery, and outpatient/community-based clinics in Canada. The OORDD was created by the Ontario Drug Policy Research Network and contains record of all deaths in Ontario where opioids are considered as contributing to the cause of death by the Office of the Chief Coroner for Ontario.

Unique cases of non-poisoning opioid-related events resulting in ED visits or hospitalization were identified by ICD-10-CA codes for mental and behavioural disorders due to

use of opioids: F11.0 (acute intoxication), F11.1 (harmful use), F11.2 (dependence syndrome), F11.3 (withdrawal state), F11.4 (withdrawal state with delirium), F11.5 (psychotic disorder), F11.6 (amnesic syndrome), F11.7 (residual and late-onset psychotic disorder), F11.8 (other mental and behavioural disorders), and F11.9 (unspecified mental and behavioural disorder). Cases were excluded if they had a query or suspected diagnosis. Non-poisoning opioid-related cases admitted to a mental health hospital were identified by DSM-IV-TR codes 305.50 (opioid abuse) and 304.00 (opioid dependence), and DSM-5 codes 305.50 (opioid use disorder, mild) and 304.00 (opioid use disorder, moderate to severe). Non-poisoning ED visits were identified from NACRS. Non-poisoning hospitalizations were identified from DAD and the Ontario Mental Health Reporting System (OMHRS). OMHRS is housed at CIHI and contains administrative and clinical data on usage of adult acute care mental health beds in Ontario. Validation studies?

Data Quality and Access

There have been no validation studies for ICD-10 codes used to capture cases of NAS, opioid poisonings, and non-poisoning opioid-related events; however, these codes have been consistently used in similar studies of opioid-related harms using administrative databases.[2,18,33] For additional information on study protocol, algorithms used, or programming code, the corresponding author can be contacted.

APPENDIX 2

Table 1. Descriptive characteristics of income quintiles.

Quintile	Mean after-tax incomes*, $CDN (sd)	Range of after-tax incomes*, $CDN	Proportion of low income residents (%)	Mean age*, yr (sd)	Mean percent receiving EI (%)	Dissemination areas, n (%)	Proportion of population (%)
Q1	77,379.16 (23,207.76)	27,550.00 - 279,470.00	0 – 6.7	40.5 (5.9)	8.0 (4.6)	3321 (19.7)	18.0
Q2	62,659.18 (16,318.30)	24,200.00 - 223,210.00	6.8 – 10.0	40.3 (5.2)	9.9 (4.6)	3494 (20.7)	22.0
Q3	53,330.04 (13,208.75)	21,570.00 - 147,200.00	10.1 - 14.5	39.7 (5.2)	10.9 (4.8)	3321 (19.7)	20.3
Q4	43,500.37 (9,030.02)	17,510.00 - 132,180.00	14.6 - 21.6	38.8 (4.9)	11.9 (4.9)	3371 (20.0)	19.2
Q5	31,616.71 (7,415.12)	5,840.00 - 73,490.00	21.7 - 86.0	36.7 (5.2)	13.0 (5.4)	3380 (20.0)	20.4

* Calculated using the median after-tax income and average age for each dissemination area in a given quintile, as provided by Statistics Canada T1FF data.

Table 2. Rates and 95% CIs of NAS per 1,000 live births, opioid poisonings per 100,000, and non-overdose events per 100,000.

Year	NAS	Opioid Poisonings			Non-poisoning visits	
	Rate per 1,000 live births (95% CI)	ED Visits Rate per 100,000 (95% CI)	Hosp. Rate per 100,000 (95% CI)	Deaths Rate per 100,000 (95% CI)	ED Visits Rate per 100,000 (95% CI)	Hosp. Rate per 100,000 (95% CI)
2003	1.08 (0.905-1.26)	15.18 (14.49-15.87)	9.70 (9.15-10.25)	2.99 (2.68-3.30)	14.06 (13.39-14.72)	12.89 (12.25-13.52)
2004	1.44 (1.42-1.64)	16.49 (15.77-17.20)	10.29 (9.73-10.86)	2.74 (2.45-3.04)	19.09 (18.32-19.86)	15.54 (14.85-16.24)
2005	1.57 (1.36-1.78)	16.65 (15.94-17.37)	10.56 (9.99-11.13)	3.54 (3.21-3.87)	22.67 (21.84-23.50)	16.84 (16.12-17.56)
2006	1.80 (1.58-2.02)	16.98 (16.26-17.70)	9.73 (9.19-10.27)	3.44 (3.12-3.77)	27.00 (26.09-27.90)	14.33 (13.68-14.99)
2007	2.25 (2.00-2.49)	17.47 (16.75-18.20)	9.71 (9.17-10.25)	3.67 (3.33-4.00)	29.62 (28.68-30.57)	15.00 (14.32-15.67)
2008	2.52 (2.26-2.78)	18.72 (17.97-19.46)	10.22 (9.66-10.77)	3.81 (3.47-4.15)	37.27 (36.21-38.32)	16.60 (15.90-17.31)
2009	3.19 (2.90-3.49)	22.20 (21.39-23.01)	11.16 (10.58-11.73)	4.07 (3.72-4.42)	46.72 (45.55-47.90)	18.39 (17.65-19.13)
2010	4.16 (3.82-4.50)	21.63 (20.83-22.42)	10.92 (10.36-11.49)	4.35 (3.99-4.70)	51.95 (50.72-53.19)	19.79 (19.03-20.55)
2011	5.31 (4.92-5.69)	22.12 (21.32-22.92)	12.10 (11.51-12.69)	4.19 (3.84-4.54)	53.12 (51.88-54.36)	20.92 (20.14-21.70)
2012	5.14 (4.76-5.52)	23.52 (22.70-24.34)	13.24 (12.62-13.85)	4.36 (4.01-4.72)	49.26 (48.07-50.44)	23.37 (22.55-24.19)
2013	5.86 (5.45-6.26)	22.51 (17.72-23.31)	12.33 (11.74-12.92)	4.72 (4.35-5.08)	43.44 (42.33-44.55)	24.54 (23.71-25.38)
2014	6.54 (6.12-6.97)	24.47 (23.64-25.30)	12.47 (11.88-13.06)	4.94 (4.57-5.31)	41.37 (40.30-42.45)	24.28 (23.45-25.11)
2015	6.37 (5.94-6.79)	26.31 (25.45-27.16)	12.65 (12.06-13.25)	5.29 (4.91-5.68)	46.61 (45.47-47.75)	25.86 (25.01-26.70)
2016	6.49 (6.06-6.92)	31.66 (30.73-32.60)	13.56 (12.95-14.17)	N/A	54.26 (53.04-55-48)	27.84 (26.96-28.71)

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) Page 1 b) Page 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.	1.1: Page 2 1.2: Page 2 1.3: Not applicable, no linkage conducted
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3		
Objectives	3	State specific objectives, including any prespecified hypotheses	Pages 3-4		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 4		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4		
Participants	6	*(a) Cohort study* - Give the		RECORD 6.1: The methods of study	

		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	a) Pages 4-5, 23-24 b) Not applicable, no matching was used	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.	6.1: Pages 23-24 6.2: Page 24 6.3: Not applicable, no linkage conducted
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Not applicable for a population health assessment	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.	7.1: Pages 23-24
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	Pages 4-6, 23-24		
Bias	9	Describe any efforts to address potential sources of bias	Page 7		

Study size	10	Explain how the study size was arrived at	Page 4		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 5-6		
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) Pages 7-8 b) Not applicable c) Page 6 d) Not applicable e) Not applicable		
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. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1: Page 24 12.2: Page 24
Linkage		..		RECORD 12.3: State whether the	12.3: Not

				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.	applicable, no linkage.
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) Page 8-9 b) Not applicable	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.	a) Pages 4-5
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) Pages 8-9 b) Pages 8-9		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or	Pages 10-11		

		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) Not applicable – population health assessment b) Not applicable c) Pages 13-14		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Pages 14-15		
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	Page 15-16	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.	Page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 15-16		

Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 15-16		
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	Page 1		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 24

*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.