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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Adverse cardiac events associated with incident opioid drug use among older adults with COPD

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Abstract
Purpose We evaluated whether incident opioid drug use was associated with adverse cardiac events among older adults with chronic obstructive pulmonary disease (COPD).
Methods This was an exploratory, retrospective cohort study using health administrative data from Ontario, Canada, from 2008 to 2013. Using a validated algorithm, we identified adults aged 66 years and older with non-palliative COPD. Hazard ratios (HR) were estimated for adverse cardiac events within 30 days of incident opioid receipt compared to controls using inverse probability of treatment weighting using the propensity score.
Results There were 134,408 community-dwelling individuals and 14,685 long-term care residents with COPD identified, 67.0 and 60.6% of whom received an incident opioid. Incident use of any opioid was associated with significantly decreased rates of emergency room (ER) visits and hospitalizations for congestive heart failure (CHF) among community-dwelling older adults (HR 0.84; 95% CI 0.73–0.97), but significantly increased rates of ischemic heart disease (IHD)-related mortality among long-term care residents (HR 2.15; 95% CI 1.50–3.09). In the community-dwelling group, users of more potent opioid-only agents without aspirin or acetaminophen combined had significantly increased rates of ER visits and hospitalizations for IHD (HR 1.38; 95% CI 1.08–1.77) and IHD-related mortality (HR 1.83; 95% CI 1.32–2.53).
Conclusions New opioid use was associated with elevated rates of IHD-related morbidity and mortality among older adults with COPD. Adverse cardiac events may need to be considered when administering new opioids to older adults with COPD, but further studies are required to establish if the observed associations are causal or related to residual confounding.

Keywords Opioids · COPD · Cardiac · Pharmacoepidemiology · Drug safety

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Introduction

Prescription opioid drugs are commonly used by individuals with chronic obstructive pulmonary disease (COPD) [1, 2], and there is evidence suggesting that their use is rising in this population [1]. Cardiac disease is also frequent in COPD [3, 4], and about one third of all COPD deaths are estimated to be cardiac-related [5]. The potential influence of opioid drugs on cardiac health is somewhat controversial. Some studies have shown that activation of opioid receptors facilitates the cardioprotective process of ischemic pre-conditioning [6–8]. However, there are potential mechanisms by which opioid

drugs may contribute to cardiac harm: reducing venous return and right ventricular output through the blunting of inspiratory neural drive, intrathoracic pressure and tidal volume [9]; substantially reducing myocardial oxygen delivery [10]; hypoxemia and hypercapnia-mediated decreases in cardiac contractility [11]; increasing cardiovascular inflammatory factors (such as fibrinogen and apolipoprotein-B) [12]; and masking warning anginal symptoms [13]. Previous observational studies have reported that prescription opioid use in the general population is associated with increased risk of myocardial infarction [14, 15] and cardiovascular-related mortality [16]. While previous clinical trials evaluating the efficacy of opioids for refractory breathlessness in advanced COPD did not report increased risk of adverse cardiac events [17–20], these studies were characterized by small sample sizes [17–20], exclusion of individuals at-risk for drug-related adverse events (e.g. individuals with certain comorbid illnesses [17–20] or those with a history of previous opioid-related negative effects [18, 19]) and limited opioid dosing [17–20]. No population-level drug safety data is available relating to the potential influence of opioid drugs on cardiac health among individuals with COPD. It is important for the medical community to be aware of possible opioid-related cardiac adverse events among individuals with COPD because both opioid drug use [1, 2] and cardiovascular comorbidity [3, 4] occur more frequently in COPD compared to the general population and individuals with COPD may be more vulnerable to potential opioid-related influences on gas exchange given pre-existing impairment in oxygenation and ventilation. The purpose of this study was to explore the association of new opioid use with risk of adverse cardiac events among older adults with COPD.

Methods

Study design A retrospective cohort design was used with population-level health administrative data from Ontario, Canada, from 1 April 2008 to 30 April 2013. Ontario is a culturally diverse province, containing about 13.5 million people (approximately 40% of Canada's total population). This study was approved by the review ethics board at Sunnybrook Health Sciences Centre.

Data sources Using unique encoded identifiers, we linked 13 health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario, Canada. A population-based database containing Ontarians with validated physician-diagnosed COPD was used. The methods used to validate COPD health administrative codes have been previously described [21]. We used a highly specific algorithm to identify individuals with COPD, based on three or more ambulatory claims for COPD within any 2-year period or one or more hospitalization(s) for COPD (specificity 95.4% [95% confidence interval (CI) 92.6–97.4%]; sensitivity 57.5% [95% CI 47.9–66.8%]) [21]. The Ontario Drug Benefit (ODB) database was also used, which contains information on all publicly funded outpatient medication dispensings to Ontarians ages 65 years and older. Drug claim coding error is very low in the ODB at 0.7% (95% CI 0.5–0.9%) [22]. Other health administrative databases used are outlined in the Online Supplement section 1.

Study population Criteria for inclusion in this study were having validated physician-diagnosed COPD, being an Ontario resident and being 66 years of age or older, all between 1 April 2008 to 31 March 2013. Although individuals younger than 66 years old were not included in this study (as drug dispensing data were not available for them in ODB), COPD is generally a disease of older adults and the majority of affected individuals are older than age 65 years [23]. Individuals receiving palliative care (based on physician service codes) in the year prior to the index date (defined below) were excluded, since opioids may be appropriately used in this group and since these individuals are anticipated to have poor health outcomes. Instead, our purpose was to evaluate for possible opioid-related adverse cardiac events in the broader, non-palliative, older adult COPD population. Community-dwelling older adults and those living in long-term care residence were examined separately, as access to healthcare providers (and hence opioid drugs) may differ between these two groups and since individuals living in long-term care residence tend to be sicker and are more likely to have poor health outcomes.

Opioid drug exposure and index date definition Table 1 lists the oral and transdermal formulation opioid drugs that we considered. Partial agonist-partial antagonist opioid agents (i.e. suboxone) and combination opioid and glutamate receptor agonists (i.e. methadone) were not included, since these are distinct classes of opioid drugs. Opioid drug users were defined by incident use of any opioid listed in Table 1 between 1 April 2008 and 31 March 2013. Similar to previous [24, 25], we defined incident use as any opioid dispensing without having received any opioid drug listed in Table 1 in the year prior to the incident date. Incident (and not prevalent) opioid use was selected, since incident use is less likely to be associated with 'healthy user' bias and since our purpose was to examine acute-onset drug-related adverse cardiac events. We counted incident use only once per individual (specifically, the first dispensing was considered, in the event criteria for incident use were met more than once during the study), and an exposed individual was not allowed to cross-over to the unexposed comparison group at any time. The index date for

Table 1 Opioid drugs available through the ODB program

Oral tablet/capsule agents			Oral liquid agents[a]	Transdermal agents[b]
Opioid-only agonists		Opioid/non-opioid combination agents		
Shorter-acting agents	Longer-acting agents			
Anileridine	Codeine sulphate	Acetaminophen-caffeine-codeine	Acetaminophen-codeine phosphate	Fentanyl transdermal
Codeine phosphate	Hydromorphone HCL ER/SR	Acetaminophen-codeine	Codeine phosphate	
Hydromorphone HCL	Levorphanol	Acetylsalicylic acid-codeine-caffeine	Morphine HCL	
Morphine HCL	Morphine sulphate ER/SR	Acetylsalicylic acid-codeine	Morphine sulphate	
Meperidine	Oxycodone HCL ER/SR	Oxycodone HCL-acetaminophen		
Oxycodone HCL	Propoxyphene HCL; dextro-propoxyphene HCL	Oxycodone HCL-acetylsalicylic acid		

Rectal and intravenous opioid formulations were not considered

ER extended release, *HCL* hydrochloride, *SR* slow release

[a] All oral liquid opioid formulations are shorter-acting

[b] Transdermal fentanyl is a longer-acting opioid agent

exposed individuals was the date the incident opioid was dispensed.

Control group Controls did not receive any opioid listed in Table 1 between 1 April 2008 and 31 March 2013. Since the index date for the exposed group involved a drug exposure, the index date for the control group similarly involved a drug exposure, in order to help minimize bias. We defined cohort entry for controls as the most recent incident non-opioid drug dispensing on or before a date chosen randomly from the accrual period, with the index date being the date the most recent incident non-opioid medication was received. Incident non-opioid drug use was defined as no receipt of a drug within the same class as the index non-opioid drug in the year prior to index. If the most recent non-opioid drug dispensing took place more than 6 months before that date, or if it took place before the start of the 2008–2013 period, then the individual was excluded. This approach to define controls has been used previously [24, 25].

Study outcomes Adverse cardiac events that we examined within 30 days after the index date included emergency room (ER) visits, hospitalizations and mortality associated with ischemic heart disease (IHD) or congestive heart failure (CHF). When an ER visit directly leads to a hospitalization, only a hospitalization event was counted. ER visits and hospitalizations for IHD and CHF were identified based on one discharge code for IHD and CHF, respectively. This algorithm of health administrative codes to identify IHD and CHF has been previously validated for diagnostic purposes and is highly specific: one discharge code for IHD has a specificity of 99.4% [95% CI 98.9–99.9%] and a sensitivity of 62.1% [95% CI 51.9–72.3%] [26], and one discharge code for CHF has a specificity of 98.6% [95% CI 98.1–99.1%] and a sensitivity of 60.6% [95% CI 50.8–70.4%] [27]). We selected a 30-day follow-up period to evaluate for possible adverse cardiac events since we expected these events to occur soon following opioid initiation. Furthermore, about 90% of all incident opioid dispensings were previously found to have a duration of 30 days or less [1].

Propensity score weighting Among individuals with COPD, opioid users are known to differ from non-users on a variety of characteristics that may influence risk of subsequent cardiac outcomes [1]. Therefore, we used inverse probability of treatment weighting (IPTW) using the propensity score [28, 29] to create weighted samples of exposed and control individuals where measured baseline covariates were balanced between the two groups. We estimated a propensity score for new opioid receipt by developing a logistic regression model with 51 covariates that included multiple markers of COPD severity (including duration of COPD, receipt of respiratory-related medications and COPD exacerbation frequency), healthcare system use, pre-existing comorbidities (including ER visit or hospitalization for IHD or CHF in the past year, as a marker of recent cardiac status stability) and other prescription medication receipt (Tables 1 and 2 in section 3 of the Online Supplement).

Sensitivity analyses First, we evaluated for adverse cardiac events by opioid type received (i.e. opioid-only agents versus combination opioid/non-opioid agents [Table 1]), since

opioid-only agents generally contain more potent opioids (like hydromorphone and fentanyl) than combination agents (most of which contain less-potent codeine) and since some combination agents contain cardio-protective aspirin as the non-opioid component [30]. Second, among users of opioid-only agents, we examined our outcomes by drug half-life type (i.e. shorter-acting versus longer-acting agents [Table 1]) to see if adverse cardiac events would be observed even among users of shorter-acting agents. Third, we evaluated our outcomes among users of opioid-only agents stratifying by COPD exacerbation history in the year prior to the index date (i.e. no exacerbation versus one or more outpatient exacerbation with no exacerbation requiring presentation to hospital versus one or more exacerbation requiring presentation to hospital). COPD exacerbation history is associated with severity of underlying airflow obstruction [31], decreased quality of life [32], risk of future exacerbations [33] and mortality [34], and Canadian [35] and newer global [36] COPD guidelines use COPD exacerbation frequency to distinguish COPD severity. Evaluating for outcomes in the subgroup of individuals with least severe disease (in this study, those experiencing no exacerbation in the year prior to index) is an established method for minimizing confounding by indication in non-randomized studies [37]. The Online Supplement section 2 describes methods relating to additional sensitivity analyses.

Statistical analysis Pre- and post-propensity score weighting, we calculated descriptive statistics and standardized differences for the exposed and control groups on all baseline covariates [29]. Using Cox proportional hazard regression models with a robust variance estimator, a hazard ratio (HR) with associated 95% confidence interval (CI) was estimated for each outcome in the propensity score weighted samples [38]. The control group was used as the reference in all analyses. All statistical analyses were conducted using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA). Two-sided tests of significance at the $p < 0.05$ level were used.

Results

Overall cohort results

There were a total of 134,408 community-dwelling individuals and 14,685 long-term care residents aged 66 years and older with COPD identified between 1 April 2008 and 31 March 2013. Incident opioid receipt occurred in 67.0 and 60.6%, respectively (Online Supplement section 3). Baseline sociodemographic and health characteristics were well-balanced between new users and controls following propensity score weighting in the both community-dwelling and long-term care resident cohorts, with standardized differences below 10% for all variables (Online Supplement section 3).

In the community-dwelling cohort, compared to controls, incident use of any opioid was associated with significantly decreased rates of ER visits or hospitalizations for CHF (HR 0.84; 95% CI 0.73–0.97) (Table 2). No significant associations were found between incident opioid use and ER visits

Table 2 Hazard ratios (HR) and confidence intervals (CI) for adverse cardiac events for the propensity score weighted community-dwelling and long-term care resident cohorts

Outcomes	Opioid use status	Number of events (%)	HR (95% CI)	*p* value
Community-dwelling cohort				
ER visit or hospital admission for IHD	New opioid users	591 (0.7)	1.04 (0.89, 1.22)	0.64
	Non-opioid users	283 (0.6)		
ER visit or hospital admission for CHF	New opioid users	798 (0.9)	0.84 (0.73, 0.97)	0.01
	Non-opioid users	473 (1.1)		
IHD-related mortality	New opioid users	227 (0.3)	0.99 (0.77, 1.29)	0.96
	Non-opioid users	114 (0.3)		
CHF-related mortality	New opioid users	31 (0.0)	0.74 (0.31, 1.79)	0.51
	Non-opioid users	21 (0.0)		
Long-term care resident cohort				
ER visit or hospital admission for IHD	New opioid users	67 (0.7)	1.76 (1.00, 3.09)	0.05
	Non-opioid users	26 (0.5)		
ER visit or hospital admission for CHF	New opioid users	92 (1.0)	1.14 (0.78, 1.67)	0.49
	Non-opioid users	55 (0.9)		
IHD-related mortality	New opioid users	174 (2.0)	2.15 (1.50, 3.09)	<0.0001
	Non-opioid users	56 (1.0)		
CHF-related mortality	New opioid users	24 (0.3)	1.52 (0.73, 3.17)	0.27
	Non-opioid users	11 (0.2)		

CHF congestive heart failure, *ER* emergency room, *IHD* ischemic heart disease

or hospitalizations for IHD or cardiac-related mortality. In the long-term resident cohort, incident use of any opioid relative to controls was associated with significantly increased rates of IHD-related mortality (HR 2.15; 95% CI 1.50–3.09). No other significant associations were observed.

Sensitivity analyses for community-dwelling cohort

By opioid-type Users of opioid-only agents relative to controls had increased rates of ER visits or hospitalizations for IHD (HR 1.38; 95% CI 1.08–1.77) and IHD-related mortality (HR 1.83; 95% CI 1.32–2.53) (Table 3). However, users of combination opioid/non-opioid agents versus controls had decreased rates of ER visits or hospitalizations for CHF (HR 0.81; 95% CI 0.71–0.94). Lower risk for ER visits or hospitalizations for CHF remained among combination opioid/non-opioid users versus controls, even after eliminating users of combination agents containing aspirin (data not shown).

By opioid half-life type Compared to controls, recipients of opioid-only formulations that were shorter- and longer-acting had higher rates of ER visits or hospitalizations for IHD (shorter-acting agents HR 1.33; 95% CI 1.01–1.74; longer-acting agents HR 1.70; 95% CI 1.01–2.89) and IHD-related mortality (shorter-acting agents HR 1.81; 95% CI 1.29–2.54; longer-acting agents HR 2.41; 95% CI 1.05–5.53) (Table 4).

By COPD exacerbation frequency Relative to controls, users of opioid-only agents with no exacerbation in the year prior to the index date had increased rates of ER visits or hospitalizations for IHD (HR 1.53; 95% CI 1.07–2.20) and IHD-related mortality (HR 1.92; 95% CI 1.18–3.12) (Table 5). Greater rates of IHD-related mortality were also observed among opioid-only agent users with ≥1 exacerbation requiring presentation to hospital (HR 1.81, 95% CI 1.08–3.02). Additional sensitivity analyses for the community-dwelling cohort are contained in the Online Supplement section 4.

Sensitivity analyses long-term care resident cohort

Refer to the Online Supplement section 5 for these analyses.

Discussion

After propensity score weighting using 51 covariates, our large, population-based cohort study demonstrated significantly increased rates of IHD-related morbidity and mortality in association with incident opioid-only formulation use among community-dwelling older adults with COPD, as well as among older adults with COPD living in long-term care residence who received any incident opioid (regardless of whether or not the opioid was combined with a non-opioid agent). Increased rates of IHD-related morbidity and mortality were also observed with opioid-only agent use among the healthiest subgroup of individuals with COPD, further strengthening our overall findings.

In the overall community-dwelling cohort, no significant positive associations were found between any incident opioid use and adverse cardiac events and there were significantly decreased rates of ER visits or hospitalizations for CHF among opioid users. These results may be explained by the fact that combination opioid/non-opioid drug formulations were included in the overall cohort analysis and these combination agents account for close to 90% of new opioid use among older adults with COPD [1]. Unlike opioid-only agents, combination opioid/non-opioid drug formulations generally contain less potent opioids (like codeine), lower

Table 3 Hazard ratios (HR) and confidence intervals (CI) for adverse cardiac events for the propensity score weighted community-dwelling cohort, distinguishing by opioid type received

Opioid formulation received	Opioid use status	ER visit or hospital admission for IHD			ER visit or hospital admission for CHF			IHD-related mortality			CHF-related mortality		
		N (%)	HR (95% CI)	*p* value	*N* (%)	HR (95% CI)	*p* value	*N* (%)	HR (95% CI)	*p* value	*N* (%)	HR (95% CI)	*p* value
Opioid-only formulation	New users	121 (0.9)	1.38 (1.08, 1.77)	0.01	165 (1.2)	1.05 (0.84, 1.30)	0.69	68 (0.5)	1.83 (1.32, 2.53)	0.0003	10 (0.1)	1.49 (0.60, 3.72)	0.39
	Non-users	288 (0.6)			518 (1.2)			122 (0.3)			23 (0.1)		
Combination opioid/non-opioid formulation	New users	468 (0.6)	1.00 (0.85, 1.18)	0.99	628 (0.8)	0.81 (0.71, 0.94)	0.004	155 (0.2)	0.84 (0.63, 1.10)	0.20	21 (0.0)	0.65 (0.26, 1.59)	0.34
	Non-users	276 (0.6)			453 (1.0)			109 (0.2)			19 (0.0)		

CHF congestive heart failure, *ER* emergency room, *IHD* ischemic heart disease

Table 4 Hazard ratios (HR) and confidence intervals (CI) for adverse cardiac events for the propensity score weighted community-dwelling cohort, distinguishing by opioid half-life type received

Opioid half-life formulation	Opioid use status	ER visit or hospital admission for IHD			ER visit or hospital admission for CHF			IHD-related mortality			CHF-related mortality		
		N (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value
Shorter-acting opioid-only formulation	New users	97 (0.8)	1.33 (1.01, 1.74)	0.04	147 (1.3)	1.12 (0.89, 1.41)	0.33	56 (0.5)	1.81 (1.29, 2.54)	0.0006	11 (0.1)	1.95 (0.79, 4.80)	0.14
	Non-users	285 (0.6)			511 (1.2)			120 (0.3)			22 (0.0)		
Longer-acting opioid-only formulation	New users	22 (1.0)	1.70 (1.01, 2.89)	0.05	16 (0.7)	0.69 (0.41, 1.18)	0.17	13 (0.6)	2.41 (1.05, 5.53)	0.04	<6[a]	[a]	[a]
	Non-users	274 (0.6)			489 (1.1)			115 (0.3)			18 (0.0)		

CHF congestive heart failure, *ER* emergency room, *IHD* ischemic heart disease

[a] Data are not presented, according to Institute of Clinical Evaluative Sciences reporting rules, because of small cell size

opioid doses are generally achievable and some contain cardio-protective aspirin as the non-opioid component. When we evaluated the generally more potent and non-aspirin-containing opioid-only agents among community-dwelling individuals, significantly increased risks for IHD-related morbidity and mortality were observed. Although the absolute risk increases for IHD-related morbidity and mortality were relatively small, they may be important at the population level, where upwards of 10% of Ontario's population over the age of 35 years old are estimated to have COPD [23]. Users of combination opioid/non-opioid agents accounted for the decreased rates of ER visits or hospitalizations for CHF observed among opioid recipients in the overall community-dwelling cohort, and the association between combination agent use and decreased CHF-related morbidity persisted even after eliminating users of aspirin-containing formulations. This finding may be explained by the lower opioid potency and dose that generally characterize combination agents, which may have been sufficient to facilitate cardio-protective ischemic pre-conditioning, but insufficient to

Table 5 Hazard ratios (HR) and confidence intervals (CI) for adverse cardiac events for the community-dwelling propensity score weighted cohort, stratified by COPD exacerbation frequency history

COPD exacerbation frequency history status	Opioid use status	ER visit or hospital admission for IHD			ER visit or hospital admission for CHF			IHD-related mortality			CHF-related mortality		
		N (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value	*N* (%) of event	HR (95% CI)	*p* value
0 exacerbations in the year prior to index	New users	64 (0.8)	1.53 (1.07, 2.20)	0.02	65 (0.8)	1.12 (0.80, 1.55)	0.51	27 (0.3)	1.92 (1.18, 3.12)	0.009	<6[a]	[a]	[a]
	Non-users	149 (0.5)			207 (0.8)			49 (0.2)			<6[a]		
≥1 outpatient respiratory exacerbations in the year prior to index	New users	24 (0.9)	1.46 (0.84, 2.56)	0.18	21 (0.8)	0.99 (0.52, 1.86)	0.97	9 (0.4)	2.13 (0.91, 5.01)	0.08	<6[a]	[a]	[a]
	Non-users	53 (0.7)			70 (0.9)			15 (0.2)			<6[a]		
≥1 exacerbations requiring presentation to hospital in the year prior to index	New users	37 (1.1)	1.15 (0.76, 1.73)	0.51	85 (2.5)	0.99 (0.72, 1.36)	0.93	37 (1.1)	1.81 (1.08, 3.02)	0.02	<6[a]	[a]	[a]
	Non-users	85 (1.0)			228 (2.6)			54 (0.6)			15 (0.2)		

CHF congestive heart failure, *ER* emergency room, *IHD* ischemic heart disease

[a] Data are not presented, according to Institute of Clinical Evaluative Sciences reporting rules, because of small cell size

contribute to negative physiologic effects, like decreasing right ventricular output and cardiac contractility or substantially reducing myocardial oxygen delivery. In previous work relating to adverse respiratory outcomes, we similarly found that combination opioid/non-opioid agents were less harmful than opioid-only agents among community-dwelling older adults with COPD [25].

In the long-term care resident cohort analysis, any opioid use was associated with increased rates of IHD-related mortality and the association with IHD-related mortality remained significantly elevated even when considering the subgroup of combination opioid/non-opioid agent users (Online Supplement section 5). The discrepant role of combination opioid/non-opioid drugs on cardiac health in the community-dwelling cohort versus the long-term care resident cohort may be due to the fact that long-term care residents are likely a less healthy group, and therefore potentially more sensitive to the adverse influences of opioid drugs, including those formulations of lower potency or dose. The increased and competing risk of IHD-related death among opioid users in the overall long-term care resident cohort analysis may explain why increased rates of cardiac morbidity events were not observed.

Compared to controls, increased cardiac harm was found among users of shorter- and longer-acting opioid-only formulations. We have previously reported that incident use of shorter-acting opioid-only agents is associated with increased respiratory-related morbidity and mortality among older adults with non-palliative COPD [25]. More variable drug blood levels and greater drug level peaks are known to be associated with use of shorter- versus longer-acting opioids [39], which may explain why we observed adverse cardiac events with the shorter-acting subclass. We also observed increased adverse cardiac events in association with opioid-only agent use among the healthiest COPD subgroup, that is, individuals having no exacerbation in the year prior to the index date. This result strengthens our overall finding of an association between opioid-only agent use and cardiac events, as such individuals would be the least likely to have received opioids for cardio-respiratory symptoms, and therefore are less likely to be influenced by confounding by indication.

Several limitations need to be acknowledged. First, causation cannot be inferred in this observational study. Second, residual confounding by unmeasured covariates and confounding by indication could be still influencing our results. Certain clinical markers of COPD severity, such as respiratory symptoms and lung function measures, were not available in our databases for incorporation in our propensity score model. However, we adjusted our analyses for multiple other indicators of COPD severity, including duration of COPD, receipt of respiratory-related medications, comorbidities and, most importantly, we stratified our analyses by COPD exacerbation frequency, which is the single best independent predictor of future exacerbation risk [33]. Information on indication for opioid receipt was also not captured in our databases, and it is possible that sicker patients were prescribed opioids to treat symptoms, and their underlying illness, and not the opioid receipt, leads to subsequent cardiac events. However, we adjusted our analyses for a total of 51 covariates (including pre-existing relevant comorbidities, like IHD, CHF and diabetes, which may increase risk for both opioid receipt and negative cardiac outcomes) and we also showed that opioid-only agent use was associated with adverse cardiac events even in the healthiest subgroup of individuals with COPD (i.e. those with no previous exacerbation). Third, we may not have excluded all individuals receiving palliative care in the year prior to the index date using physician service codes. If some individuals receiving palliative care remained, confounding by indication may have contributed to the finding of increased cardiac-related death among opioid users. However, the possible residual inclusion of individuals receiving palliative care would unlikely explain the greater cardiac-related ER visits and hospitalizations among opioid recipients. Fourth, our results may not be generalizable to the entire older adult, non-palliative COPD population, since our COPD definition, while highly specific, had modest sensitivity [21]. Fifth, we may have under-estimated the number of IHD- and CHF-related ER visits and hospitalizations occurring, since these outcome definitions were associated with high specificity, but modest sensitivity [26, 27]. Finally, we were unable to estimate the effect of COPD on the risk of adverse cardiac events due to the study design, as both those exposed and those not exposed to opioids were required to have pre-existing COPD. This design decision was made because our primary objective was to examine the effect of opioids on adverse cardiac events in the COPD population, and thus, we wanted the exposed and unexposed subjects to be similar in every way, except in their exposure to opioids. However, it well-known and previously described [3, 4] that COPD is risk factor for cardiac disease.

In conclusion, incident opioid use among older adults with non-palliative COPD was associated with elevated rates for IHD-related morbidity and mortality, specifically among opioid-only formulation recipients and among long-term care residents. Therefore, decisions to use opioid drugs in the older adult non-palliative COPD population may need to take into consideration potential risk for adverse cardiac events. However, further studies are needed to determine if the observed associations between incident opioid use and adverse cardiac events are causal or due to unresolved confounding.

Authors' contributions NTV, XW, PAC, DSL, ALS, DEO, SSG and PAR contributed substantially to the study design, data analysis and interpretation and the writing of the manuscript.

Compliance with ethical standards This study was approved by the review ethics board at Sunnybrook Health Sciences Centre.

Conflicts of interest All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: NTV had support from Godfrey S. Pettit Respirology Block Term Grant for the submitted work; XW, PAC, DSL, ALS, DEO, SSG and PAR had no support from any organization for the submitted work; DEO received grants and personal fees from Boehringer Ingelheim, grants and personal fees from Astra Zeneca, grants from GlaxoSmithKline and personal fees from Novartis, in the previous 3 years; NTV, XW, PAC, DSL, ALS, DEO, SSG and PAR had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and NTV, XW, PAC, DSL, ALS, DEO, SSG and PAR had no other relationships or activities that could appear to have influenced the submitted work.

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