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PHARMACOEPIDEMIOLOGY

Incident diuretic drug use and adverse respiratory events among older adults with chronic obstructive pulmonary disease

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AIMS

Diuretic drugs may theoretically improve respiratory health outcomes in chronic obstructive pulmonary disease (COPD) through several possible mechanisms, but they might also lead to respiratory harm. We evaluated the association of incident oral diuretic drug use with respiratory-related morbidity and mortality among older adults with COPD.

METHODS

This was a population-based, retrospective cohort study using health administrative data from Ontario, Canada, for the period 2008–2013. We identified adults aged 66 years and older with nonpalliative COPD using a validated algorithm. Respiratory-related morbidity and mortality were evaluated within 30 days of incident oral diuretic drug use compared to nonuse using Cox proportional hazard regression and applying inverse probability of treatment weighting using the propensity score to minimize confounding.

RESULTS

Out of 99 766 individuals aged 66 years and older with COPD identified, incident diuretic receipt occurred in 51.7%. Relative to controls, incident diuretic users had significantly increased rates for hospitalization for COPD or pneumonia [hazard ratio (HR) 1.22, 95% confidence interval (CI) 1.07–1.40], as well as more emergency room visits for COPD or pneumonia (HR 1.35, 95% CI 1.18–1.56), COPD or pneumonia-related mortality (HR 1.41; 95% CI 1.04–1.92) and all-cause mortality (HR 1.20, 95% CI 1.06–1.35). The increased respiratory-related morbidity and mortality observed were specifically as a result of loop diuretic use.

CONCLUSIONS

Incident diuretic drugs, and more specifically loop diuretics, were associated with increased rates of respiratory-related morbidity and mortality among older adults with nonpalliative COPD. Further studies are needed to determine if this association is causative or due to unresolved confounding.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Diuretic drugs may theoretically improve respiratory health outcomes among individuals with chronic obstructive pulmonary disease (COPD), but they may also contribute to respiratory harm.
- There are minimal and conflicting data regarding the potential respiratory effects of systemic diuretic drugs among individuals with COPD.

WHAT THIS STUDY ADDS

- New diuretic drug use, and particularly use of loop diuretics, is associated with elevated rates of respiratory-related morbidity and mortality among older adults with COPD.
- There is a potential for adverse respiratory outcomes in association with new diuretic drug use among older adults with COPD.

Introduction

More than 10% of individuals aged 40 years and older around the globe are estimated to have chronic obstructive pulmonary disease (COPD) [1]. Cardiovascular comorbidity [2, 3] and persisting respiratory symptoms despite maximal conventional therapy [4, 5] commonly occur in COPD. As a result, diuretic drugs may be prescribed in COPD for a variety of reasons: pulmonary hypertension and cor pulmonale; pulmonary oedema; systemic hypertension; and empirically for severe dyspnoea refractory to maximal conventional therapy. Diuretic drugs may theoretically improve respiratory health outcomes in COPD through several possible mechanisms. Diuretics may reduce pulmonary hypertension (either subclinical or overt) and cor pulmonale by decreasing preload to the heart and they can also reduce pulmonary oedema. The presence of pulmonary hypertension in COPD is associated with increased mortality risk [6] and symptoms related to excessive fluid overload may lead an individual with COPD to present to hospital for acute care [7]. Acetazolamide (a specific type of diuretic drug) is also known to have respiratory stimulant properties. Acetazolamide inhibits the renal carbonic anhydrase enzyme, which reduces serum bicarbonate and contributes to metabolic acidosis, which in turn increases minute ventilation through peripheral and central chemoreceptor stimulation [8]. By stimulating minute ventilation and improving gas exchange, acetazolamide may mitigate dyspnoea crises and respiratory exacerbations among individuals with COPD.

However, use of diuretic drugs may also lead to respiratory-related harm among individuals with COPD. With the exception of acetazolamide, all other diuretic drugs (and particularly loop diuretics) have the potential to increase serum bicarbonate and arterial pH, which can then dampen peripheral and central chemoreceptor activity. Hypercapnia, which can occur as a result, is associated with increased risks of respiratory exacerbation [9] and mortality [9–11]. Another potential complication of nonpotassium sparing diuretic drug use is hypokalaemia, which is known to be linked to potential respiratory muscle weakness and acute respiratory failure [12, 13]. There are minimal and conflicting data regarding the potential respiratory effects of diuretic drugs among individuals with COPD [14–19], with few previous studies focusing on systemic formulation diuretics [18, 19] and clinically important respiratory health outcomes [19]. The purpose of this study was to evaluate the association of new oral diuretic use with respiratory-related morbidity and mortality among older adults with COPD.

Methods

Study design

This was a retrospective cohort study using health administrative data from Ontario, Canada, from 1 April 2008 to 30 April 2013. Ontario is Canada's most populous province (13.5 million people); it is culturally diverse and it has a universal, single-payer health care system. The review ethics board at Sunnybrook Health Sciences Centre approved this study.

Data sources

Thirteen Ontario health administrative databases at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario, Canada were linked at an individual person level using unique coded identifiers. COPD health administrative codes were previously validated [20] and a database of individuals with physician-diagnosed COPD was created. For this study, a highly-specific algorithm of health administrative codes was used to identify COPD diagnosis: 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%]) [20]. All publicly-funded outpatient medication dispensed to Ontarians aged 65 years and older are recorded in the Ontario Drug Benefit (ODB) database. The ODB has very low drug claim coding error at 0.7% (95% CI 0.5–0.9%) [21]. The Ontario Health Insurance Plan claims database contains information on patient contact with physicians in both ambulatory and hospital settings, the National Ambulatory Care Reporting System database contains information on emergency room (ER) visits and the Canadian Institute for Health Information (CIHI) Discharge Abstract Database contains information on hospitalizations. The Registered Persons Database contains information on mortality and cause of death data are recorded in the Office of the Registrar General – Deaths database. All other health administrative databases used are described in the Supporting Information.

Study population

To be included in the study, individuals had to meet all the following criteria between 1 April 2008 to 31 March 2013: have validated physician-diagnosed COPD; be an Ontario resident; and be age 66 years or older. Those receiving palliative care (based on physician service codes) in the year prior to the index date (defined below) were excluded to minimize potential bias, as such individuals may be more likely to receive diuretics and have high likelihood of poor outcomes.

Exposed and control groups with index date definitions

Exposed group. All oral diuretic drugs considered in this study are listed in the Supporting Information. Only oral formulations were included, since intravenous agents are unlikely to be used in the outpatient setting. Diuretic drug users were defined by incident use of any diuretic drug (regardless of whether the diuretic was on its own or combined with another drug in a single pill) between 1 April 2008 and 31 March 2013. Although some diuretic drugs were combined with another cardiac medication in a single pill, we ensured that exposed and control individuals were well-balanced on receipt of nondiuretic cardiac drugs (see below). Incident use was defined as no diuretic drug receipt in the year prior to the incident date. Prevalent drug use was not considered to minimize *healthy user* bias and since our purpose was to examine for acute-onset drug-related events. If criteria for incident drug use were met more than once during the study, only the first dispensing was considered, and an exposed individual was not allowed to cross-over to the control group at any time. The index date for exposed individuals was the date the incident diuretic was dispensed.

Control group. Controls did not receive any diuretic drug between 1 April 2008 and 31 March 2013. We elected to define control group entry by a drug exposure, since exposed group entry involved drug receipt. Using a similar approach as previous [22, 23], control group entry was defined as the most recent of any incident nondiuretic medication claim on or before a date chosen randomly from the accrual period. Incident nondiuretic drug use was defined as no receipt of a drug within the same class as the index nondiuretic drug in the year prior to the incident date. If the most recent nondiuretic drug dispensing took place >6 months before the randomly selected date from the accrual period, or if it took place before the start of the 2008–2013 period, then the individual was excluded. The index date for control individuals was the date the incident nondiuretic drug was dispensed.

Study outcomes

The primary outcome was hospitalization for COPD or pneumonia within 30 days after the index date, since this is a common and clinically-important complication of COPD, associated with significant morbidity and mortality [7, 24]. Other outcomes examined within 30 days after the index date included: outpatient respiratory exacerbations (defined similar to previous [22, 23] as oral corticosteroid or respiratory antibiotic receipt within ±7 days of a physician clinic/office visit for COPD or pneumonia, with the corticosteroid or antibiotic prescription having a supply of 5–21 days); ER visits for COPD or pneumonia that did not directly result in a hospitalization; admission to an intensive care unit (ICU) during a hospitalization for COPD or pneumonia; COPD or pneumonia-related mortality; and, all-cause mortality. COPD and pneumonia diagnoses were based on relevant International Classification of Diseases (ICD) codes (*e.g.*, in ICD-10: J41, J42, J43, J44 for COPD; J09–18, J20–22, J40 for pneumonia). A 30-day follow-up period was selected, since we found this to be the mean duration of incident diuretic dispensing and since our intention was to evaluate for acute-onset drug-related benefits or harms.

Propensity score weighting

We anticipated exposed individuals to differ from controls on demographic and health characteristics that would influence risk of diuretic receipt and subsequent respiratory outcomes. Therefore, inverse probability of treatment weighting using the propensity score [25, 26] was employed to create weighted samples of exposed and control individuals, where measured baseline covariates were balanced between the two groups. A propensity score for new diuretic receipt was developed using logistic regression modelling with 55 different covariates, including markers of COPD severity, health care use, comorbidities, other cardiac and noncardiac medication receipt and demographic variables. The full list of variables included in the propensity score can be found in the Supporting Information and an abridged list is shown in Table 1.

Sensitivity analyses

First, we evaluated our outcomes stratifying by COPD exacerbation history in the year prior to the index date (defined as a three-level, mutually-exclusive variable: no exacerbation *vs.* one or more outpatient exacerbation with no exacerbation requiring presentation to hospital *vs.* one or more exacerbation requiring presentation to hospital). COPD exacerbation history is an important marker of disease severity, as it is associated with a greater degree of airflow obstruction [27], poorer quality of life [28], future exacerbation risk [29] and mortality [30]. Previous COPD exacerbation is known to be the strongest predictor of future exacerbation [29], and Canadian [24] and newer global [7] COPD guidelines use COPD exacerbation frequency to distinguish COPD severity. Evaluating for outcomes across subgroups of differing COPD severity helps minimize possible "healthy user" bias (by examining outcomes in the sickest subgroup of patients) and confounding by indication (by examining outcomes in the healthiest subgroup of patients).

Second, outcomes were examined stratifying by whether or not congestive heart failure (CHF) was present within 5 years prior to the index date. The purpose of this analysis was to minimize possible confounding by indication, by evaluating outcomes in the healthier subgroup of individuals without pre-existing CHF.

Third, we examined outcomes distinguishing by the type of diuretic received (i.e., loop diuretic *vs.* potassium-sparing diuretic *vs.* thiazide diuretic *vs.* carbonic anhydrase inhibitor – see Supporting Information for a list of diuretic drugs by subclasses). The purpose of this analysis was to

Table 1

Baseline cohort characteristics, before and after propensity score weighting (abridged version[a])

	Before propensity score weighting			After propensity score weighting		
	New diuretic users	Nondiuretic users	Standardized difference[b]	New diuretic users	Nondiuretic users	Standardized difference[b]
	n = 51 612	*n* = 48 154		*n* = 51 431	*n* = 48 473	
Age (mean + SD)	78.3 ± 7.4	76.3 ± 7.6	0.27	77.5 ± 7.4	77.5 ± 7.9	0.00
Females	49.1%	46.3%	0.06	47.8%	48.1%	0.01
Low income as per ODB flag	25.7%	20.5%	0.12	23.4%	23.5%	0.00
Income quintile						
1 (lowest)	24.5%	22.9%	0.04	24.0%	24.1%	0.00
2	22.3%	21.8%	0.01	22.0%	21.9%	0.00
3	19.2%	19.2%	0.00	19.1%	19.1%	0.00
4	17.7%	18.6%	0.02	18.1%	18.0%	0.00
5 (highest)	15.9%	17.2%	0.03	16.5%	16.5%	0.00
Missing data	0.3%	0.4%	0.00	0.4%	0.4%	0.00
Rural residence	17.0%	16.2%	0.02	16.6%	16.4%	0.00
Living in long-term care residence	9.8%	9.4%	0.01	10.2%	10.1%	0.00
COPD exacerbation frequency in past year						
0	56.2%	64.8%	0.18	60.3%	60.2%	0.00
≥1 not requiring ER/hospital presentation	16.8%	19.1%	0.06	17.7%	17.7%	0.00
≥1 requiring ER/hospital presentation	27.0%	16.0%	0.27	22.0%	22.1%	0.00
COPD exacerbation in past 30 days	16.9%	10.2%	0.20	13.5%	12.8%	0.02
Duration of COPD						
< 2 years	23.4%	33.3%	0.22	28.7%	28.6%	0.00
2–5 years	17.8%	16.8%	0.03	17.1%	17.2%	0.00
> 5 years	58.8%	49.9%	0.18	54.2%	54.3%	0.00
Respiratory medications in past 6 months						
Short/long-acting β-agonist	40.2%	33.4%	0.14	37.0%	37.1%	0.00
Short/long-acting anticholinergic	40.7%	36.0%	0.10	38.6%	39.0%	0.01
Inhaled corticosteroid	13.4%	11.6%	0.05	12.5%	12.8%	0.01
Combination inhaled corticosteroid-long acting β-agonist inhaler	35.1%	30.0%	0.11	32.6%	32.6%	0.00
Oral corticosteroid	17.7%	12.0%	0.16	15.1%	15.4%	0.01
Theophylline	2.4%	1.6%	0.06	2.0%	2.1%	0.01
Respiratory antibiotic	47.2%	43.5%	0.07	45.5%	45.6%	0.00
Non-COPD pulmonary disease[c]	48.9%	44.6%	0.09	46.9%	47.2%	0.01
Ischaemic heart disease[c]	36.4%	25.6%	0.24	31.7%	32.0%	0.01
Congestive heart failure[c]	33.3%	12.4%	0.51	23.4%	23.6%	0.00
ER visit/hospitalization for ischemic heart disease or congestive heart failure in the year prior	20.8%	6.5%	0.43	14.0%	14.0%	0.00

Numbers represent percentages unless otherwise stated.
COPD, chronic obstructive pulmonary disease; ER, emergency room; ODB, Ontario Drug Benefit; SD, standard deviation
[a]The full propensity score model can be found in the Supporting Information
[b]Standardized differences of >0.10 are thought to indicate potentially meaningful differences
[c]Presence of comorbidities was based on 5-year look-back from the index date

examine for possible diuretic subclass effects, particularly among carbonic anhydrase inhibitors, which have the unique potential protective effect of inducing metabolic acidosis and stimulating minute ventilation. If the incident diuretic drug was a combination of two diuretic subclasses in a single pill (e.g. hydrochlorothiazide–spironolactone), these drugs were considered in each of the two respective diuretic subclass analyses.

Finally, we performed a sensitivity analysis where we evaluated our adverse respiratory outcomes among new diuretic users [who were not concomitantly receiving angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) drugs] *vs*. new ACEI/ARB users (who were not concomitantly receiving diuretic drugs). The purpose of this final analysis was to help further minimize possible confounding by indication and potential outcome misclassification (between respiratory and cardiac events), as both diuretic and ACEI/ARB drugs may be prescribed for cardiovascular reasons, and in contrast to diuretics, ACEI/ARB drugs are not associated with potential complications of metabolic alkalosis or hypokalaemia. Similar to our main analyses, incident diuretic (or ACEI/ARB) use was defined as no diuretic (or ACEI/ARB) drug receipt in the year prior to the incident date. Concomitant diuretic (or ACEI/ARB) use was defined as a dispensing for a diuretic (or ACEI/ARB) drug within 90 days prior to the index date (i.e. the date of incident drug receipt). The propensity score was re-estimated for each of our sensitivity analyses.

Statistical analysis

Descriptive statistics and standardized differences for the exposed and control groups on all baseline covariates were calculated before and after propensity score weighting [26]. Since we examined for multiple, potentially competing outcomes, Cox proportional hazard regression modelling with a robust variance estimator was used to estimate a hazard ratio (HR) with associated 95% confidence interval (CI) for each outcome in the propensity score weighted samples [31]. Since an individual theoretically may have experienced any of our nonmortality outcomes more than once during the follow-up period, we also estimated a rate ratio with associated 95% CI for nonmortality outcomes using Poisson regression with generalized estimating equations methods [32] (this analysis is presented in the Supporting Information). 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

Out of 99 766 individuals aged 66 years and older with COPD identified between 1 April 2008 and 31 March 2013, incident diuretic receipt occurred in 51.7% (Table 1 and Supporting Information). The most commonly prescribed diuretic type was loop diuretics (58.6%), followed by thiazides (38.4%), potassium-sparing (5.8%) and anhydrase inhibitors (2.0%). After propensity score weighting, baseline characteristics were well-balanced between exposed individuals and controls, with standardized differences below 10% for all variables (Table 1 and Supporting Information).

Compared to controls, recipients of incident diuretics had significantly increased rates for hospitalizations for COPD or pneumonia (HR 1.22, 95% CI 1.07–1.40; Table 2). ER visits for COPD or pneumonia (HR 1.35, 95% CI 1.18–1.56), COPD or pneumonia-related mortality (HR 1.41; 95% CI 1.04–1.92) and all-cause mortality (HR 1.20, 95% CI 1.06–1.35) were also greater among incident diuretic users. No significant associations were observed between diuretic use and outpatient respiratory exacerbations or admissions to ICU.

Sensitivity analyses

By COPD exacerbation history. Among individuals with no exacerbation in the year prior to the index date, new users had increased rates of hospitalizations for COPD or pneumonia (HR 1.44, 95% CI 1.17–1.76; Table 3). ER visits for COPD or pneumonia (HR 1.55, 95% CI 1.22–1.97), COPD or

Table 2

Hazard ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort

Outcomes	Diuretic use status	Number of events (%)	HR (95% CI)	*P*-value
Outpatient respiratory exacerbation	New diuretic users	2222 (4.3%)	0.97 (0.91–1.04)	0.43
	Nondiuretic users	2148 (4.4%)		
ER visit for COPD or pneumonia	New diuretic users	705 (1.4%)	1.35 (1.18–1.56)	<0.001
	Nondiuretic users	491 (1.0%)		
Hospital admission COPD or pneumonia	New diuretic users	963 (1.9%)	1.22 (1.07–1.40)	0.003
	Nondiuretic users	742 (1.5%)		
ICU admission during a hospitalization for COPD or pneumonia	New diuretic users	138 (0.3%)	1.30 (0.88–1.91)	0.19
	Nondiuretic users	100 (0.2%)		
COPD or pneumonia-related mortality	New diuretic users	212 (0.4%)	1.41 (1.04–1.92)	0.03
	Nondiuretic users	142 (0.3%)		
All-cause mortality	New diuretic users	1115 (2.2%)	1.20 (1.06–1.35)	0.003
	Nondiuretic users	878 (1.8%)		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HR, hazard ratio; ICU, intensive care unit

Table 3

Hazard ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, stratified by COPD exacerbation frequency

COPD exacerbation frequency	Diuretic use status	Outpatient respiratory exacerbation		ER visit for COPD or pneumonia		Hospital admission for COPD or pneumonia		ICU admission during hospitalization for COPD or pneumonia		COPD or pneumonia-related mortality		All-cause 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	*n* (%)	HR (95% CI), *P*-value	*n* (%)	HR (95% CI), *P*-value
No exacerbation in the year prior to index	New users	602 (2.1%)	0.89 (0.79–1.00), 0.05	216 (0.7%)	1.55 (1.22–1.97), 0.0003	267 (0.9%)	1.44 (1.17–1.76), 0.0005	30 (0.1%)	1.44 (0.76–2.72), 0.26	76 (0.3%)	1.94 (1.21–3.13), 0.006	515 (1.8%)	1.43 (1.21–1.69), <0.001
	Non users	736 (2.3%)		151 (0.5%)		202 (0.6%)		22 (0.1%)		43 (0.1%)		391 (1.2%)	
≥1 outpatient respiratory exacerbation in the year prior to index	New users	656 (7.6%)	1.03 (0.91–1.16), 0.67	107 (1.2%)	1.78 (1.29–2.44), 0.0004	134 (1.6%)	1.39 (1.05–1.85), 0.02	24 (0.3%)	2.48 (1.08–5.71), 0.03	21 (0.2%)	1.11 (0.47–2.63), 0.82	143 (1.7%)	1.50 (1.07–2.11), 0.02
	Non users	688 (7.4%)		65 (0.7%)		104 (1.1%)		10 (0.1%)		21 (0.2%)		103 (1.1%)	
≥1 exacerbation requiring presentation to hospital in the year prior to index	New users	1098 (7.9%)	0.97 (0.86–1.10), 0.63	439 (3.1%)	1.10 (0.91–1.33), 0.40	648 (4.6%)	1.06 (0.87–1.29), 0.56	98 (0.7%)	1.04 (0.63–1.72), 0.88	130 (0.9%)	1.13 (0.72–1.75), 0.60	512 (3.7%)	0.93 (0.76–1.13), 0.45
	Non users	620 (8.1%)		220 (2.9%)		336 (4.4%)		52 (0.7%)		63 (0.8%)		303 (3.9%)	

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HR, hazard ratio; ICU, intensive care unit

pneumonia-related mortality (HR 1.94; 95% CI 1.21–3.13) and all-cause mortality (HR 1.43, 95% CI 1.21–1.69) were also increased in the new users. Among individuals with one or more outpatient exacerbation in the year prior to the index date, new users had higher rates of ER visits (HR 1.78, 95% CI 1.29–2.44), hospitalizations (HR 1.39, 95% CI 1.05–1.85) and ICU admissions (HR 2.48; 95% CI 1.08–5.71) for COPD or pneumonia, as well as higher all-cause mortality (HR 1.50, 95% CI 1.07–2.11). No other significant associations were observed.

By pre-existing CHF. Among individuals without pre-existing CHF, new users had increased rates of hospitalizations (HR 1.45, 95% CI 1.27–1.66), ER visits (HR 1.37, 95% CI 1.18–1.59), and ICU admissions (HR 1.61; 95% CI 1.11–2.33) for COPD or pneumonia, plus COPD or pneumonia-related mortality (HR 2.05; 95% CI 1.50–2.81) and all-cause mortality (HR 1.81, 95% CI 1.59–2.07; Table 4). Among individuals with pre-existing CHF, new users had lower all-cause mortality rates compared to controls (HR 0.70; 95% CI 0.58–0.85).

By diuretic subclass. Compared to controls, new recipients of loop diuretics had increased rates of hospitalizations for COPD or pneumonia (HR 1.36, 95% CI 1.16–1.60), as well as greater rates of outpatient respiratory exacerbations (HR 1.11; 95% CI 1.02–1.21), ER visits for COPD or pneumonia (HR 1.62, 95% CI 1.38–1.90), ICU admissions for COPD or pneumonia (HR 1.67; 95% CI 1.08–2.58), plus higher all-cause mortality (HR 1.31, 95% CI 1.13–1.51; Table 5). New users of thiazide diuretics has decreased rates of outpatient respiratory exacerbations relative to controls (HR 0.75; 95% CI 0.66–0.84); however, no other outcomes were significant. No significant associations were observed for recipients of potassium-sparing diuretics and carbonic anhydrase inhibitors.

Diuretic drug users vs. ACEI/ARB users. Compared to new ACEI/ARB users, new diuretic users were found to have significantly increased rates of outpatient respiratory exacerbations (HR 1.27; 95% CI 1.02–1.59), COPD or pneumonia-related mortality (HR 2.12; 95% CI 1.01–4.45) and all-cause mortality (HR 2.40; 95% CI 1.74–3.31; Table 6). No significant associations were observed between diuretic use and COPD or pneumonia-related ER visits, hospitalizations or admissions to ICU.

Discussion

Our large, population-based cohort study showed the novel finding that incident diuretic drug use (particularly use of loop diuretics) among older adults with COPD is associated with increased rates of respiratory-related morbidity and mortality. Our overall findings are strengthened by the fact that we observed negative respiratory outcomes with diuretic use even in healthier subgroups of individuals with COPD (such as those without history of respiratory exacerbation and those without pre-existing CHF) and when the comparison group was new drug use with a similar prescribing indication (i.e. ACEI/ARB use).

Table 4

Hazard ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, stratified by pre-existing known congestive heart failure

Pre-existing CHF status	Diuretic use status	Outpatient respiratory exacerbation		ER visit for COPD or pneumonia		Hospital admission for COPD or pneumonia		ICU admission during hospitalization for COPD or pneumonia		COPD or pneumonia-related mortality		All-cause 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	*n* (%)	HR (95% CI), *P*-value	*n* (%)	HR (95% CI), *P*-value
No known pre-existing CHF	New users	1450 (4.2%)	1.00 (0.93–1.08), 0.91	435 (1.3%)	1.37 (1.18–1.59), <0.001	551 (1.6%)	1.45 (1.27–1.66), <0.001	78 (0.2%)	1.61 (1.11–2.33), 0.01	122 (0.4%)	2.05 (1.50–2.81), <0.001	643 (1.9%)	1.81 (1.59–2.07), <0.001
	Nonusers	1776 (4.2%)		392 (0.9%)		470 (1.1%)		60 (0.1%)		74 (0.2%)		439 (1.0%)	
Known pre-existing CHF	New users	816 (4.7%)	0.88 (0.75–1.04), 0.14	291 (1.7%)	1.28 (0.93–1.75), 0.13	480 (2.8%)	0.95 (0.73–1.22), 0.67	69 (0.4%)	0.98 (0.48–2.01), 0.95	100 (0.6%)	0.78 (0.46–1.33), 0.37	539 (3.1%)	0.70 (0.58–0.85), 0.0002
	Nonusers	312 (5.3%)		78 (1.3%)		172 (2.9%)		24 (0.4%)		43 (0.7%)		260 (4.4%)	

CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HR, hazard ratio; ICU, intensive care unit

Table 5

Hazard ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, distinguishing by diuretic drug type received

Diuretic drug subclass	Diuretic use status	Outpatient respiratory exacerbation		ER visit for COPD or pneumonia		Hospital admission for COPD or pneumonia		ICU admission during hospitalization for COPD or pneumonia		COPD or pneumonia-related mortality		All-cause 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	*n* (%)	HR (95% CI), *P*-value	*n* (%)	HR (95% CI), *P*-value
Loop diuretic	New users	1555 (5.3%)	1.11 (1.02–1.21), 0.02	509 (1.7%)	1.62 (1.38–1.90), <0.001	727 (2.5%)	1.36 (1.16–1.60), 0.0002	113 (0.4%)	1.67 (1.08–2.58), 0.02	160 (0.5%)	1.35 (0.95–1.94), 0.10	901 (3.1%)	1.31 (1.13–1.51), 0.0004
	Nonusers	2342 (4.7%)		527 (1.1%)		896 (1.8%)		113 (0.2%)		199 (0.4%)		1158 (2.3%)	
Potassium-sparing diuretic	New users	103 (3.4%)	0.81 (0.62–1.06), 0.13	29 (0.9%)	1.07 (0.70–1.63), 0.75	37 (1.2%)	1.04 (0.70–1.55), 0.85	≤5 [a]	0.79 (0.27–2.34), 0.67	9 (0.3%)	1.38 (0.67–2.86), 0.38	55 (1.8%)	1.36 (1.00–1.86), 0.05
	Nonusers	1996 (4.1%)		421 (0.9%)		556 (1.2%)		71 (0.1%)		98 (0.2%)		641 (1.3%)	
Thiazide diuretic	New users	606 (3.0%)	0.75 (0.66–0.84), <0.001	187 (0.9%)	1.11 (0.88–1.40), 0.38	199 (1.0%)	0.91 (0.73–1.14), 0.43	27 (0.1%)	0.96 (0.39–2.35), 0.92	29 (0.1%)	0.80 (0.45–1.45), 0.47	195 (1.0%)	0.82 (0.62–1.08), 0.16
	Nonusers	1930 (4.0%)		405 (0.8%)		521 (1.1%)		68 (0.1%)		87 (0.2%)		570 (1.2%)	
Carbonic anhydrase inhibitor	New users	34 (3.2%)	0.76 (0.55–1.05), 0.09	≤5[a]	0.50 (0.23-1.08), 0.08	16 (1.5%)	1.38 (0.85–2.24), 0.20	≤5[a]	1.57 (0.58-4.27), 0.38	≤5[a]	1.50 (0.57-3.98), 0.41	18 (1.7%)	1.34 (0.77–2.32), 0.30
	Nonusers	1994 (4.1%)		417 (0.9%)		539 (1.1%)		68 (0.1%)		94 (0.2%)		607 (1.3%)	

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HR, hazard ratio; ICU = intensive care unit

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

Table 6

Hazard ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort with new ACEI/ARB users serving as the control group

Outcomes	Diuretic use status	Number of events (%)	HR (95% CI)	*P*-value
Outpatient respiratory exacerbation	New diuretic users	140 (4.4%)	1.27 (1.02–1.59)	0.04
	New ACEI/ARB users	1035 (3.5%)		
ER visit for COPD or pneumonia	New diuretic users	47 (1.5%)	1.26 (0.88–1.79)	0.21
	New ACEI/ARB users	354 (1.2%)		
Hospital admission COPD or pneumonia	New diuretic users	62 (2.0%)	1.41 (0.97–2.06)	0.07
	New ACEI/ARB users	412 (1.4%)		
ICU admission during a hospitalization for COPD or pneumonia	New diuretic users	6 (0.2%)	0.94 (0.43–2.07)	0.89
	New ACEI/ARB users	60 (0.2%)		
COPD or pneumonia-related mortality	New diuretic users	18 (0.6%)	2.12 (1.01–4.45)	0.05
	New ACEI/ARB users	79 (0.3%)		
All-cause mortality	New diuretic users	98 (3.1%)	2.40 (1.74–3.31)	<0.0001
	New ACEI/ARB users	385 (1.3%)		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; HR, hazard ratio; ICU, intensive care unit; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Data on the potential respiratory effects of systemic formulation diuretic drugs in COPD have been minimal and conflicting. Diuretics have been shown to improve certain clinical parameters in COPD, such as plasma brain natriuretic peptide level and pulmonary artery pressure [18]. A randomized controlled trial of patients with COPD in the ICU receiving intravenous actezolamide 500–1000 mg daily *vs*. placebo found no significant difference in the duration of mechanical ventilation or weaning duration [19]. In contrast to our study, none of the aforementioned trials reported increased risk for adverse respiratory outcomes in association with diuretic use. However, some previous trials did not evaluate for possible drug-related adverse events [18] or were unable to detect them because they enrolled small numbers of selected individuals and tested limited drug doses and duration [18]. In contrast, our study incorporated large numbers of individuals, including those vulnerable to potential drug side-effects that clinical trials typically exclude (e.g. the elderly and individuals with comorbidities), evaluated real-world diuretic drug use and examined for clinically-important outcomes. The fact that diuretic drugs are known to potentially contribute to metabolic alkalosis with consequent hypercapnia and hypokalaemia, provides a rationale for why adverse respiratory events may have occurred.

We observed increased respiratory-related morbidity and mortality in association with diuretic use among healthier COPD subgroups, such as those without history of respiratory exacerbation and those without pre-existing CHF. We also found increased respiratory-related morbidity and mortality associated with new diuretic use when compared to new ACEI/ARB use, which is noteworthy as both drug groups would be prescribed for similar reasons and recipients of both drug groups would be at increased risk of acute cardiac events, which might masquerade as acute respiratory events. All the aforementioned subgroup analysis results strengthen our overall finding of an association between incident diuretic use and negative respiratory events. Although adverse respiratory events were not found to be elevated among new diuretic users with previous respiratory exacerbation requiring presentation to hospital (and these individuals would probably be more susceptible to negative outcomes), this may be related to selective diuretic prescribing in this sicker group, possibly out of concern for contributing to hypercapnia or other adverse event (e.g. dehydration). While adverse respiratory events were also not observed among the sicker subgroup of individuals with pre-existing CHF, this may be explained by the fact that diuretic drugs were reasonably prescribed in these individuals given their CHF and cardiac-related benefits were derived from therapy. The fact that incident diuretic drug receipt was associated with respiratory harm across a spectrum of outcomes (i.e. ER visits, hospitalizations and death) also supports the robustness of our findings. While the absolute adverse event rate increases were relatively small, they may be clinically important at the population level, as upwards of 10% of Ontario's population over age 35 years is estimated to have COPD [33] and over 50% of our COPD cohort was found to be receiving diuretic drugs.

Loop diuretic use drove the overall association with adverse respiratory events and this may be as a result of this drug subclass' well-known potential to cause metabolic alkalosis (which in turn can contribute to hypercapnia) and hypokalaemia. While thiazides and carbonic anhydrase inhibitors were not found to be associated with increased rates of negative respiratory events, these drug classes are less likely to cause metabolic alkalosis, as thiazides have relatively weak diuretic ability and are used more as antihypertensives and carbonic anhydrase inhibitors usually contribute to metabolic acidosis. Potassium-sparing diuretics may not have been associated adverse respiratory events because they protect from hypokalaemia. Although carbonic anhydrase inhibitor receipt was not found to protect from adverse respiratory events, this subgroup analysis may have been underpowered to detect such a benefit due to small sample sizes.

Although our analyses were adjusted for 55 covariates and we demonstrated increased rates of adverse respiratory events in association with diuretic use in healthier COPD subgroups and when compared to use of another drug class with similar prescribing indication, we cannot exclude confounding by

indication or the influence of unmeasured clinical covariates (e.g. respiratory symptoms, lung function measures, smoking, acid–base status) as potential explanations for our findings. For instance, a physician may see a patient with COPD who is struggling with dyspnoea, and, after all else fails, they may prescribe a trial of a loop diuretic to see if the diuretic improves the patient's respiratory status, whether or not the patient has a history of CHF. Similarly, if a COPD patient develops right heart failure with peripheral oedema, this may also prompt an incident prescription for a diuretic. In both cases, the patient had a pre-existing increased risk for respiratory-related morbidity and mortality, with the diuretic prescription serving as a marker of a sicker patient, and not being the causal factor behind the patients' possible subsequent poor outcome. We may also 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 increased rates of death observed among diuretic users. However, the possible residual inclusion of individuals receiving palliative care would unlikely explain the greater rates of respiratory-related outpatient exacerbations, ER visits and hospitalizations among diuretic recipients. Finally, while our COPD definition was highly specific (so we could be certain that individuals included in our study truly had COPD), it had modest sensitivity [20], so our findings may not be generalizable to the entire older adult nonpalliative COPD population.

In conclusion, incident diuretic drug use (and specifically, loop diuretic receipt) was associated with increased rates of respiratory-related morbidity and mortality among older adults with nonpalliative COPD. Our study exposes a potential for adverse respiratory outcomes in association with diuretic drug administration in this population. However, further studies are needed to confirm if our results are causal or due to residual confounding.

Competing Interests

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: A.S.G. and S.D.A. had support from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund (HSRF) Capacity Award for the submitted work; N.T.V., X.W., P.A.C., D.E.O. and T.M.O. had no support from any organization for the submitted work; D.E.O. received grants and personal fees from Boehringer Ingelheim, grants and personal fees from Astra Zeneca, grants from GlaxoSmithKline, personal fees from Novartis, in the previous 3 years; N.T.V., X.W., P.A.C., D.E.O., S.D.A., T.M.O. and A.S.G. no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; N.T.V., X.W., P.A.C., D.E.O., S.D.A., T.M.O. and A.S.G. had no other relationships or activities that could appear to have influenced the submitted work.

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References

1 Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, *et al*. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. Lancet 2007; 370: 741–50.

2 Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest 2005; 128: 2640–6.

3 Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, *et al*. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol 2006; 16: 63–70.

4 Elkington H, White P, Addington-Hall J, Higgs R, Edmonds P. The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. Palliat Med 2005; 19: 485–91.

5 Lynn J, Ely EW, Zhong Z, McNiff KL, Dawson NV, Connors A, *et al*. Living and dying with chronic obstructive pulmonary disease. J Am Geriatr Soc 2000; 48: S91–100.

6 Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, *et al*. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 1995; 107: 1193–8.

7 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2017. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/ (Accessed September 2017).

8 Wagenaar M, Teppema L, Berkenbosch A, Olievier C, Folgering H. Effect of low-dose acetazolamide on the ventilatory CO2 response during hypoxia in the anaesthetized cat. Eur Respir J 1998; 12: 1271–7.

9 Terzano C, Conti V, Di Stefano F, Petroianni A, Ceccarelli D, Graziani E, *et al*. Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. Lung 2010; 188: 321–9.

10 Coleta KD, Silveira LV, Lima DF, Rampinelli EA, Godoy I, Godoy I. Predictors of first-year survival in patients with advanced COPD treated using long-term oxygen therapy. Respir Med 2008; 102: 512–8.

11 Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, Midgren B, Ekström MP. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res 2014; 15: 30.

12 Dorin RI, Crapo LM. Hypokalemic respiratory arrest in diabetic ketoacidosis. JAMA 1987; 257: 1517–8.

13 Krentz AJ, Ryder RE. Hypokalemia-induced respiratory failure complicating treatment of diabetic ketoacidosis. J Diabetes Complications 1994; 8: 55–6.

14 Sudo T, Hayashi F, Nishino T. Responses of tracheobronchial receptors to inhaled furosemide in anesthetized rats. Am J Respir Crit Care Med 2000; 162: 971–5.

15 Ong KC, Kor AC, Chong WF, Earnest A, Wang YT. Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 169: 1028–33.

16 Jensen D, Amjadi K, Harris-McAllister V, Webb KA, O'Donnell DE. Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. Thorax 2008; 63: 606–13.

17 Sheikh Motahar Vahedi H, Mahshidfar B, Rabiee H, Saadat S, Shokoohi H, Chardoli M, *et al*. The adjunctive effect of nebulized furosemide in COPD exacerbation: a randomized controlled clinical trial. Respir Care 2013; 58: 1873–7.

18 Zhang J, Zhao G, Yu X, Pan X. Intravenous diuretic and vasodilator therapy reduce plasma brain natriuretic peptide levels in acute exacerbation of chronic obstructive pulmonary disease. Respirology 2012; 17: 715–20.

19 Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, *et al*. DIABOLO investigators. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: a randomized clinical trial. JAMA 2016; 315: 480–8.

20 Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. J COPD 2009; 6: 388–94.

21 Levy R, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario drug benefit database. Can J Clin Pharmacol 2003; 10: 67–71.

22 Vozoris NT, Fischer HD, Wang X, Stephenson AL, Gershon AS, Gruneir A, *et al*. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2014; 44: 332–40.

23 Vozoris NT, Wang X, Fischer HD, Bell CM, O'Donnell DE, Austin PC, *et al*. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2016; 48: 683–93.

24 O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, *et al*. Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respir J 2008; 15S: 1A–8A.

25 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 2011; 46: 399–424.

26 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015; 34: 3661–79.

27 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57: 847–52.

28 Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004; 23: 698–702.

29 Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, *et al*. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010; 363: 1128–38.

30 Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, *et al*. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (study to understand prognoses and preferences for outcomes and risks of treatments). Am J Respir Crit Care Med 1996; 154: 959–67.

31 Austin PC. The performance of different propensity-score methods for estimating marginal hazard ratios. Stat Med 2013; 32: 2837–49.

32 Frome EL. The analysis of rates using Poisson regression methods. Biometrics 1983; 39: 665–74.

33 Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. Arch Intern Med 2010; 170: 560–56.

Supporting Information

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Table S1 Rate ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort
Table S2 Rate ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, stratified by chronic obstructive pulmonary disease exacerbation frequency
Table S3 Rate ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, stratified by pre-existing known congestive heart failure
Table S4 Rate ratios and 95% confidence intervals for outcomes in the propensity score weighted cohort, distinguished by diuretic drug type received