ERJ Express. Published on June 25, 2018 as doi: 10.1183/13993003.00475-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Vozoris NT, Wang X, Austin PC, *et al*. SEROTONERGIC ANTIDEPRESSANT USE AND MORBIDITY AND MORTALITY AMONG OLDER ADULTS WITH COPD. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.00475-2018).

SEROTONERGIC ANTIDEPRESSANT USE AND MORBIDITY AND MORTALITY AMONG OLDER ADULTS WITH COPD

Running title: Serotonergic antidepressants and COPD

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Funding: This research was funded by the University of Toronto, Pettit Respirology Block Term Grant. This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. We thank Brogan Inc., Ottawa for use of their Drug Information Database. P.C. Austin was supported in part by a Career Investigator Award from the Heart and Stroke Foundation. A.S. Gershon was supported in part by a Canadian Institutes of Health Research New Investigator Award. P.A. Rochon holds the Retired Teachers of Ontario/ERO Chair in Geriatric Medicine at the University of Toronto.

Take home message for social media: Serotonergic antidepressants are associated with increased adverse respiratory outcomes in older adults with COPD.

ABSTRACT

We evaluated the relationship between new selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) drug use and respiratory-related morbidity and mortality among older adults with chronic obstructive pulmonary disease (COPD).

This was retrospective, population-based, cohort study using Ontario, Canada, heath administrative data. Individuals ages 66 years of age and older, with validated, physician-diagnosed COPD (n = 131,718) were included. New SSRI/SNRI users were propensity score matched 1:1 to controls on 40 relevant covariates to minimize potential confounding.

Among propensity-scored matched community-dwelling individuals, new SSRI/SNRI users compared to non-users had significantly higher rates of hospitalization for COPD or pneumonia (hazard ratio [HR] 1.15; 95% confidence interval [CI] 1.05-1.25), ER visits for COPD or pneumonia (HR 1.13; 95% CI 1.03-1.24), COPD or pneumonia-related mortality (HR 1.26; 95% CI 1.03-1.55) and all-cause mortality (HR 1.20; 95% CI 1.11-1.29). Respiratory-specific and all-cause mortality rates were also higher among long term care home residents newly starting SSRI/SNRI drugs versus controls.

New use of serotonergic antidepressants was associated with small, but significant, increases in rates of respiratory-related morbidity and mortality among older adults with COPD. Further research is needed to clarify if the observed associations are causal or instead reflect unresolved confounding.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is estimated to affect more than 10% of individuals ages 40 years and older world-wide [1]. Recurrent acute respiratory exacerbations (i.e., sustained worsening of respiratory symptoms that require additional therapy) are common in COPD and are associated with reduced quality of life, need for hospitalization and death [2]. Depression and anxiety frequently occur in COPD (affecting upwards of 70-80% of individuals) [3-5] and the presence of comorbid psychiatric disease in COPD is known to be associated with increased exacerbation risk and mortality [6-7]. Serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), are recommended as first-line pharmacotherapy for major depression and generalized anxiety disorder [8-9]. Depression and anxiety could heighten the perception of respiratory symptoms (like dyspnea) in COPD, and by better controlling altered mood, SSRI and SNRI drugs might theoretically indirectly improve respiratory health outcomes in COPD. However, the few clinical trials conducted with individuals with COPD have not clearly demonstrated that SSRI and SNRI drugs are effective for depression and anxiety in this population [10-12]. Furthermore, in a few, small-sized trials where SSRI and SNRI drugs were evaluated among individuals with COPD as a direct treatment for advanced-level, refractory dyspnea, a beneficial effect was not demonstrated [12-14].

There is a theoretical concern that SSRI and SNRI drugs could lead to respiratory harm among individuals with COPD through several potential mechanisms. First, tolerability data from previous randomized controlled trials involving SSRI and SNRI drugs show that an estimated 10-20% of drug recipients experience side-effects of fatigue and sleepiness [15-19].

Possible resulting drug-related respiratory depression, with hypoxemia and hypercapnea, could lower the threshold for an acute respiratory exacerbation. Second, an estimated 10-30% of SSRI and SNRI drug recipients experience side-effects of nausea and vomiting [15-19], which could contribute to aspiration-related respiratory tract infection (especially if compounded by side-effects of fatigue and sleepiness) and result in acute respiratory exacerbation. Third, SSRI and SNRI drugs may predispose to respiratory exacerbation by lowering the threshold for infection through adverse health effects on immune cell quantity and function [20-23]. Finally, increased extracellular concentrations of serotonin (which SSRI and SNRI drugs produce) have been linked to reduced clearance of apoptotic cells [24], which could then lead to inflammation and plugging of the airways [25], and thereby, respiratory tract infection and exacerbation. The need for further research into the impact of SSRI/SNRI drugs in COPD has been advocated [10].

The purpose of this study was to evaluate the relationship between new SSRI and SNRI drug use and respiratory-related morbidity and mortality among older adults with COPD.

METHODS

Study design. This was a population-based, retrospective cohort study using heath administrative data for the province of Ontario (13.5 million people) for the period April 1, 2008 to March 31, 2014.

Data sources. Thirteen health administrative databases held at the Institute of Clinical Evaluative Sciences (ICES) were linked at an individual-person level using unique coded identifiers. One database contained individuals with validated, physician-diagnosed COPD. Individuals with COPD were identified by a previously developed, highly-specific algorithm of

COPD codes: three or more ambulatory claims for COPD within any 2-year period or one or more COPD hospitalization(s) (specificity 95.4%; sensitivity 57.4%) [26]. A second database was the Ontario Drug Benefit (ODB) database, which contained information on all outpatient drug dispensings to individuals ages 65 years and older. Drug claim coding error in the ODB is very low (0.7%) [27]. Other databases containing information on ambulatory visits, emergency room (ER) visits, hospitalizations and death are outlined in the Online Supplement.

Study population. To be included in this study, individuals had to meet the following criteria between April 1, 2008 and December 31, 2013: have validated, physician-diagnosed COPD; be an Ontario resident; and, be 66 years of age and older. An end enrolment date of December 31, 2013 was selected, so that all individuals included in the study had a 90-day follow-up period (up to the end-of-study date of March 31, 2014) in which to evaluate for outcomes. Although individuals younger than 66 years of age were not included (because drug dispensing data were not available for them in the ODB), the majority of individuals with COPD are 65 years and older [28]. Individuals with claims for palliative care (based on physician service codes) in the year prior to the index date (which is defined below) were excluded, as these individuals are more likely to receive SSRI/SNRI drugs and have poor health outcomes, and their inclusion could then serve to potentially bias results. Individuals living in the community versus in long-term care (LTC) homes at the time of the index date were examined separately, in order to minimize bias, as LTC home residents would likely have poorer health outcomes and increased chances for drug exposure compared to community-dwelling individuals.

Exposed and control groups with index date definitions. The exposed group consisted of new SSRI or SNRI drug users, defined (using a previously published approach [29-30]) as receipt of any SSRI or SNRI drug between April 1, 2008 and December 31, 2013, without having a SSRI or SNRI drug in the year prior. All SSRI and SNRI drugs covered by the ODB were considered (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine). New use was only counted once per individual, and if an individual met criteria for new use more than once during the study, then only the first dispensing was considered. We elected to study new, and not prevalent, SSRI/SNRI drug use in order to minimize potential 'healthy user' bias associated with prevalent use and since our purpose was to examine for acute-onset drug-related outcomes. The index date for the exposed group was the day of new SSRI/SNRI drug dispensing.

Individuals in the control group received no SSRI or SNRI drug between April 1, 2008 and December 31, 2013. Individuals entered the control group by receiving any other new drug on or before a date chosen randomly from the accrual period. New drug use for the control group was defined as no receipt, within the past year, of a drug within the same class as the index control drug [29-30]. If the most recent control 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 [29-30]. The index date for control individuals was the date the new non-SSRI/SNRI drug was dispensed.

Outcomes. The primary outcome was time to hospitalization for COPD or pneumonia, since this is a clinically-important event among individuals with COPD, as it is associated with significant morbidity and mortality [2]. Secondary outcomes included: outpatient respiratory

exacerbation (defined as receipt of an oral corticosteroid or respiratory antibiotic 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 [29-30]); ER visit 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). All outcomes were evaluated during a 90-day period following the index date. We selected 90-day follow-up period since it was our intent to examine for acute-onset drug-related outcomes and since it is recognized that it can take up to several weeks before SSRI and SNRI drugs have full effect [31].

Propensity score matching. Because exposed and control individuals were anticipated to differ on demographic and health characteristics that would influence exposure to SSRI and SNRI drugs and risk for respiratory outcomes, we used 1:1 propensity score matching to create matched samples of exposed and control individuals, in order to reduce bias [32]. A 1:1 matching ratio was selected, since this was previously shown to minimize bias and inclusion of more control individuals resulted in minimal precision increase [33]. Individuals were matched on the logit of the propensity score using a width caliper equal to 0.2 of the standard deviation of the logit of the propensity score [34]. A propensity score for new SSRI/SNRI drug receipt was developed using a logistic regression model with 40 relevant covariates, including markers of COPD severity (i.e., frequency and recency of prior COPD exacerbation, duration of COPD, receipt of COPD medications), comorbidities, health care system use, other relevant prescription

drug receipt (i.e., opioids, benzodiazepines, smoking cessation drugs) and demographics. The full list of variables included in the propensity score model can be found in the Online Supplement and an abridged list is shown in Table 1.

Sensitivity analyses. Several sensitivity analyses were performed. First, because COPD exacerbation history is an important marker of disease severity, we evaluated our outcomes stratifying by COPD exacerbation history in the year prior to the index date. International COPD guidelines use COPD exacerbation frequency to distinguish COPD severity [2] and COPD exacerbations are associated with a greater degree of airflow obstruction [35], poorer quality of life [36], future exacerbation risk [37] and mortality [38]. We defined COPD exacerbation history as a three-level, mutually-exclusive variable: no exacerbation versus 1 or more outpatient exacerbation, with no exacerbation requiring presentation to hospital versus 1 or more exacerbation requiring presentation to hospital. Second, because having comorbid psychiatric disease in the setting of COPD is known to be associated with increased exacerbation risk and mortality [6-7], we evaluated our outcomes stratifying by the presence of any physician-diagnosed psychiatric disease in the five years prior to the index date. These two sensitivity analyses evaluate outcomes across subgroups of differing COPD severity, thereby minimizing possible "healthy user" bias (by examining outcomes in the sickest subgroup of individuals) and possible confounding by indication (by examining outcomes in the healthiest subgroup of individuals). Exposed and control individuals were matched at the index date on: the propensity score; COPD exacerbation frequency in the year prior to the index date; and, psychiatric disease in the five years prior to the index date (the latter two variables were matched on to facilitate our

planned sensitivity analyses by these variables). Additional sensitivity analyses are presented in the Online Supplement.

Statistical analysis. Before and after propensity score matching, we calculated descriptive statistics with standardized differences for the exposed and control groups on all baseline covariates [39]. For all non-mortality outcomes, we used cause-specific hazard models to estimate the effect of SSRI/SNRI use on the hazard of the outcome after accounting for the competing risk of death. For COPD or pneumonia-related mortality, we used cause-specific hazard models to account for the competing risk of death due to other causes. For all-cause mortality, we used a Cox model to regress the cause-specific hazard of death on exposure status. SSRI/SNRI use was the sole independent variable in all models. For all models, a robust variance estimator was used to account for the matched nature of the sample [40] and hazard ratios (HR) and 95% confidence intervals (CI) were obtained. Number needed to harm (NNH) was determined by calculating the inverse of the absolute risk difference (ARD). All statistical analyses were conducted using SAS Enterprise Guide 9.4.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between April 1 2008 and December 31 2013, 131,718 older adults with COPD (118,611 community-dwelling individuals and 13,107 LTC home residents) were identified. Of the 118,611 community-dwelling individuals, 29,835 (25.2%) were new SSRI/SNRI users (Figure 1). After propensity score matching, 28,360 new users were matched to an equivalent number of controls. No matched control was found for 1475 (4.9%) of new SSRI/SNRI users. New users and controls were well-balanced on baseline characteristics, with standardized differences being

below 10% for all variables (Table 1 and Online Supplement). The LTC home resident cohort analysis is presented in the Online Supplement

Compared to non-users, new SSRI/SNRI users had significantly higher rates of hospitalization for COPD or pneumonia (ARD 0.5%; HR 1.15, 95% CI 1.05-1.25; NNH 200), as well as ER visits for COPD or pneumonia (ARD 0.3%; HR 1.13, 95% CI 1.03-1.24; NNH 333), COPD or pneumonia-related mortality (ARD 0.1%; HR 1.26, 95% CI 1.03-1.55; NNH 1000) and all-cause mortality (ARD 0.8%; HR 1.20, 95% CI 1.11-1.29; NNH 125) (Table 2). There was a significantly decreased rate of outpatient exacerbations among users (HR 0.91; 95% CI 0.86-0.96) and there was no significant association with ICU admissions during hospitalizations for COPD or pneumonia (HR 1.07; 95% CI 0.85-1.34).

In the subgroup of individuals with no exacerbation in the year prior to index and those with >=1 outpatient respiratory exacerbation in the year prior to index, new versus non-users had significantly decreased rates of outpatient exacerbation (HR 0.80; 95% CI 0.72-0.88 and HR 0.90; 95% CI 0.81-0.99, respectively) (Table 3). In the subgroup of individuals with >=1 exacerbation requiring hospitalization in the year prior to index, new versus non-users had significantly increased rates of hospitalization for COPD or pneumonia (HR 1.23; 95% CI 1.10-1.38) and COPD or pneumonia-related mortality (HR 1.45; 95% CI 1.11-1.88), but these associations did not extend to other COPD exacerbation frequency subgroups. There were significantly increased rates of all-cause mortality among new versus non-users across all COPD exacerbation frequency subgroups (no exacerbation in the year prior to index: HR 1.13; 95% CI 1.01-1.27; >=1 outpatient respiratory exacerbation in the year prior to index: HR 1.33; 95% CI

1.07-1.66; >=1 exacerbation requiring hospitalization in the year prior to index: HR 1.23; 95% CI 1.10-1.39). No other associations were statistically significant.

In the subgroup of individuals without pre-existing psychiatric disease, new versus non-users had significantly increased rates of hospitalization for COPD or pneumonia (HR 1.30; 95% CI 1.10-1.54), ICU admission during hospitalizations for COPD or pneumonia (HR 1.81; 95% CI 1.12-2.93), COPD or pneumonia-related mortality (HR 1.76; 95% CI 1.21-2.55) and all-cause mortality (HR 1.71; 95% CI 1.47-1.98) (Table 4). In the subgroup of individuals with pre-existing psychiatric disease, new versus non-users had significantly decreased rate of outpatient exacerbation (HR 0.90; 95% CI 0.85-0.96). No other associations were statistically significant.

DISCUSSION

To our knowledge, our large, population-based study is the first to show that, among older adults with COPD, new users of SSRI or SNRI drugs have modest, but statistically significant, increases in rates of respiratory-related morbidity and mortality, as well as all-cause mortality, than controls matched on a wide range of covariates. The fact that similar results were found among subgroups of individuals with less severe COPD strengthens the credibility of our overall findings.

In the overall community-dwelling cohort, we found that new SSRI or SNRI use among older adults with COPD was associated with increased rates of various adverse events (i.e., ER visits, hospitalizations and death) and this consistency across a spectrum of outcomes strengthens the likelihood for a causal link between drug receipt and respiratory harm. While outpatient respiratory exacerbations were found to be significantly less frequent among new versus non-

users, this result may be explained by the increased and competing risk of other adverse respiratory events (e.g., ER visits, hospitalization) and death among new users. The reduced rates of outpatient respiratory exacerbation observed may also be as a result of SSRI/SNRI drugs (through their potentially deleterious respiratory effects) intensifying the severity of milder exacerbations or decreasing an individual's ability to cope with an exacerbation, thereby leading to an ER visit or hospital admission. While ICU admission during hospitalizations for COPD or pneumonia was not significantly associated with new SSRI/SNRI drug receipt, the relatively small numbers of individuals experiencing this specific outcome may explain this non-significant finding. We acknowledge that the absolute adverse event rates of our positive outcomes are relatively small, and therefore, they may not be clinically significant or they may not have remained positive had additional covariates been controlled for. However, our modestly elevated HRs may be clinically meaningful when one considers them at a population level. SSRI/SNRI drugs may lead to adverse respiratory outcomes among individuals with COPD thorough several possible mechanisms: by promoting sleepiness [15-19], which may then potentially lead to respiratory depression; by causing vomiting side-effects [15-19], which may then lead to aspiration (especially if fatigue and sleepiness are also present); by decreasing immune cell quantity and function [20-23]; and, by reducing clearance of apoptotic cells in the airways, which may then lead to airway plugging [24-25].

By balancing the exposed and control groups through propensity score matching on a large number of important and relevant variables (including multiple markers of COPD severity, multiple comorbidities, health care system utilization, other prescription drug receipt and sociodemographic characteristics), the chances that our findings are explained by such factors are minimized. Selecting incident receipt of a non-SSRI/SNRI drug to define control group entry

also served to decrease the likelihood that recent health status change or differences in health-seeking behaviour explain our findings among exposed versus control individuals. Our main findings are strengthened by the fact that we observed increased rates of adverse outcomes among healthier subgroups of individuals with COPD, as these groups would be less likely to be influenced by confounding by indication. Specifically, we observed increased all-cause mortality in the subgroup of individuals with no prior respiratory exacerbation and we also found increased rates of morbidity and mortality among those without previously diagnosed psychiatric disease. The fact that increased rates of adverse events were not observed among new SSRI/SNRI recipients relative to controls among those with established psychiatric disease (and instead, a significantly decreased rate of outpatient exacerbations was found in the exposed group) may indicate that these drugs, when reasonably prescribed as treatment for mood disorder, facilitate more stable respiratory health, by potentially reducing depression and anxiety symptoms. In contrast, the finding of increased adverse respiratory outcomes among SSRI/SNRI recipients without diagnosed psychiatric disease suggests risk for harm when these drugs are prescribed off-label, for reasons other than established psychiatric disease (e.g., treatment of insomnia, or mood symptoms where mood disorder criteria are not met).

Increased rates of negative respiratory events associated with SSRI/SNRI use were found not only occur at higher drug dose levels, but extended even to lower drug dose levels (see online supplement 1 for this sensitivity analysis). However, the absence of clear dose-response relationship between SSRI/SNRI drugs and our outcomes raises the possibility of residual confounding influencing our results. Although we observed increased rates of respiratory-related morbidity and mortality in association with new SSRI/SNRI use among older adults with COPD, these drugs appear preferable from a respiratory safety perspective when compared head-to-head

with benzodiazepines (see online supplement 1 for this sensitivity analysis), which have similar prescribing indications and which we have previously found to also be linked with increased risk of adverse respiratory outcomes in COPD [29].

As with all observational studies, a true causal link between SSRI/SNRI drug exposure and adverse outcomes cannot be concluded from our results alone. Our results could be influenced by residual confounding from unmeasured differences between the exposed and control groups. For example, we were unable to adjust for baseline respiratory or mood symptoms, smoking or lung function, as such clinical data were unavailable in our health administrative databases. We may not have eliminated from our analysis all individuals receiving palliative care using physician service codes and these individuals would have increased mortality risk. However, the residual inclusion of individuals receiving palliative care would unlikely explain our findings of increased ER visits and hospitalizations for COPD or pneumonia among the exposed group. While the identification of individuals with COPD in this study was based on a previously validated algorithm of health administrative codes, the classification of our outcomes (e.g., hospitalization, mortality, etc.) as COPD or pneumonia-related was not validated. Our findings may not apply to individuals with COPD, who are under 66 years of age, since these individuals were not included in our study. Finally, indication for SSRI/SNRI drug receipt was not available in our drug database. Nevertheless, we performed sensitivity analyses stratifying by COPD exacerbation frequency and by presence of psychiatric disease, and these analyses serve as a proxies for drug indication.

Implications of findings for clinical practice. Our findings should not be interpreted to indicate that use of SSRI/SNRI drugs should be absolutely avoided in individuals with COPD and comorbid psychiatric disease. Instead, our results should prompt prescribers to consider the

potential for increased respiratory-related morbidity and mortality in SSRI/SNRI prescribing decision-making (especially when off-label drug use is being considered), to counsel patients about potential drug respiratory side-effects when prescribing SSRIs/SNRIs and to monitor for potential adverse respiratory effects when SSRI/SNRI drugs are initiated. Although SSRI/SNRI drugs were found to be associated with increased respiratory-related morbidity and mortality in this study, prescribers may want to consider using these medications to manage psychiatric symptoms over benzodiazepines, which appear to be associated with an even higher risk of adverse respiratory outcomes in COPD. Our findings also potentially highlight the importance of pursuing psychotherapy [41-42] and pulmonary rehabilitation [43] to help manage psychiatric disease in COPD, before turning to psychoactive medications.

In conclusion, new SSRI/SNRI drug use was associated with small, but significantly increased rates of respiratory-related morbidity and mortality among older adults with COPD. If this relationship is confirmed by future research, the potential for adverse respiratory outcomes may need to be considered when prescribing SSRI and SNRI drugs to older adults with COPD.

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Figure 1. Flow diagram outlining exposed and control group identification in the community-dwelling cohort

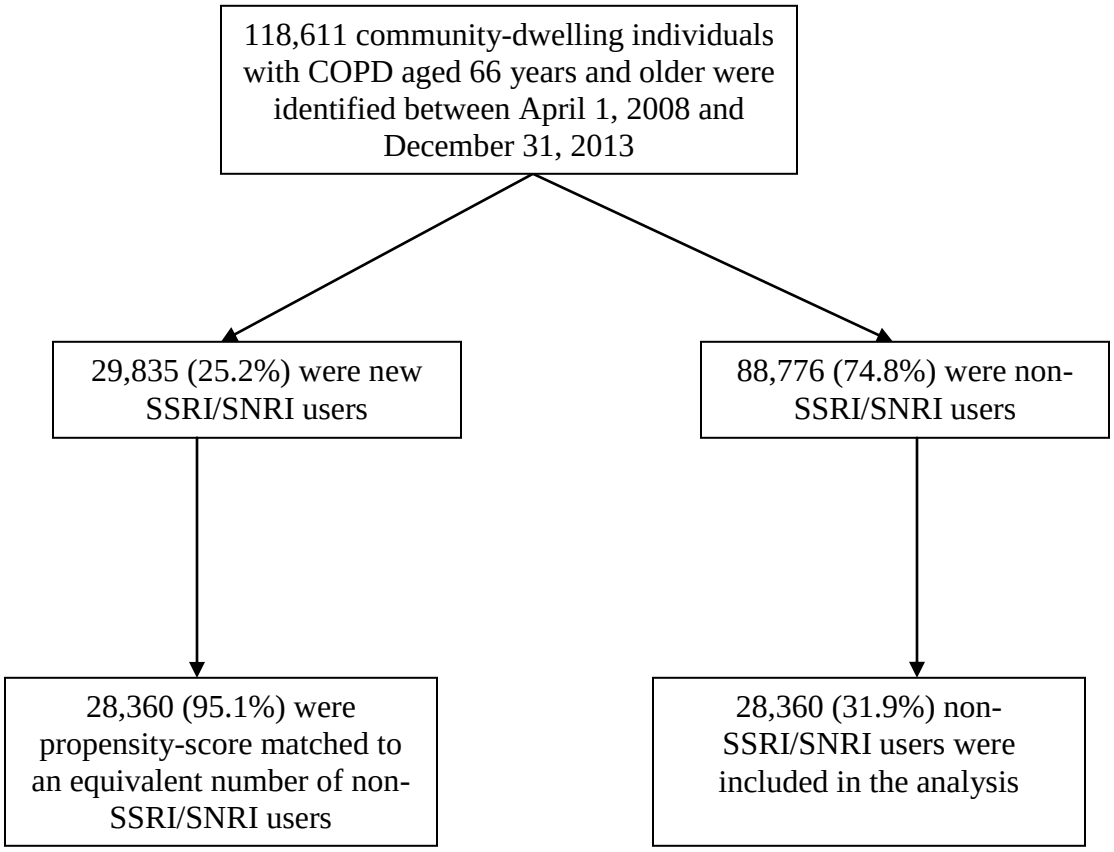

Table 1. Baseline characteristics of community-dwelling cohort, before and after propensity score matching (abridged set of covariates[a])

	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[b]**	**New SSRI/SNRI users**	**Non-SSRI/SNRI users**	**Standardized difference[b]**
	N=29,835	N=88,776		N=28,360	N=28,360	
Age (mean + standard deviation)	77.4 ± 7.2	76.9 ± 7.5	0.07	77.4 ± 7.2	77.5 ± 7.7	0.01
% female	55.7%	44.9%	0.22	54.6%	54.5%	0.0006
COPD exacerbation frequency past year (%)						
0	58.1%	61.5%	0.07	58.6%	58.6%	0
>=1 outpatient exacerbation	17.2%	18.5%	0.03	17.1%	17.1%	0
>=1 exacerbation requiring hospital presentation	24.7%	20.0%	0.11	24.2%	24.2%	0
COPD exacerbation in the past 30 days (%)	9.9%	10.9%	0.03	10.0%	9.8%	0.004
Duration of COPD year prior (%)						
< 2 years	20.8%	32.6%	0.27	21.7%	22.1%	0.009
2-5 years	18.6%	17.4%	0.03	18.8%	18.5%	0.006
> 5 years	60.6%	50.0%	0.21	59.5%	59.4%	0.003
Respiratory medications in the past 6 months (%)						
Short/long-acting beta agonists	40.3%	36.4%	0.08	39.7%	39.4%	0.007
Short/long-acting anticholinergics	41.2%	39.2%	0.04	40.8%	40.8%	0.0003
Inhaled corticosteroids	12.3%	12.1%	0.006	12.3%	12.3%	0.002
Combination inhaled corticosteroid-long acting beta agonist inhalers	36.4%	33.2%	0.07	35.9%	35.8%	0.002
Oral corticosteroids	17.8%	13.9%	0.11	17.3%	17.1%	0.003
Theophylline	2.2%	1.8%	0.03	2.2%	2.2%	0.003
Respiratory antibiotics	48.1%	44.3%	0.08	47.5%	47.5%	0.0003

Table 1 continued from previous page						
	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	Non-SSRI/ SNRI users	Standardized difference[b]	New SSRI/SNRI users	Non-SSRI/SNRI users	Standardized difference[b]
	N=29,835	N=88,776		N=28,360	N=28,360	
Total number of outpatient visits in the past 12 months (mean + standard deviation)	16.2 ± 11.6	13.9 ± 10.0	0.21	15.9 ± 11.5	15.9 ± 10.9	0.0003
Total number of hospitalizations in the past 12 months (mean + standard deviation)	0.7 ± 1.1	0.5 ± 0.9	0.20	0.6 ± 1.1	0.6 ± 1.1	0.005
Any ICU admission in the past 12 months (%)	9.9%	7.5%	0.08	9.6%	9.6%	0.0002
Johns Hopkins Adjusted Clinical Group[C] (%)						
Bottom tertile	27.2%	39.2%	0.26	28.2%	28.0%	0.004
Middle tertile	27.5%	29.2%	0.04	27.8%	27.9%	0.001
Top tertile	45.3%	31.5%	0.29	44.0%	44.1%	0.003
Psychotic psychiatric disease[d,e] (%)	9.5%	4.2%	0.21	8.5%	8.4%	0.005
Non-psychotic psychiatric disease[d,f] (%)	75.9%	42.9%	0.71	74.7%	74.8%	0.004
Benzodiazepine in the past 6 months (%)	38.3%	17.9%	0.47	35.6%	35.4%	0.004
Oral/transdermal opioid in the past 6 months (%)	35.1%	22.5%	0.28	33.3%	33.1%	0.004
Smoking cessation drug[g] in the past 12 months (%)	2.9%	1.7%	0.08	2.6%	2.5%	0.007

[a]The full list of covariates included in the propensity score model can be found in the Online Supplement.

[b]Standardized differences of > 0.10 are thought to indicate potentially meaningful differences.

[C]This is a measure of patient morbidity burden, using hospitalization and ambulatory visit data based on a 2-year look-back from the index date. The Johns Hopkins ACG(r) System Ver XX.

[d]Presence of comorbidities was based on 5-year look-back from the index date. .

[e]Includes schizophrenia, bipolar disorder and paranoid states.

[f]Includes depression disorders, anxiety disorders, phobias, stress disorders, dissociative and somatization disorders, eating disorders, personality disorders, mental and behavioural disorders due to substance abuse, and tic disorders.

[g]Includes Wellbutrin and Varenicline.

Table 2. Hazard ratios and confidence intervals for outcomes in the propensity score matched community-dwelling cohort

Outcomes	Status of SSRI/SNRI use	Number of events (%)	HR (95% CI, p-value)
Outpatient respiratory exacerbation	New SSRI or SNRI users	2406(8.5%)	0.91 (0.86-0.96, 0.0006)
	Non- SSRI or SNRI users	2619(9.2%)	Referent
ER visit for COPD or pneumonia	New SSRI or SNRI users	918(3.2%)	1.13 (1.03-1.24, 0.009)
	Non- SSRI or SNRI users	812(2.9%)	Referent
Hospital admission COPD or pneumonia	New SSRI or SNRI users	1105(3.9%)	1.15 (1.05-1.25, 0.002)
	Non- SSRI or SNRI users	965(3.4%)	Referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI or SNRI users	154(0.5%)	1.07 (0.85-1.34, 0.56)
	Non- SSRI or SNRI users	144(0.5%)	Referent
COPD/pneumonia-related mortality	New SSRI or SNRI users	204(0.7%)	1.26 (1.03-1.55, 0.03)
	Non- SSRI or SNRI users	163(0.6%)	Referent
All-cause mortality	New SSRI or SNRI users	1355(4.8%)	1.20 (1.11-1.29, <0.0001)
	Non- SSRI or SNRI users	1141(4.0%)	Referent

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

Table 3. Hazard ratios and confidence intervals for outcomes in the propensity score matched community-dwelling cohort, stratified by COPD exacerbation frequency

COPD exacerbation frequency status	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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
0 exacerbation in the year prior to index	New users	704 (4.2%)	0.80 (0.72-0.88), <0.0001	255 (1.5%)	1.14 (0.95-1.36), 0.16	277 (1.7%)	0.98 (0.83-1.15), 0.77	39 (0.2%)	0.83 (0.54-1.27), 0.39	51 (0.3%)	1.14 (0.76-1.70), 0.53	589 (3.5%)	1.13 (1.01-1.27), 0.04
	Non-users	875 (5.3%)		224 (1.3%)		284 (1.7%)		47 (0.3%)		45 (0.3%)		523 (3.1%)	
>=1 outpatient respiratory exacerbation in the year prior to index	New users	720 (14.8%)	0.90 (0.81-0.99), 0.04	138 (2.8%)	1.25 (0.97-1.60), 0.08	144 (3.0%)	1.20 (0.94-1.53), 0.14	20 (0.4%)	1.54 (0.76-3.10), 0.23	16 (0.3%)	0.73 (0.39-1.40), 0.35	182 (3.7%)	1.33 (1.07-1.66), 0.01
	Non-users	787 (16.2%)		111 (2.3%)		120 (2.5%)		13 (0.3%)		22 (0.5%)		138 (2.8%)	
>=1 exacerbation requiring presentation to hospital in the year prior to index	New users	982 (14.3%)	1.02 (0.93-1.12), 0.66	525 (7.6%)	1.10 (0.98-1.25), 0.11	684 (10.0%)	1.23 (1.10-1.38), 0.0002	95 (1.4%)	1.13 (0.84-1.52), 0.41	137 (2.0%)	1.45 (1.11-1.88), 0.006	584 (8.5%)	1.23 (1.10-1.39), 0.0006
	Non-users	957 (13.9%)		477 (6.9%)		561 (8.2%)		84 (1.2%)		96 (1.4%)		480 (7.0%)	

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

Table 4. Hazard ratios and confidence intervals for outcomes in the propensity score matched community-dwelling cohort, stratified by presence of pre-existing psychiatric disease

Pre-existing psychiatric disease[a] status	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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	HR (95% CI), p-value	N (%)	N (%)	HR (95% CI), p-value
No known pre-existing psychiatric disease	New users	552 (8.2%)	0.92 (0.82-1.04), 0.17	215 (3.2%)	1.20 (0.98-1.46), 0.07	307 (4.5%)	1.30 (1.10-1.54), 0.002	47 (0.7%)	1.81 (1.12-2.93), 0.02	76 (1.1%)	1.76 (1.21-2.55), 0.003	453 (6.7%)	1.71 (1.47-1.98), <0.0001
	Non-users	594 (8.8%)		180 (2.7%)		237 (3.5%)		26 (0.4%)		44 (0.7%)		270 (4.0%)	
Known pre-existing psychiatric disease	New users	1854 (8.6%)	0.90 (0.85-0.96), 0.002	703 (3.3%)	1.11 (1.00-1.24), 0.05	798 (3.7%)	1.10 (0.99-1.21), 0.06	107 (0.5%)	0.91 (0.70-1.18), 0.46	128 (0.6%)	1.08 (0.84-1.39), 0.55	902 (4.2%)	1.04 (0.95-1.14), 0.41
	Non-users	2025 (9.4%)		632 (2.9%)		728 (3.4%)		118 (0.5%)		119 (0.6%)		871 (4.0%)	

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

[a] An individual was considered to have psychiatric disease if any one of the following conditions were present: schizophrenia; bipolar disorder; paranoid states; depression disorders; anxiety disorders; phobias; stress disorders; dissociative and somatization disorders; eating disorders; personality disorders; mental and behavioural disorders due to substance abuse; and, tic disorders.

ONLINE SUPPLEMENT

Section 1: Listing and brief description of other health administrative databases used

a. Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) - contains information on all hospital admissions

b. ICES congestive heart failure (CHF) database - contains individuals with validated physician-diagnosed CHF [1]

c. ICES hypertension database - contains individuals with validated physician-diagnosed hypertension [2]

d. National Ambulatory Care Reporting System - contains information on all emergency room (ER) visits

e. Ontario Cancer Registry - a validated provincial cancer registry [3]

f. Ontario Diabetes Database - contains individuals with validated physician-diagnosed diabetes [4]

g. Ontario Health Insurance Plan (OHIP) database - contains information on all patient contact with physicians in both ambulatory and hospital settings

h. Ontario Mental Health Reporting System (OMHRS) - contains information on all mental health hospital admissions

i. Office of the Registrar General - Deaths (ORGD) - contains information on cause of death

j. Registered Persons Database - contains demographic information and date of death (if available) of all Ontarians

k. Same-Day Surgery database - contains information on surgical procedures not requiring overnight hospital stays

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Section 2: Baseline characteristics of community-dwelling cohort, before and after propensity score matching (full list of covariates included in the propensity score model[a])

	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[b]**	**New SSRI/SNRI users**	**Non-SSRI/SNRI users**	**Standardized difference[b]**
	N=29,835	N=88,776		N=28,360	N=28,360	
Age (mean + SD)	77.4 ± 7.2	76.9 ± 7.5	0.07	77.4 ± 7.2	77.5 ± 7.7	0.01
% female	55.7%	44.9%	0.22	54.6%	54.5%	0.0006
Low income as per ODB flag (%)	24.0%	20.6%	0.08	23.6%	23.6%	0.0001
Income quintile (%)						
1 (lowest)	24.4%	22.9%	0.04	24.3%	24.6%	0.006
2	22.1%	22.1%	0.0008	22.1%	21.9%	0.005
3	19.1%	19.6%	0.01	19.1%	19.0%	0.003
4	17.9%	18.6%	0.02	18.1%	18.1%	0.0005
5 (highest)	16.1%	16.4%	0.01	16.1%	16.2%	0.002
Missing data	0.4%	0.4%	0.005	0.4%	0.4%	0.001
% rural setting	17.2%	16.9%	0.008	17.1%	17.3%	0.003
COPD exacerbation frequency past year (%)						
0	58.1%	61.5%	0.07	58.6%	58.6%	0
>=1 outpatient exacerbation	17.2%	18.5%	0.03	17.1%	17.1%	0
>=1 exacerbation requiring hospital presentation	24.7%	20.0%	0.11	24.2%	24.2%	0
COPD exacerbation in the past 30 days (%)	9.9%	10.9%	0.03	10.0%	9.8%	0.004
Duration of COPD year prior (%)						
< 2 years	20.8%	32.6%	0.27	21.7%	22.1%	0.009
2-5 years	18.6%	17.4%	0.03	18.8%	18.5%	0.006
> 5 years	60.6%	50.0%	0.21	59.5%	59.4%	0.003

Table continued from previous page						
	Before propensity score matching			**After propensity score matching**		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[b]**	**New SSRI/SNRI users**	**Non-SSRI/SNRI users**	**Standardized difference[b]**
	N=29,835	N=88,776		N=28,360	N=28,360	
Respiratory medications in the past 6 months (%)						
Short/long-acting beta agonists	40.3%	36.4%	0.08	39.7%	39.4%	0.007
Short/long-acting anticholinergics	41.2%	39.2%	0.04	40.8%	40.8%	0.0003
Inhaled corticosteroids	12.3%	12.1%	0.006	12.3%	12.3%	0.002
Combination inhaled corticosteroid-long acting beta agonist inhalers	36.4%	33.2%	0.07	35.9%	35.8%	0.002
Oral corticosteroids	17.8%	13.9%	0.11	17.3%	17.1%	0.003
Theophylline	2.2%	1.8%	0.03	2.2%	2.2%	0.003
Respiratory antibiotics	48.1%	44.3%	0.08	47.5%	47.5%	0.0003
Total number of outpatient visits in the past 12 months (mean + SD)	16.2 ± 11.6	13.9 ± 10.0	0.21	15.9 ± 11.5	15.9 ± 10.9	0.0003
Total number of hospitalizations in the past 12 months (mean + SD)	0.7 ± 1.1	0.5 ± 0.9	0.20	0.6 ± 1.1	0.6 ± 1.1	0.005
Any ICU admission in the past 12 months (%)	9.9%	7.5%	0.08	9.6%	9.6%	0.0002
Any surgery in the past 12 months (%)	10.3%	9.1%	0.04	10.0%	10.0%	0.0007
Johns Hopkins Adjusted Clinical Group[c] (%)						
Bottom tertile	27.2%	39.2%	0.26	28.2%	28.0%	0.004
Middle tertile	27.5%	29.2%	0.04	27.8%	27.9%	0.001
Top tertile	45.3%	31.5%	0.29	44.0%	44.1%	0.003

Table continued from previous page						
	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	Non-SSRI/ SNRI users	Standardized difference[b]	New SSRI/SNRI users	Non-SSRI/SNRI users	Standardized difference[b]
	N=29,835	N=88,776		N=28,360	N=28,360	
Non-COPD pulmonary disease[d] (%)	50.5%	46.9%	0.07	50.2%	50.0%	0.004
Ischemic heart disease[d] (%)	35.7%	33.5%	0.05	35.4%	35.7%	0.005
Congestive heart failure[d] (%)	30.0%	27.5%	0.06	29.8%	30.3%	0.01
ER visit/hospitalization for ischemic heart disease or congestive heart failure in the year prior (%)	16.5%	13.1%	0.09	16.1%	16.1%	0.002
Hypertension[d] (%)	81.2%	78.8%	0.06	81.1%	81.2%	0.005
Atherosclerosis[d] (%)	7.7%	7.4%	0.01	7.7%	7.7%	0.002
Diabetes[d] (%)	34.8%	33.7%	0.02	34.7%	35.3%	0.01
Previous stroke and cerebrovascular disease[d] (%)	15.6%	11.4%	0.13	15.1%	15.2%	0.001
Cancer[d] (%)	23.3%	24.9%	0.04	23.5%	23.7%	0.004
Musculoskeletal or connective tissue disease[d] (%)	93.4%	89.6%	0.14	93.2%	93.2%	0.001
Osteoporosis[d] (%)	17.1%	14.7%	0.06	16.9%	16.8%	0.004
Psychotic psychiatric disease[d,e] (%)	9.5%	4.2%	0.21	8.5%	8.4%	0.005
Non-psychotic psychiatric disease[d,f] (%)	75.9%	42.9%	0.71	74.7%	74.8%	0.004

Table continued from previous page						
	Before propensity score matching			**After propensity score matching**		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[b]**	**New SSRI/SNRI users**	**Non-SSRI/SNRI users**	**Standardized difference[b]**
	N=29,835	N=88,776		N=28,360	N=28,360	
Sleep disorder[d] (%)	60.1%	55.1%	0.10	59.9%	60.1%	0.004
Total number of non-SSRI/SNRI drugs received in the past year (mean + SD)	13.8 ± 6.8	11.4 ± 6.1	0.37	13.5 ± 6.6	13.5 ± 6.6	0.004
Benzodiazepine in the past 6 months (%)	38.3%	17.9%	0.47	35.6%	35.4%	0.004
Oral/transdermal opioid in the past 6 months (%)	35.1%	22.5%	0.28	33.3%	33.1%	0.004
Smoking cessation drug[g] in the past 12 months (%)	2.9%	1.7%	0.08	2.6%	2.5%	0.007
Spirometry in the past 12 months (%)	26.7%	28.5%	0.04	26.8%	26.5%	0.005
% cohort entry in flu season[h]	38.5%	37.0%	0.03	38.2%	38.2%	0.0004

ER = emergency room; ODB = Ontario Drug Benefit; SD = standard deviation

[a]An abridged version of this table is found in the manuscript proper.

[b]Standardized differences of > 0.10 are thought to indicate potentially meaningful differences.

[c]This is a measure of patient morbidity burden, using hospitalization and ambulatory visit data based on a 2-year look-back from the index date. The Johns Hopkins ACG(r) System Ver XX.

[d]Presence of comorbidities was based on 5-year look-back from the index date.

[e]Includes schizophrenia, bipolar disorder and paranoid states.

[f]Includes depression disorders, anxiety disorders, phobias, stress disorders, dissociative and somatization disorders, eating disorders, personality disorders, mental and behavioural disorders due to substance abuse, and tic disorders.

[g]Includes Wellbutrin and Varenicline.

[h]Defined as November 1 to March 31.

Section 3: Additional sensitivity analyses for community-dwelling cohort

Methods for additional sensitivity analyses

Several additional sensitivity analyses were performed. First, we evaluated our outcomes distinguishing by whether a new SSRI or a new SNRI drug was received. The purpose of this analysis was to examine for possible drug class effects, since SSRI and SNRI drugs have differing neurotransmitter reuptake selectivities [1] and these differences may influence respiratory outcome risk. For example, SSRI drugs have more serotonin reuptake selectivity than SNRI drugs [1] and serotonin has been linked to reduced apoptotic cells clearance [2], which may in turn increase airway tract inflammation and plugging, and thereby, chances for respiratory tract infection [3].

Second, among individuals receiving citalopram (which was found to be the most commonly dispensed SSRI/SNRI, received by 35.2% of community-dwelling new SSRI/SNRI users and 48.0% of long term care resident new SSRI/SNRI users), we evaluated our outcomes by citalopram daily dose to examine for a possible dose-response relationship and to determine if adverse event risk possibly extended to 'lower dose' levels. We limited this sensitivity analysis to citalopram users, since this was the most commonly dispensed SSRI/SNRI drug and since it was not possible to convert the eight different SSRI/SNRI drugs covered by the Ontario Drug Benefit (ODB) program into 'milligram equivalents' of a single drug formulation. We considered two different citalopam dose levels: <20 mg/day (lower dose) and >=20 mg/day (higher dose). A threshold of 20 mg/day was chosen to distinguish 'lower' versus 'higher' citalopram daily dose levels, since the number of drug recipients was roughly evenly split above and below this threshold.

We previously reported that, among older adults with COPD, new use of another psychoactive medication class (benzodiazepine agonists) was associated with increased risk for adverse respiratory events [4]. Therefore, we performed a final sensitivity analysis where we evaluated our outcomes among new SSRI/SNRI drug users, but with the control group limited to new benzodiazepine users, in order to compare the respiratory safety profile of SSRI/SNRI drugs to benzodiazepines. New benzodiazepine use was defined as a dispensing for a benzodiazepine drug, with no benzodiazepine drug receipt in the year prior. For this sensitivity analysis, we excluded concomitant benzodiazepine users from the exposed group and concomitant SSRI/SNRI users from the control group, in order to minimize group contamination. Using a similar approach as previous [5], we defined concomitant use of either drug as receipt of the respective drug within 90 days prior to the index date. The propensity score was re-estimated for this specific sensitivity analysis, since a new control definition was used.

A final sensitivity analysis was performed where we evaluated our outcomes among new SSRI/SNRI drug users, but with the control group limited to new tricyclic antidepressant users. Tricyclic antidepressants, like SSRI/SNRI drugs, have serotonergic reuptake activity (albeit weaker) and the purpose of this sensitivity analysis was to examine whether risk of adverse respiratory events would be higher with receipt of the more serotonergic SSRI/SNRI drugs. New tricyclic antidepressant use was defined as a dispensing for a tricyclic antidepressant, with no tricyclic antidepressant drug receipt in the year prior. For this sensitivity analysis, we excluded concomitant tricyclic antidepressant users from the exposed group and concomitant SSRI/SNRI users from the control group, in order to minimize group contamination. Using a similar approach as previous [5], we defined concomitant use of either drug as receipt of the respective drug within 90 days prior to the index date. Because we observed that there were more exposed

than control individuals in this sensitivity analysis, we elected to balance the two groups on measured covariates using inverse probability of treatment weighting (IPTW) using the propensity score [6-7] (rather than using propensity score matching methods), in order to minimize loss of exposed individuals.

Results and discussion of additional sensitivity analyses

By SSRI versus SNRI drug class. Individuals receiving a new SSRI drug versus controls had significantly increased rates of hospital admission for COPD or pneumonia (HR 1.20; 95% CI 1.09-1.32), ER visits for COPD or pneumonia (HR 1.14; 95% CI 1.03-1.27), COPD or pneumonia-related mortality (HR 1.35; 95% CI 1.08-1.69) and all-cause mortality (HR 1.26; 95% CI 1.16-1.38), but significantly decreased rate of outpatient exacerbation (HR 0.90; 95% CI 0.85-0.96) (Table 1 in this section). There were no significant associations observed between new SNRI drug receipt and any of our outcomes. While these results suggest that it is drugs with greater serotonin reuptake selectivity that predispose to increased risk for adverse respiratory outcomes, the SNRI user subgroup may have been under-powered to detect for potentially significant results, as far fewer individuals in the exposed group received SNRI drugs versus SSRI drugs (SNRI recipients comprised 20.9% of new SSRI/SNRI drug users in the community-dwelling cohort).

By citalopram daily dose category. Individuals receiving lower daily doses of citalopram compared to controls had significantly increased rates of hospital admission for COPD or pneumonia (HR 1.45; 95% CI 1.20-1.74), COPD or pneumonia-related mortality (HR 2.31; 95% CI 1.40-3.81) and all-cause mortality (HR 1.48; 95% CI 1.26-1.75) (Table 2 in this

section). Significantly increased rate of all-cause mortality was observed among individuals receiving higher daily doses of citalopram compared to controls (HR 1.25; 95% CI 104-1.51). No other significant associations were observed in either group. The fact that increased rates of adverse respiratory outcomes were observed among individuals receiving lower daily doses of citalopram indicates that potential respiratory safety concerns regarding SSRI/SNRI drug use in COPD extend to lower drug dose levels. The finding of a greater number of 'positive results' in the lower versus higher daily citalopram dose category, and the finding of a higher HR for all-cause mortality in the lower versus higher daily citalopram dose group, suggests residual confounding may be effecting the results. However, the aforementioned findings may also reflect that our drug dose categorization was not fully accurate. A minority of individuals in both drug dose groups were simultaneously receiving more than one SSRI/SNRI drug, and this occurred more frequently in the lower (6.6%) versus higher (3.0%) citalopram dose group. It was not possible to convert other concomitant SSRI/SNRI drug use, when present, into 'citalopram milligram equivalents' and this limitation results in some degree of drug dose categorization inaccuracy.

With new benzodiazepine users serving as controls. Compared to new benzodiazepine users, new SSRI/SNRI users had significantly decreased rates of outpatient exacerbation (HR 0.82; 95% CI 0.76-0.89), COPD or pneumonia-related mortality (HR 0.75; 95% CI 0.59-0.94) and all-cause mortality (HR 0.75; 95% CI 0.68-0.82) (Table 3 in this section). No other significant associations were found. Although both new SSRI/SNRI drug use and new benzodiazepine drug use [4] are independently associated with increased adverse respiratory risk when compared to new, but non-specific, drug receipt in the older adult COPD population, the

results of this sensitivity analysis suggest that benzodiazepine drugs predispose to greater adverse respiratory risk than SRRI/SNRI drugs when compared head-to-head.

With new tricyclic antidepressant users serving as controls. Compared to new tricyclic antidepressant users, new SSRI/SNRI users had significantly increased rates of hospital admission for COPD or pneumonia (HR 1.18; 95% CI 1.03-1.37), COPD or pneumonia-related mortality (HR 1.57; 95% CI 1.07-1.29) and all-cause mortality (HR 1.39; 95% CI 1.22-1.59) (Table 4 in this section). No other significant associations were found. These findings suggest that it is the serotonergic activity of SSRI/SNRI drugs (which is present to a greater degree in these medications compared to tricyclic antidepressants) that is responsible for increased risk of adverse respiratory outcomes.

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Table 1. Hazard ratios and confidence intervals for outcomes in the community-dwelling propensity matched cohort, distinguishing by SSRI/SNRI drug type received

SSRI/SNRI drug type received	SSRI/SNRI status	Outpatient exacerbation		ER visit outcome		Hospital admission outcome		ICU outcome		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)
SSRI drugs	New users	1903 (8.5%)	0.90 (0.85-0.96), 0.0009	737 (3.3%)	1.14 (1.03-1.27), 0.01	922 (4.1%)	1.20 (1.09-1.32), 0.0001	131 (0.6%)	1.15 (0.89-1.48), 0.28	178 (0.8%)	1.35 (1.08-1.69), 0.009	1163 (5.2%)	1.26 (1.16-1.38), <0.0001
	Non- users	2088 (9.3%)		645 (2.9%)		769 (3.4%)		114 (0.5%)		133 (0.6%)		929 (4.1%)	
SNRI drugs	New users	505 (8.6%)	0.94 (0.84-1.06), 0.33	181 (3.1%)	1.08 (0.88-1.33), 0.47	183 (3.1%)	0.93 (0.76-1.12), 0.44	23 (0.4%)	0.77 (0.44-1.32), 0.34	26 (0.4%)	0.87 (0.51-1.47), 0.60	193 (3.3%)	0.91 (0.75-1.11), 0.35
	Non- users	531 (9.0%)		168 (2.8%)		197 (3.3%)		30 (0.5%)		30 (0.5%)		212 (3.6%)	

Table 2. Hazard ratios and confidence intervals for outcomes in the community-dwelling propensity matched cohort, distinguishing by citalopram daily dose

Citalo-pram daily dose	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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
Lower dose (< 20 mg/day)	New users	449 (8.4%)	0.93 (0.82-1.06), 0.29	175 (3.3%)	1.08 (0.88-1.33), 0.47	267 (5.0%)	1.45 (1.20-1.74), 0.0001	25 (0.5%)	0.78 (0.46-1.32), 0.35	50 (0.9%)	2.31 (1.40-3.81), 0.001	335 (6.3%)	1.48 (1.26-1.75), <0.0001
	Non-users	477 (8.9%)		162 (3.0%)		186 (3.5%)		32 (0.6%)		22 (0.4%)		229 (4.3%)	
Higher dose (>=20 mg/day)	New users	380 (8.2%)	0.93 (0.81-1.07), 0.30	146 (3.1%)	1.01 (0.80-1.26), 0.95	184 (4.0%)	1.14 (0.93-1.40), 0.20	31 (0.7%)	1.41(0.82-2.44), 0.22	33 (0.7%)	0.83 (0.52-1.32), 0.44	246 (5.3%)	1.25 (1.04-1.51), 0.02
	Non-users	406 (8.7%)		145 (3.1%)		162 (3.5%)		22 (0.5%)		40 (0.9%)		198 (4.3%)	

Table 3. Hazard ratios and confidence intervals for outcomes in the community-dwelling propensity matched cohort, where the control group was new benzodiazepine drug users

Outcomes	Status of SSRI/SNRI use	Number of events (%)	HR (95% CI, p-value)
Outpatient respiratory exacerbation	New SSRI or SNRI users	1175(7.8%)	0.82 (0.76-0.89), <0.0001
	New benzodiazepine users	1410(9.4%)	referent
ER visit for COPD or pneumonia	New SSRI or SNRI users	449(3.0%)	0.91 (0.80-1.03), 0.13
	New benzodiazepine users	495(3.3%)	referent
Hospital admissions COPD or pneumonia	New SSRI or SNRI users	579(3.9%)	1.01 (0.90-1.13), 0.86
	New benzodiazepine users	573(3.8%)	referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI or SNRI users	76(0.5%)	0.96 (0.70-1.32), 0.81
	New benzodiazepine users	79(0.5%)	referent
COPD/pneumonia-related mortality	New SSRI or SNRI users	118(0.8%)	0.75 (0.59-0.94), 0.01
	New benzodiazepine users	156(1.0%)	referent
All-cause mortality	New SSRI or SNRI users	798(5.3%)	0.75 (0.68-0.82), <0.0001
	New benzodiazepine users	1054(7.0%)	referent

Table 4. Hazard ratios and confidence intervals for outcomes in the community-dwelling propensity matched cohort, where the control group was tricyclic antidepressant drug users

Outcomes	Status of SSRI/SNRI use	Number of events (%)	HR (95% CI, p-value)
Outpatient respiratory exacerbation	New SSRI or SNRI users	2121 (8.4%)	0.93 (0.86-1.01, 0.10)
	New tricyclic users	1047 (9.0%)	referent
ER visit for COPD or pneumonia	New SSRI or SNRI users	793 (3.1%)	1.00 (0.87-1.16, 0.99)
	New tricyclic users	366 (3.1%)	referent
Hospital admissions COPD or pneumonia	New SSRI or SNRI users	965 (3.8%)	1.18 (1.03-1.37, 0.02)
	New tricyclic users	378 (3.2%)	referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI or SNRI users	140 (0.6%)	1.22 (0.84-1.77, 0.30)
	New tricyclic users	53 (0.5%)	referent
COPD or pneumonia-related mortality	New SSRI or SNRI users	186 (0.7%)	1.57 (1.07-2.29, 0.02)
	New tricyclic users	55 (0.5%)	referent
All-cause mortality	New SSRI or SNRI users	1274 (5.1%)	1.39 (1.22-1.59, <0.001)
	New tricyclic users	426 (3.7%)	referent

Section 4: Results of long-term care home resident cohort analysis

Overall cohort results

Between April 1, 2008 and December 31, 2013, 13,107 long-term care home residents with COPD were identified and 6231 (47.5%) of them were new SSRI/SNRI users (Figure 1 in this section). After propensity score matching, 5053 new users were matched to an equivalent number of controls. No matched control was found for 1178 (18.9%) of new SSRI/SNRI users. New users and controls were well-balanced on baseline characteristics, with standardized differences being below 10% for all variables (Table 1 in this section).

Compared to controls, new SSRI/SNRI users had significantly higher rates of COPD or pneumonia-related mortality (ARD 0.09%; HR 1.42, 95% CI 1.13-1.80; NNH 111) and all-cause mortality (ARD 4.5%; HR 1.32, 95% CI 1.19-1.46; NNH 22), but decreased significantly decreased rate of outpatient exacerbation (HR 0.84; 95% CI 0.72-0.97) (Table 2 in this section). No other significant associations were observed. These results are similar to the community-dwelling cohort, with the exception that in the community-dwelling cohort significantly increased rates of hospital admission for COPD or pneumonia and ER visits for COPD or pneumonia were also found. The aforementioned differences between the two cohorts may be explained by the fact that far fewer long-term care home residents were available for analysis (13,107 long-term care residents versus 118,611 community-dwelling individuals) and more SSRI/SNRI users went entirely unmatched in the long-term care home resident cohort (18.9% in long-term care versus 4.9% in the community). In addition, patterns of hospital referral may be different for long-term care residents as compared to community-dwelling older adults. For example, long-term care residents with COPD may receive care on-site within the nursing home

setting for COPD or pneumonia, thereby potentially resulting in fewer ER visits and hospitalizations for these conditions than would be seen with community-dwelling individuals with similar conditions. This difference helps to justify the approach used in this study, where community-dwelling older adults and long-term care residents were examined separately.

Sensitivity analyses

By COPD exacerbation frequency. In the subgroup of individuals with no exacerbation in the year prior to index, new versus non-users had significantly decreased rates of outpatient exacerbations (HR 0.75; 95% 0.58-0.98) (Table 3 in this section). In the subgroup of individuals with >=1 exacerbation requiring hospitalization in the year prior to index, significantly lower rates of ER visits for COPD or pneumonia was found among new versus non-users (HR 0.61; 95% 0.38-0.99). A significantly increased rate of COPD or pneumonia-related mortality was observed among new versus non-users in the subgroup with >=1 outpatient respiratory exacerbation in the year prior to index (HR 2.82; 95% CI 1.18-6.77). There were significantly increased rates of all-cause mortality among new versus non-users across all COPD exacerbation frequency subgroups (no exacerbations in the year prior to index: HR 1.31; 95% CI 1.14-1.50; >=1 outpatient respiratory exacerbation in the year prior to index: HR 1.96; 95% CI 1.35-2.86; >=1 exacerbation requiring hospitalization in the year prior to index: HR 1.23; 95% CI 1.03-1.46). No other associations were statistically significant. A fairly similar pattern of results was seen in the community-dwelling cohort.

By previously diagnosed psychiatric disease. In the subgroup of individuals without pre-existing psychiatric disease, there were significantly increased rates of COPD or pneumonia-

related mortality (HR 1.68; 95% CI 1.17-2.42) and all-cause mortality (HR 1.45; 95% CI 1.24-1.71) among new users compared to controls (Table 4 in this section). In the subgroup of individuals with pre-existing psychiatric disease, new users compared to controls had significantly lower rate of outpatient exacerbation (HR 0.80; 95% CI 0.67-0.97), but significantly higher all-cause mortality rate (HR 1.23; 95% CI 1.08-1.41). There were no other significant associations observed. While increased mortality risk associated with SSRI/SNRI drug use was found among individuals without pre-existing psychiatric disease in both the community-dwelling and long-term care home resident cohorts, this finding was observed to extend to those with pre-existing psychiatric disease among long-term care home residents.

By SSRI versus SNRI drug class. Individuals receiving a new SSRI drug versus controls had significantly decreased rate of outpatient exacerbation (HR 0.84; 95% CI 0.71-0.98) and significantly increased rates of COPD or pneumonia-related mortality (HR 1.42; 95% CI 1.11-1.81) and all-cause mortality (HR 1.29; 95% CI 1.15-1.44) (Table 5 in this section). Compared to controls, individuals receiving a new SNRI drug had significantly higher rate of all-cause mortality (HR 1.56; 95% CI 1.18-2.08). No other associations were statistically significant. Similar to community-dwelling individuals, new SSRI use was found to be associated with increased risk of death among long-term care home residents, but unlike the community-dwelling cohort, increased mortality risk additionally extended to new SNRI use in the long-term care home resident group.

By citalopram daily dose category. Compared to controls, individuals receiving lower daily doses of citalopram had significantly decreased rate of outpatient exacerbation (HR 0.68;

95% CI 0.52-0.88), but significantly increased rate of all-cause mortality (HR 1.22; 95% CI 1.02-1.46) (Table 6 in this section). Individuals receiving higher daily doses of citalopram versus controls also had significantly increased rate of all-cause mortality (HR 1.34; 95% CI 104-1.73). No other associations were statistically significant. Similar to the community-dwelling group, increased all-cause mortality was found to extend to lower dose citalopram users in the long-term care home resident cohort, but in addition, a dose-response relationship between citalopram and mortality was observed in the long-term care home group. Although there were a greater number of significantly increased adverse outcomes in association with lower dose citalopram use in the community-dwelling group, the smaller overall size of the long-term care home resident group, and the fact that more exposed individuals went unmatched in the latter cohort, may have contributed to an inability to detect more significant findings.

With new benzodiazepine users serving as controls. Compared to new benzodiazepine users, new SSRI/SNRI users had significantly decreased rates of COPD or pneumonia-related mortality (HR 0.61; 95% CI 0.48-0.78) and all-cause mortality (HR 0.63; 95% CI 0.57-0.71) (Table 7 in this section). No other outcomes were found to be statistically significant. A similar pattern of results was observed in the community-dwelling cohort.

With new tricyclic antidepressant users serving as controls. There were no significant associations observed between incident SSRI/SNRI drug use and our adverse respiratory outcomes, when new tricyclic antidepressant users formed the control group (Table 8 in this section). This sensitivity analysis may have been under-powered to detect potentially true

significant differences, given that in the relatively larger community-dwelling group significant differences were seen between exposed and control individuals.

Figure 1. Flow diagram outlining exposed and control group identification in the long-term care home resident cohort

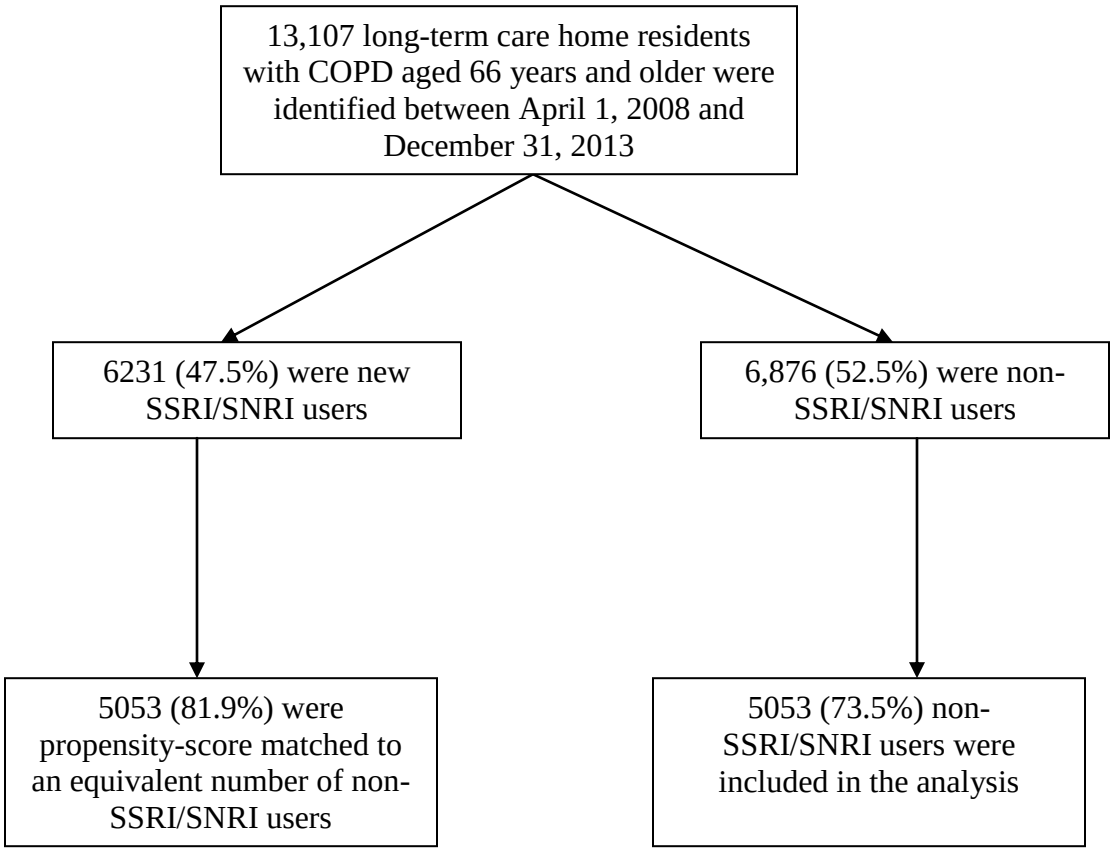

Table 1. Baseline characteristics of long-term care home resident cohort, before and after propensity score matching (full list of covariates included in the propensity score model)

	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[a]**	**New SSRI/SNRI users**	**Non-SSRI/ SNRI users**	**Standardized difference[a]**
	N=6,231	N=6,876		N=5,053	N=5,053	
Age (mean + SD)	83.8 ± 7.1	85.4 ± 7.5	0.23	84.5 ± 6.9	84.6 ± 7.6	0.01
% female	58.4%	59.8%	0.03	59.3%	59.3%	0.0008
Low income as per ODB flag (%)	37.6%	40.2%	0.05	38.7%	39.1%	0.009
Income quintile (%)						
1 (lowest)	25.1%	26.1%	0.02	25.9%	26.1%	0.005
2	20.4%	19.4%	0.02	19.8%	20.6%	0.02
3	20.3%	19.6%	0.02	19.8%	19.5%	0.008
4	18.1%	17.7%	0.01	18.0%	17.8%	0.005
5 (highest)	15.3%	16.3%	0.03	15.8%	15.3%	0.01
Missing data	0.8%	0.9%	0.01	0.8%	0.7%	0.009
% rural setting	18.7%	15.8%	0.08	17.4%	17.4%	0.0005
COPD exacerbation frequency in the past year (%)						
0	64.9%	63.1%	0.04	66.0%	66.0%	0
>=1 outpatient exacerbation	7.9%	11.0%	0.11	8.6%	8.6%	0
>=1 exacerbation requiring hospital presentation	27.2%	25.9%	0.03	25.5%	25.5%	0
COPD exacerbation in the past 30 days (%)	5.7%	9.2%	0.13	6.5%	6.2%	0.01
Duration of COPD year prior (%)						
< 2 years	20.6%	30.3%	0.22	24.2%	23.6%	0.01
2-5 years	17.2%	17.1%	0.003	17.5%	17.6%	0.001
> 5 years	62.2%	52.7%	0.19	58.3%	58.9%	0.01

Table 1 continued from previous page						
	Before propensity score matching			**After propensity score matching**		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference[a]**	**New SSRI/SNRI users**	**Non-SSRI/ SNRI users**	**Standardized difference[a]**
	N=6,231	N=6,876		N=5,053	N=5,053	
Respiratory medications in the past 6 months (%)						
Short/long-acting beta agonists	37.3%	39.9%	0.05	37.8%	37.9%	0.002
Short/long-acting anticholinergics	38.4%	41.0%	0.05	39.5%	39.8%	0.006
Inhaled corticosteroids	13.1%	16.1%	0.08	14.2%	14.3%	0.003
Combination inhaled corticosteroid-long acting beta agonist inhalers	27.3%	26.1%	0.03	26.7%	26.6%	0.002
Oral corticosteroids	13.1%	12.8%	0.009	12.5%	12.3%	0.008
Theophylline	1.6%	1.3%	0.02	1.6%	1.4%	0.02
Respiratory antibiotics	48.7%	55.5%	0.14	51.7%	52.0%	0.006
Total number of outpatient visits in the past 12 months (mean + SD)	18.9 ± 16.7	18.7 ± 14.4	0.01	18.5 ± 15.9	18.6 ± 14.1	0.005
Total number of hospitalizations in the past 12 months (mean + SD)	0.93 ± 1.17	0.78 ± 1.09	0.1358	0.84 ± 1.11	0.83 ± 1.14	0.012
Any ICU admission in the past 12 months (%)	602 (9.7%)	494 (7.2%)	0.0893	406 (8.0%)	414 (8.2%)	0.0058
Any surgery in the past 12 months (%)	700 (11.2%)	584 (8.5%)	0.092	481 (9.5%)	485 (9.6%)	0.0027
Johns Hopkins Adjusted Clinical Group[b] (%)						
Bottom tertile	29.3%	40.3%	0.23	34.4%	35.0%	0.01
Middle tertile	23.2%	21.7%	0.04	23.4%	22.9%	0.01
Top tertile	47.5%	38.0%	0.19	42.2%	42.1%	0.003
Non-COPD pulmonary disease[c] (%)	42.5%	38.0%	0.09	39.8%	39.4%	0.009
Ischemic heart disease[c] (%)	39.8%	34.8%	0.10	37.7%	37.7%	0.0004

Table 1 continued from previous page						
	Before propensity score matching			After propensity score matching		
	New SSRI/SNRI users	Non-SSRI/ SNRI users	Standardized difference[a]	New SSRI/SNRI users	Non-SSRI/ SNRI users	Standardized difference[a]
	N=6,231	N=6,876		N=5,053	N=5,053	
Congestive heart failure[c] (%)	46.5%	47.1%	0.01	46.9%	47.1%	0.004
ER visit/hospitalization for ischemic heart disease or congestive heart failure in the year prior (%)	23.2%	20.0%	0.08	21.4%	21.2%	0.004
Hypertension[c] (%)	84.9%	81.7%	0.09	83.7%	83.6%	0.003
Atherosclerosis[c] (%)	8.4%	8.4%	0.0005	8.3%	8.3%	0.0007
Diabetes[c] (%)	38.7%	36.7%	0.04	37.9%	37.9%	0.0004
Previous stroke and cerebrovascular disease[c] (%)	31.3%	29.1%	0.045	30.2%	30.5%	0.007
Cancer[c] (%)	22.5%	21.8%	0.02	22.2%	22.0%	0.005
Musculoskeletal or connective tissue disease[c] (%)	92.8%	91.2%	0.06	92.1%	92.1%	0
Osteoporosis[c] (%)	16.8%	16.6%	0.006	16.6%	16.5%	0.002
Psychotic psychiatric disease[c,e] (%)	21.9%	19.8%	0.05	21.1%	21.4%	0.007
Non-psychotic psychiatric disease[c,f] (%)	61.6%	49.7%	0.24	57.0%	56.8%	0.004
Sleep disorder[c] (%)	53.2%	48.4%	0.10	50.4%	50.8%	0.008
Total number of non-SSRI/SNRI drugs received in the past year (mean + SD)	15.8 ± 8.0	15.9 ± 6.9	0.01	15.9 ± 7.8	15.9 ± 7.0	0.001

Table 1 continued from previous page						
	Before propensity score matching			**After propensity score matching**		
	New SSRI/SNRI users	**Non-SSRI/ SNRI users**	**Standardized difference**[a]	**New SSRI/SNRI users**	**Non-SSRI/ SNRI users**	**Standardized difference**[a]
	N=6,231	N=6,876		N=5,053	N=5,053	
Benzodiazepine in the past 6 months (%)	32.5%	28.9%	0.08	31.2%	31.7%	0.01
Oral/transdermal opioid in the past 6 months (%)	34.2%	29.8%	0.09	32.7%	32.6%)	0.003
Smoking cessation drug[g] **in the past 12 months (%)**	1.6%	1.1%	0.04	1.3%)	1.3%)	0.007
Spirometry in the past 12 months (%)	8.0%	5.1%	0.12	6.1%	6.0%)	0.003
% cohort entry in flu season[h]	39.1%	33.8%	0.11	36.5%	36.3%	0.005

ER = emergency room; ODB = Ontario Drug Benefit; SD = standard deviation

[a]Standardized differences of > 0.10 are thought to indicate potentially meaningful differences.

[b]This is a measure of patient morbidity burden, using hospitalization and ambulatory visit data based on a 2-year look-back from the index date. The Johns Hopkins ACG(r) System Ver XX.

[c]Presence of comorbidities was based on 5-year look-back from the index date.

[e]Includes schizophrenia, bipolar disorder and paranoid states.

[f]Includes depression disorders, anxiety disorders, phobias, stress disorders, dissociative and somatization disorders, eating disorders, personality disorders, mental and behavioural disorders due to substance abuse, and tic disorders.

[g]Includes Wellbutrin and Varenicline.

[h]Defined as November 1 to March 31.

Table 2. Hazard ratios and confidence intervals for outcomes in the propensity score matched long term care home resident cohort

Outcomes	Status of SSRI/SNRI use	Number of events (%)	HR (95% CI, p-value)
Outpatient respiratory exacerbation	New SSRI or SNRI users	299(5.9%)	0.84 (0.72-0.97), 0.02
	Non- SSRI or SNRI users	355(7.0%)	Referent
ER visit for COPD or pneumonia	New SSRI or SNRI users	87(1.7%)	0.99 (0.74-1.33), 0.94
	Non- SSRI or SNRI users	88(1.7%)	Referent
Hospital admissions COPD or pneumonia	New SSRI or SNRI users	218(4.3%)	1.05 (0.88-1.27), 0.56
	Non- SSRI or SNRI users	207(4.1%)	Referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI or SNRI users	20(0.4%)	1.05 (0.56-1.98), 0.87
	Non- SSRI or SNRI users	19(0.4%)	Referent
COPD/pneumonia-related mortality	New SSRI or SNRI users	169(3.3%)	1.42 (1.13-1.80), 0.003
	Non- SSRI or SNRI users	122(2.4%)	Referent
All-cause mortality	New SSRI or SNRI users	808(16.0%)	1.32 (1.19-1.46), <0.0001
	Non- SSRI or SNRI users	631(12.5%)	Referent

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

Table 3. Hazard ratios and confidence intervals for outcomes in the propensity score matched long term care home resident cohort, stratified by COPD exacerbation frequency

COPD exacerbation frequency status	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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
0 exacerbation in the year prior to index	New users	100 (3.0%)	0.75 (0.58-0.98), 0.03	48 (1.4%)	1.23 (0.82-1.87), 0.32	88 (2.6%)	1.13 (0.84-1.53), 0.43	6 (0.2%)	1.00 (0.32-3.10), 1.00	70 (2.1%)	1.43 (0.99-2.06), 0.05	462 (13.9%)	1.31 (1.14-1.50), 0.0001
	Non-users	132 (4.0%)		39 (1.2%)		78 (2.3%)		6 (0.2%)		50 (1.5%)		361 (10.8%)	
>=1 outpatient respiratory exacerbation in the year prior to index	New users	72 (16.6%)	0.91 (0.67-1.23), 0.53	12 (2.8%)	2.41 (0.84-6.90), 0.10	22 (5.1%)	1.38 (0.74-2.58), 0.31	<6[a]	1.00 (0.14-7.12), 1.00	19 (4.4%)	2.82 (1.18-6.77), 0.02	73 (16.8%)	1.96 (1.35-2.86), 0.0005
	Non-users	78 (18.0%)		<6[a]		16 (3.7%)		<6[a]		7 (1.6%)		39 (9.0%)	
>=1 exacerbation requiring presentation to hospital in the year prior to index	New users	127 (9.9%)	0.87 (0.69-1.10), 0.24	27 (2.1%)	0.61 (0.38-0.99), 0.05	108 (8.4%)	0.96 (0.73-1.24), 0.74	12 (0.9%)	1.09 (0.48-2.49), 0.83	80 (6.2%)	1.28 (0.92-1.77), 0.14	273 (21.2%)	1.23 (1.03-1.46), 0.02
	Non-users	145 (11.3%)		44 (3.4%)		113 (8.8%)		11 (0.9%)		65 (5.1%)		231 (18.0%)	

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

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

Table 4. Hazard ratios and confidence intervals for outcomes in the propensity score matched long term care home resident cohort, stratified by presence of pre-existing psychiatric disease

Pre-existing psychiatric disease[a] status	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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 (%)
No known pre-existing psychiatric disease	New users	105 (5.7%)	0.90 (0.70-1.16), 0.41	27 (1.5%)	0.77 (0.46-1.28), 0.31	77 (4.1%)	1.12 (0.82-1.53), 0.49	10 (0.5%)	1.67 (0.61-4.60), 0.32	76 (4.1%)	1.68 (1.17-2.42), 0.005	338(18.2%)	1.45 (1.24-1.71), <0.0001
	Non-users	116 (6.2%)		35 (1.9%)		69 (3.7%)		6 (0.3%)		47 (2.5%)		242(13.0%)	
Known pre-existing psychiatric disease	New users	194 (6.1%)	0.80 (0.67-0.97), 0.020	60 (1.9%)	1.13 (0.79-1.64), 0.50	141 (4.4%)	1.02 (0.81-1.29), 0.84	10 (0.3%)	0.77 (0.34-1.76), 0.53	93 (2.9%)	1.27 (0.94-1.71), 0.13	470(14.7%)	1.23 (1.08-1.41), 0.002
	Non-users	239 (7.5%)		53 (1.7%)		138 (4.3%)		13 (0.4%)		75 (2.3%)		389 (12.2%)	

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

[a] An individual was considered to have psychiatric disease if any one of the following conditions were present: schizophrenia; bipolar disorder; paranoid states; depression disorders; anxiety disorders; phobias; stress disorders; dissociative and somatization disorders; eating disorders; personality disorders; mental and behavioural disorders due to substance abuse; and, tic disorders.

Table 5. Hazard ratios and confidence intervals for outcomes in the long term care home resident propensity matched cohort, distinguishing by SSRI/SNRI drug class received

SSRI/SNRI drug class received	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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
SSRI drugs	New users	266 (6.1%)	0.84 (0.71-0.98), 0.03	81 (1.8%)	1.03 (0.75-1.40), 0.87	185 (4.2%)	1.02 (0.84-1.25), 0.83	17 (0.4%)	1.13 (0.57-2.27), 0.72	152 (3.5%)	1.42 (1.11-1.81), 0.005	698 (15.9%)	1.29 (1.15-1.44), <0.0001
	Non-users	316 (7.2%)		79 (1.8%)		181 (4.1%)		15 (0.3%)		110 (2.5%)		557 (12.7%)	
SNRI drugs	New users	33 (5.0%)	0.84 (0.53-1.33), 0.45	6 (0.9%)	0.66 (0.24-1.88), 0.44	33 (5.0%)	1.28 (0.78-2.10), 0.33	<6[a]	0.75 (0.17-3.37), 0.71	18 (2.7%)	1.57 (0.75-3.27), 0.23	111 (16.8%)	1.56 (1.18-2.08), 0.002
	Non-users	39 (5.9%)		9 (1.4%)		26 (3.9%)		<6[a]		12 (1.8%)		74 (11.2%)	

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

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

Table 6. Hazard ratios and confidence intervals for outcomes in the long term care home resident propensity matched cohort, distinguishing by citalopram daily dose

Citalo-pram daily dose	SSRI/ SNRI status	Outpatient exacerbation		ER visit for COPD or pneumonia		Hospital admission COPD or pneumonia		ICU admission during a 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
Lower dose (< 20 mg/day)	New users	89 (5.7%)	0.68 (0.52-0.88), 0.004	33 (2.1%)	1.38 (0.82-2.32), 0.23	67 (4.3%)	1.23 (0.87-1.74), 0.25	6 (0.4%)	1.00 (0.32-3.11), 1.00	49 (3.1%)	1.39 (0.90-2.15), 0.14	245 (15.6%)	1.22 (1.02-1.46), 0.03
	Non-users	130 (8.3%)		24 (1.5%)		55 (3.5%)		6 (0.4%)		36 (2.3%)		205 (13.1%)	
Higher dose (>=20 mg/day)	New users	46 (5.3%)	0.86 (0.58-1.27), 0.45	11 (1.3%)	0.73 (0.35-1.55), 0.42	34 (3.9%)	0.89 (0.56-1.42), 0.62	<6[a]	3.00 (0.31-28.90), 0.34	23 (2.7%)	1.13 (0.62-2.05), 0.70	136 (15.7%)	1.34 (1.04-1.73), 0.02
	Non-users	53 (6.1%)		15 (1.7%)		38 (4.4%)		<6[a]		21 (2.4%)		104 (12.0%)	

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

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

Table 7. Hazard ratios and confidence intervals for outcomes in the long term care home resident propensity matched cohort, where the control group was new benzodiazepine drug users

Outcomes	SSRI/SNRI use status	Number of events (%)	HR (95% CI), p-value
Outpatient respiratory exacerbation	New SSRI/SNRI users	188 (5.7%)	0.84 (0.70-1.02), 0.08
	New benzodiazepine users	221 (6.7%)	referent
ER visit for COPD or pneumonia	New SSRI/SNRI users	63(1.9%)	0.95 (0.67-1.35), 0.79
	New benzodiazepine users	66 (2.0%)	referent
Hospital admissions COPD or pneumonia	New SSRI/SNRI users	153 (4.6%)	1.06 (0.85-1.33), 0.61
	New benzodiazepine users	144 (4.4%)	Referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI/SNRI users	15 (0.5%)	0.75 (0.38-1.47), 0.40
	New benzodiazepine users	20 (0.6%)	referent
COPD or pneumonia-related mortality	New SSRI/SNRI users	102 (3.1%)	0.61 (0.48-0.78), 0.0001
	New benzodiazepine users	156 (4.7%)	referent
All-cause mortality	New SSRI/SNRI users	534 (16.2%)	0.63 (0.57-0.71), <0.0001
	New benzodiazepine users	783 (23.8%)	referent

Table 8. Hazard ratios and confidence intervals for outcomes in the long-term care home resident propensity matched cohort, where the control group was tricyclic antidepressant drug users

Outcomes	Status of SSRI/SNRI use	Number of events (%)	HR (95% CI, p-value)
Outpatient respiratory exacerbation	New SSRI or SNRI users	333 (5.9%)	0.79 (0.55-1.14, 0.20)
	New tricyclic users	48 (7.4%)	referent
ER visis for COPD or pneumonia	New SSRI or SNRI users	98 (1.7%)	1.29 (0.61-2.75, 0.50)
	New tricyclic users	9 (1.3%)	referent
Hospital admissions COPD or pneumonia	New SSRI or SNRI users	258 (4.5%)	0.87 (0.59-1.29, 0.48)
	New tricyclic users	34 (5.2%)	referent
ICU admission during a hospitalization for COPD or pneumonia	New SSRI or SNRI users	30 (0.5%)	0.80 (0.34-1.90, 0.61)
	New tricyclic users	<6[a]	referent
COPD or pneumonia-related mortality	New SSRI or SNRI users	186 (3.3%)	1.07 (0.63-1.81, 0.81)
	New tricyclic users	20 (3.1%)	referent
All-cause mortality	New SSRI or SNRI users	890 (15.7%)	1.04 (0.82-1.32, 0.74)
	New tricyclic users	97 (15.0%)	referent

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